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THE STRUCTURE OF THE CAUDATE NUCLEUS OF THE CAT: LIGHT AND ELECTRON MICROSCOPY

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[Plates 54 to 61]

The caudate nucleus of the cat appears to be homogeneous when examined with the light or electron microscope, except for a layer beneath the ependyma where there is a high concentration of glial cells and few neurons. In sections of brains stained with thionin the nerve cells in the caudate nucleus fall into three size groups: less than 8 μm, 9 to 18 μm, greater than 20 μm. Examination of material impregnated with the Golgi technique shows that there are six cell types (one small, four medium and one large), and these are distinguishable on the basis of the size of the cell somata and the appearance and arrangement of their dendrites. One type of medium cell with many dendritic spines forms over 95 % of the cell population. The large and one medium cell type are tentatively identified as the source of the efferent fibres of the nucleus. These efferent fibres and the axons of the remaining medium cell types have collateral branches. Three groups of possible afferent fibres have been identified, and these and the collateral branches of the intrinsic neurons form a dense plexus whose individual fibres cross dendrites rather than lie parallel to them. Six cell types may also be distinguished with the electron microscope, and four of these can be correlated directly with those seen in Golgi impregnated material. Several kinds of dendrites are present, the commonest having numerous spines. Fewer spines are present on other varieties of dendrite, and those dendrites which are varicose have no spines. Numerous fine, non-myelinated axons are present.

Introduction

The basal ganglia form a conspicuous part of the forebrain and well-defined clinical syndromes have long been known to be associated with lesions which involve them, but the details of the structure and function of these masses are largely unknown. The present anatomical study is concerned with the striatum, composed of two parts, the caudate nucleus and the putamen, which are grouped together because of their similarities in development, microscopic structure and connexions.

The lack of knowledge of the function of the striatum and the fact that the connexions of this relatively large part of the forebrain have only recently begun to be elucidated are due to a number of factors. Of these difficulties perhaps the foremost is the deep position of both the caudate nucleus and the putamen in the cerebral hemisphere, which makes it difficult to place lesions within the nuclei without simultaneously damaging the adjacent white matter of the corpus callosum or internal and external capsules, either directly or by interference with the blood supply. Early anatomical studies of the afferent connexions of the region were also hampered by the lack of a staining method for axonal degeneration because the afferent fibres to the striatum are now known to be thinly myelinated or unmyelinated. Since such a method became available (Nauta & Gygax 1954) there has been a considerable advance in the knowledge of the fibre pathways connected with this region.

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Two significant findings regarding the afferent connexions of the striatum in recent years have been, first, that the intralaminar nuclei of the thalamus project to the caudate nucleus and putamen, and secondly, that the entire extent of the neocortex projects to them also. The projection from the intralaminar nuclei to the striatum had been inferred from human neuro-pathological material (Vogt & Vogt 1941; McLardy 1948), and was shown experimentally using the method of retrograde cell degeneration (Droogleever-Fortuyn 1953; Powell & Cowan 1954, 1956). Most of the intralaminar nuclei are too small to place lesions within them and trace the resultant axonal degeneration, but the centromedian nucleus in the monkey is an exception, and, in this case, the projection to the caudate nucleus and putamen has been shown in a direct manner by axonal degeneration techniques following an electrolytic lesion within the nucleus (Mehler 1966). It is not known whether the intralaminar nuclei project to the striatum alone or whether they also send axonal branches to the cerebral cortex.

A projection of the cortex upon the striatum has long been suspected (see Mettler 1942), but only within the last decade has it become unequivocally established that the whole of the cortex projects in a topographically well-organized manner to both the caudate nucleus and putamen of the same side (Webster 1961, 1965; Carman, Cowan & Powell 1963; Kemp & Powell 1970) with a small bilateral projection from the sensori-motor region (Carman, Cowan, Powell & Webster 1965; Kemp & Powell 1970). As with the thalamo-striate projection, it is not known whether the cortical afferent fibres are collaterals of axons passing to lower levels of the brain or whether they arise from cortical neurons which project only to the striatum. Material impregnated with the Golgi method has shown fibres in the internal capsule with branches passing into the neuropil of the caudate nucleus (Cajal 1911; Webster 1961), but it is not possible to say whether these are the collaterals of ascending or descending axons.

Though the thalamo-striate and cortico-striate projections are now well established, the possibility of a pathway from the substantia nigra still gives rise to controversy. The weight of anatomical evidence appeared to be against a substantial nigro-striate projection (see Mettler 1970), but recent anatomical (Nauta & Mehler 1969) and histochemical (Andén, Dahlström, Fuxe & Larsson 1965) work tends to support the presence of such connexions. Another projection from the midbrain to the striatum has been shown by Nauta & Kuypers (1957), who found that lesions of the midbrain tegmentum at the level of the red nucleus gave rise to terminal degeneration in the caudate nucleus and the putamen.

Until about twenty years ago the interpretation of data from recording evoked potentials with a gross electrode could be based on such a knowledge of the major afferent connexions of the region being studied. With the increasing use of micro- and intracellular electrodes more detailed information has been needed concerning the precise site of termination of the afferent fibres on different parts of the cell. The primary aim of the present study was to obtain such information about the termination of the afferent fibres to the striatum in the cat. Experimental studies are undoubtedly required for the unequivocal demonstration of the termination of the fibres in different afferent pathways to a particular region, but a thorough knowledge of the appearance of the structure in normal material would facilitate the interpretation of the experimental studies.

Relatively little is known of the structure and intrinsic organisation of the caudate nucleus and putamen. Examination of material stained by the Nissl method (Brockhaus 1942; Namba 1957) has contributed little except to emphasize that the region contains many small cells and that there are no obvious subdivisions, though some differentiation may be possible on the basis

of cell density (Namba 1957). Studies of Golgi impregnated material (Cajal 1911; Leontovich 1954) have given a more complete impression of the cells and their processes and again emphasize the predominance of medium-sized stellate cells which have characteristics of interneurons. The details of neuronal interrelationships cannot be determined in such material as synaptic contacts cannot be identified. Though the juxtaposition of terminals and a cell body, dendrite or dendritic spine show that such a contact could occur, it is not definite evidence for the presence of a synapse, as electron microscopic examination of any region of the nervous system shows that there is frequently apposition of axon terminals and cell somata or dendritic processes without the appearance of any synaptic specialization. In this paper the general appearance of the caudate nucleus and the cell types and their dendrites will be described, and it will be seen that a correlation of the findings from electron microscopy and Golgi impregnated material has been particularly valuable. The details of the normal morphology of the synapses and the results of experimental studies will be considered separately in subsequent papers.

Material and methods

The observations which will be described in this paper were made either with the light microscope on material stained with thionin or impregnated with the Golgi–Kopsch method or on tissue prepared for electron microscopy.

The Golgi–Kopsch method (see Colonnier 1964) was used to impregnate the caudate nucleus and putamen from the brains of 18 cats. The animals were perfused with saline followed by a mixture of 4 % formaldehyde and 1 % glutaraldehyde in a phosphate buffer. Slices of the caudate nucleus and putamen, not more than 1.5 mm thick and cut in several different planes (coronal, sagittal, horizontal and oblique), were impregnated and embedded in low viscosity nitrocellulose. Sections were cut at 100 μm and mounted under cover-slips using a neutral mountant. The sections were examined at different magnifications, including under a × 100 oil-immersion objective, and drawings of various features were made using a Zeiss drawing attachment. Series of sections of several cat brains, stained with thionin, were also available.

The electron microscopic observations were made on normal and experimental material, 28 animals being used. The animals were perfused, under hypothermia, with a balanced salt solution and with the same aldehyde mixture used for the material impregnated with the Golgi method. After removal from the skull the brain was stored in the perfusion mixture overnight before small cubical blocks of approximately 1 mm side were removed from different parts of the head of the caudate nucleus and from the putamen. The blocks were washed in phosphate buffer containing 10 % sucrose, post-fixed in osmium tetroxide and dehydrated; they were embedded in Araldite. In order to identify the exact region required for thin sections, a 'thick', 1 μm section of the whole block was cut and stained for light microscopical examination by the method of Richardson, Jarett & Finke (1960); the block was then trimmed to give thin sections from selected areas. Two sizes of sections were used: (1) for routine scanning the sections were approximately 500 μm^2 and were mounted on meshed grids and (2) smaller sections of between100 and 200 μm^2. The latter sections were either mounted on fine meshed grids or as serial sections on grids with a single hole 1 mm by 2 mm coated with a thin film of Formvar; up to 50 such sections could be mounted on one grid in two or three ribbons, and series of up to 150 consecutive sections were used. The sections were stained with lead citrate (Reynolds

1963) and 5 % uranyl acetate, and were examined with a Siemens Elmiskop 1 or a Philips EM 200 electron microscope.

Results

Light microscopy

Thionin stained material

The caudate nucleus is a homogeneous structure when examined with the light microscope in sections stained with thionin. There is a high concentration of nerve cells which are scattered in an irregular and apparently random manner throughout the neuropil, except for a narrow zone, relatively free of neurons, beneath the ependyma of the lateral ventricle in which there is a large number of glial cells (Brockhaus 1942). There is no such border at the junctions with the internal capsule and subcallosal fasciculus, where nerve cells can be seen immediately adjacent to the myelinated fibres which form these tracts. Throughout the rest of the nucleus small clusters of neurons are present and within these groups pairs of cells are often very close to one another. Glial cells are frequently seen lying against the nerve cell somata and more than one of these satellite cells may be associated with a neuron. The average diameter of the most numerous group of nerve cells is 12 to 14 μm, though there is a range from 9 to 18 μm. There are two other numerically small groups of cells, one larger than 20 μm in diameter and the other less than 8 μm. Each of these groups forms less than 1 % of the total. Most of the medium-sized cells have large, pale, round nuclei with a narrow rim of pale cytoplasm, but a few, those towards the upper limit of the range, have fairly prominent Nissl bodies and nuclei with one or more indentations. Other cells in this size range have indented nuclei but no other distinguishing feature. Indented nuclei are also found in the group of large cells which can be distinguished from the cells in the medium size group not only on the basis of size, but also by their large amount of Nissl substance. The cells in the small size group are similar in diameter to many of the glial cells but the former have pale, oval or round nuclei with definite nucleoli which differentiates them from the glial cells which have irregular and often dark nuclei with clumped chromatin and ill-defined nucleoli. The cytoplasm of the small neurons is usually uniformly dark with no definite Nissl bodies.

The appearance of the putamen is similar to that of the caudate nucleus (Brockhaus 1942). Here, however, the borders have no distinguishing features as it is bounded on all sides by regions composed almost entirely of myelinated fibres.

Golgi impregnated material

There are two very striking features of the caudate nucleus after impregnation with the Golgi method. First, in well impregnated material there is an exceptionally complex axonal plexus (figures 6 and 8, plate 54) forming a dense felt-like mass which completely invests the constituent neurons and their processes; this plexus receives a large number of collateral branches from the axons of the intrinsic cells (figure 7, plate 54). The second remarkable feature, which is more obvious in less well impregnated material, is the great preponderance of one cell type though several other varieties can be recognized. The cells of all types are distributed evenly throughout the nucleus and most of them are stellate with round or oval dendritic fields which do not seem to have any specific orientation. In a few cases the cells are fusiform and the dendritic field is very elongated as the dendrites tend to arise from the two poles of the cell body, but again there does not seem to be any specificity in their orientation.

These features are also characteristic of the putamen; careful examination of its structure shows that it is similar in all respects to the caudate nucleus.

In a sample of 1593 cells from the caudate nucleus 96 % of the population was of one cell type (figure 1). This cell has a rounded or polygonal cell body which varies in diameter between 12 and 18 μm. Its main characteristic is the large number of dendritic spines, and, over the region of their highest concentration, they are often difficult to see as separate entities, even at high magnification. Usually there are five or six dendrites and they may arise from any point round the cell body; these main stem dendrites often branch about 20 μm from their origin

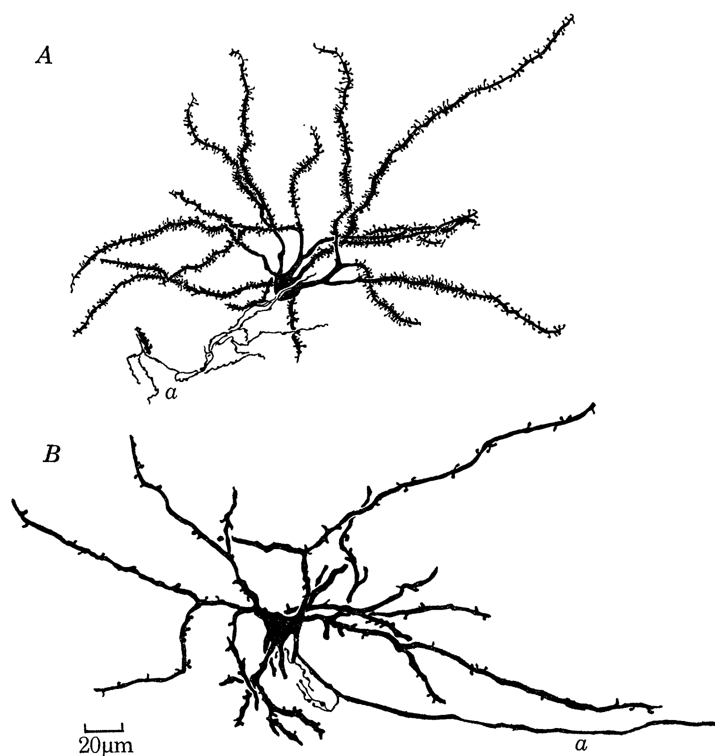


FIGURE 1. Camera lucida drawing of a medium spiny cell (*A*) and of a medium long axon cell (*B*). *a*, axon. Both at same magnification

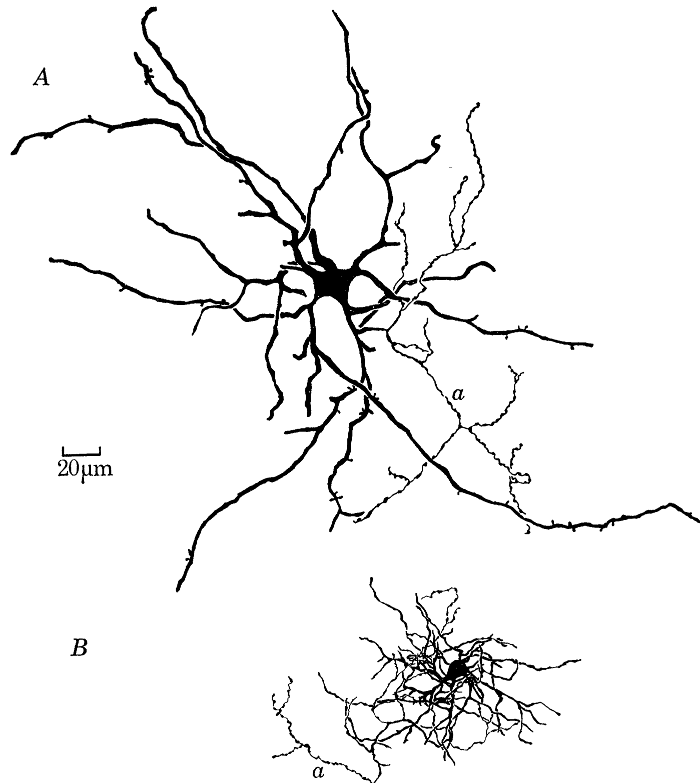
but may do so sooner, and one further branching of the secondary dendrites often occurs. Some dendrites are unbranched. Spines are very rare over the first 20 μm of the dendrite, but after this become frequent, reaching an average number of 26 per 20 μm length of dendrite between 60 and 80 μm from the cell body though the density may be higher. More peripherally the number of spines decreases slowly to a mean figure of about 17 per 20 μm between 160 and 180 μm from the cell soma and continues at this level to the end of the dendrite. The majority of spines are composed of an enlarged head on a thin stalk but their size and the length of the stalk vary considerably, some spines being over 2 μm long while others are sessile; branched spines are fairly common. It has not been possible to relate the size of the spine head to the length of the stalk or either of these parameters to the position of the spine along the dendrite. The average length of the dendrites is 180 μm though some may reach 240 μm. The axon of this cell may start from the soma or from a main stem dendrite and is smooth; the main part of the axon is invariably shorter than the dendrites and in about half the cells it turns back on

itself after about 60 μm. Several fine collateral branches arise from the axon, occasionally within 40 μm of its beginning, but usually more distally. The peripheral part of the main axon is often beaded and the fine branches usually begin from these enlargements which are also present on the collaterals. The main axon and its branches may travel in any direction forming a three-dimensional system, but though the plexus is quite profuse it rarely extends beyond 200 μm from the cell body so that the ramifications of these fibres are mainly within the limits of the spread of the dendritic tree of the parent cell.

Although originally only three other types of cell were recognized (Kemp 1968*b*), five can now be clearly differentiated and of these, three, comprising about 3 % of the remainder of the cells, fall into the same size group as those already described. One of these three varieties, which is a little more common than the others, has a cell body slightly larger than the average for this group and is polygonal or spindle shaped (figure 1). Between four and six dendrites arise from the cell soma, either from the points of the polygon or from the ends of the spindle; the main stem dendrites often bifurcate immediately after leaving the perikaryon and the peripheral dendrites commonly branch one or more times. The dendrites, which may be 250 μm or more long, are thicker than those associated with the cells with spiny dendrites. There are few dendritic spines and these are fairly evenly distributed along the whole length of the dendrites and are more or less uniform in shape with moderately long stalks, though some are sessile. The axon may arise from the cell body, often from that part which does not give rise to the dendrites, or from a basal dendrite (figure 3). The axon appears to travel for quite long distances without any decrease in size which suggests that it could be a long axon cell, and Cajal (1911) and Leontovich (1954) described cells of this size which sent their axons outside the nucleus. Axon collaterals usually arise from the region between 20 and 60 μm from the beginning of the axon, but they are usually short and do not form a profuse network. The main axon and the collaterals have varicosities, and though these are larger on the main axon they are more obvious on the collaterals as the fibre is finer.

Other cells in this group have cell diameters at the upper limit of the size range and are usually rounded and have four or five dendrites which can begin at any point round the soma (figure 2.) The dendrites may branch within 10 μm of leaving the cell body and further branching may occur at any point along their length. They are slender and may be over 300 μm long, the part nearest the perikaryon being regular though the peripheral parts are often slightly varicose. There are very few small spines on the dendrites and these tend to be distally placed. The axon can begin from the cell soma or a basal dendrite and may divide into equal parts a short distance from the cell. In other respects the axon is very similar to that of the cell with many spines in that it gives rise to several branching, frequently beaded collaterals. These often travel quite long distances but usually within the radius of the dendritic tree, and the swellings on them are often larger than those on the collaterals of other types of cell. These cells may be confused with the medium-sized long axon cell in cases where the dendrites are poorly impregnated or leave the section but can be differentiated from them by their slender dendrites and very few spines.

The final cell variety in this group has a rounded cell body from which five to seven dendrites arise (figure 2 and figures 10, 11 and 13, plate 55). Characteristically these dendrites are not more than 120 μm long and though the short main stem dendrites are straight their branches are very varicose (figure 11, plate 55) and twisting with many secondary branches; the ramification can be so complex that at low magnification there is an apparent halo round the cell soma. There



Camera lucida drawing of a medium-size smooth cell (*A*) and of a cell with varicose dendrites (*B*). *a*, axon. Both at same magnification.

FIGURE 3. Camera lucida drawings showing the types of axons which arise from the intrinsic neurons of the caudate nucleus. The axons are from the cells shown in figures 1*B*, 2*B* and 4*A*. *a*, axon.

are no dendritic spines. In such cells the axon is difficult to identify as the enlargements on the dendrites are joined by very narrow regions so that they cannot be clearly distinguished from axon collaterals. However, in some of the less varicose examples a short axon can be seen which gives rise to a number of densely beaded collaterals (figure 3). Some of these fibres may travel outside the extent of the dendritic field but a number of branches terminate close to the perikaryon.

The two remaining cell types together comprise just over 1 % of the total. The commoner is a very large cell (figure 4), generally fusiform, in which the mean of the length of the major

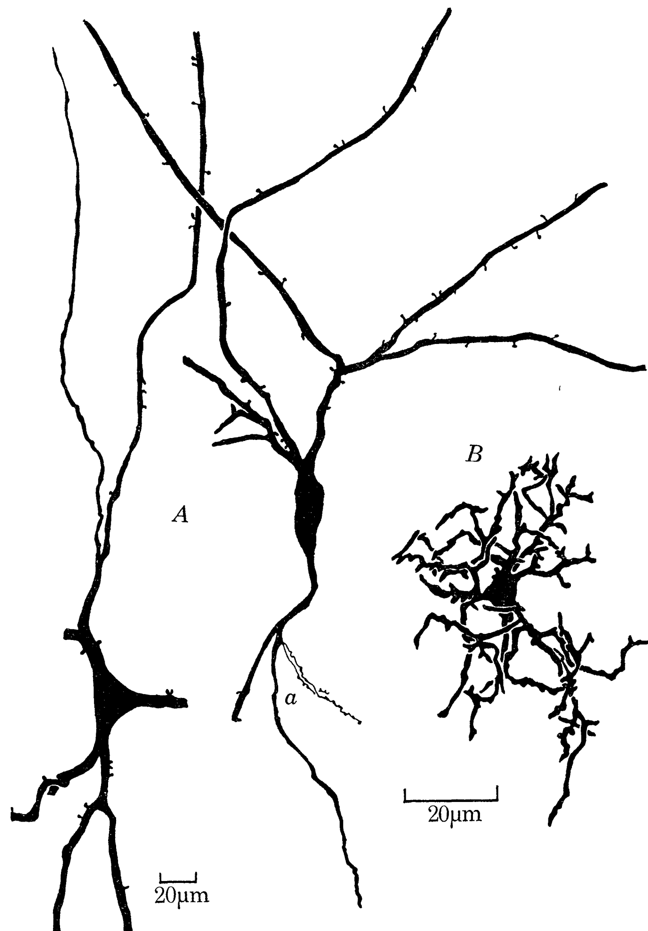


FIGURE 4. Camera lucida drawing of giant cells (*A*) and of a small cell (*B*). It should be noted that the two types of cell have been drawn at different magnifications. *a*, axon.

and minor axes is between 22 and 30 μm. Several dendrites commonly arise from the poles of the cell though they may be given off from other parts of the cell body. The dendrites, which are large and more or less straight, are often more than 1 mm long and usually give rise to several branches; there are few spines which are scattered irregularly along their length. The axon may arise from a main stem dendrite some distance from the cell soma (figure 3); there are few axon collaterals which branch infrequently and have occasional varicosities, some of which are very large. The axon often travels for a considerable distance without change in diameter, suggesting that it could be a long axon cell; it is similar to one of the long axon cells described by Cajal (1911).

The other cell type is the smallest, with a diameter between 5 and 9 μm, though the cell body is irregular (figure 4 and figure 12, plate 55). It has six to nine dendrites which are 50 to 60 μm long, uneven in diameter and with many branches forming a complex network round the cell body. The dendrites are varicose and have short twig-like branches which are larger than spines and do not have their characteristic swollen head. No axon has been seen arising from these cells.

Although the characteristic dense axonal plexus of the caudate nucleus receives a large contribution from the axons and collateral branches of the intrinsic cells, three other varieties of axons can be distinguished. One of these is fine and generally found in bundles which do not often change direction, though the individual fibres have a wavy outline and do not branch

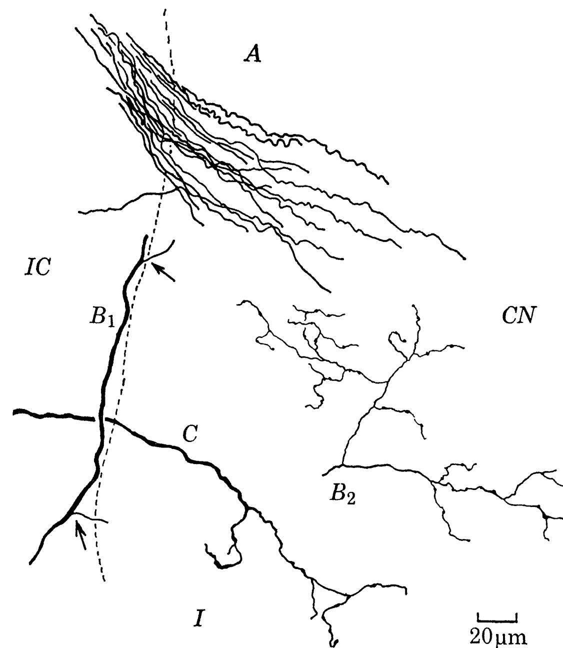


FIGURE 5. Camera lucida drawings of three possible types of afferent fibre. *A*, bundle of straight fibres passing between the internal capsule and the caudate nucleus; B_1, a fibre in the internal capsule with collateral branches (arrows) extending into the caudate nucleus; B_2, branching fibre in the caudate nucleus of similar diameter to the collaterals shown in B_1, *C*; fibre crossing the boundary between the internal capsule and the caudate nucleus and branching in the latter. *CN*, caudate nucleus; *IC*, internal capsule.

(figure 5). These bundles may be close to the internal capsule, and some have been seen in continuity crossing the boundary between it and the nucleus. The components of the bundle may diverge and occasionally isolated fibres of this type have been seen, but as continuity between these fibres and the intrinsic cells of the caudate nucleus has not been observed, they may be one variety of afferent fibre. The second axon is moderately fine and divides into two branches, each of which gives rise to fine, branching, beaded fibres, indistinguishable from the collateral axons of the intrinsic cells (figure 5). Because axons similar in diameter to the unbranched part of these fibres have been found arising, at right angles, as collateral branches from the fibres of the internal capsule and passing into the nucleus (figure 5) it is probable that they form a second group of afferent fibres. The third type of axon is thicker than that just described and also branches within the nucleus though less profusely (figure 5 and figure 7, plate 54). This type of fibre has also been seen in continuity crossing the border between the

internal capsule and the caudate nucleus and may therefore be identified as another form of afferent.

An interesting finding is that the individual fibres of the axonal plexus tend to cross the dendrites of all types of intrinsic cells passing from one dendrite to another of the same, or different, cells, and do not lie parallel to them (figure 8, plate 54). Similarly, axons rarely follow the contour of the cell body but approach a cell very closely and then change direction away from it. The enlargements on the axon collaterals often approach spines or dendrites in the same plane, suggesting the possibility of a synaptic contact. In this context the only collaterals which have been identified are those of medium spiny cells, and these have been seen approaching the dendritic spines of other similar cells very closely. It must be emphasized that this finding only suggests that a relationship could exist between the processes and is not positive evidence for the presence of a synapse.

Electron microscopy

Examination of the caudate nucleus at the higher magnification possible with the electron microscope confirms and extends the observations made with the light microscope. All parts of the nucleus have a similar structure, the cell bodies of the neurons being scattered in a dense neuropil of dendrites, myelinated and non-myelinated fibres, axon terminals, and glial cells and their processes (figure 14, plate 56). As the border with the ventricle is approached the number of nerve cells decreases while glial cells appear more frequently and the glial processes become larger. About 50 μm beneath the ventricular surface a bundle of nerve fibres, between 10 and 30 μm wide, runs in an oblique dorso-ventral direction. Most of the constituent fibres are between 0.5 and 1 μm in diameter though a few larger fibres of up to 3 μm are also present. The inner margins of this bundle contain scattered nerve terminals and dendritic processes, but these are rare on the side nearest the ventricle. The region between the myelinated fibres and the ependyma of the ventricular surface is about 20 μm across and composed almost entirely of astrocytes, containing many fibrils, oligodendrocytes and some dark cells with dark nuclei and clumped chromatin, granular cytoplasm and enlarged cisternae of granular endoplasmic reticulum; the latter cells seem to be very similar to the cells described by Mori & Leblond (1969) as microglia. The features of the ependymal layer have been described in detail by Brightman & Palay (1963), and though their description relates mainly to the 3rd and 4th ventricles and the aqueduct of Sylvius there would appear to be no difference in their observations in the rat and its appearance in the cat.

The structure of the caudate nucleus close to the internal capsule or subcallosal fasciculus is the same as in the main part of the nucleus, and at both these borders there is an abrupt change from an area containing few myelinated fibres to one in which they comprise the main feature. Bundles of fibres can be seen passing between the internal capsule and the nucleus, and in coronal sections these are most often sectioned obliquely but may also be cut transversely. The size of these fibres is very similar to those in the bundle beneath the ependyma and are, on average, smaller than those in the internal capsule. Some mingling of other units of the neuropil, such as non-myelinated nerve fibres, nerve terminals and dendritic processes occurs in the fibre bundles, and, to a lesser extent, at the edge of the internal capsule. Groups of myelinated fibres are also present in the central part of the nucleus and these travel obliquely as in coronal, sagittal or horizontal sections the fibres are usually cut obliquely or transversely. The myelinated fibres in these fascicles are similar in size to those leaving the internal capsule.

The clusters of cells seen with the light microscope are also apparent with the electron microscope, and some cells may lie very close together with no intervening processes between the cell membranes (Adinolfi & Pappas 1968; Kemp 1968*a*). Glial cells are often seen in apposition to nerve cell somata (figure 16, plate 57 and figure 20, plate 59) and there is sometimes more than one such satellite. Three different sizes of nerve cell somata are present; a few large cells between 22 and 30 μm in diameter, others of medium size (10 to 20 μm) comprising the majority of the neurons, and some small cells of between 5 and 9 μm in diameter.

The features described above also apply to the putamen and more detailed examination of this region, with the electron microscope, shows that it is similar in all respects to the caudate nucleus. The work of Adinolfi (1970) suggests that the putamen is slightly different in structure from the caudate nucleus, and at present it is difficult to find an explanation for these conflicting observations.

The largest cells of the caudate nucleus are often fusiform and have an indented nucleus (Adinolfi & Pappas 1968) with uniformly distributed granular material (figure 16, plate 57). There is a large amount of cytoplasm with many stacks of granular endoplasmic reticulum forming typical Nissl bodies and the concentration of ribosomes, both free and in rosettes, is fairly high. The mitochondria of these cells are always large and pale with few cristae, and this does not seem to be due to poor fixation as the mitochondria in the surrounding profiles have the normal dark appearance with many cristae. There are often several stacks of Golgi cisternae which commonly form quite complex systems, and though they are frequently perinuclear they may also be situated more peripherally at the origin of the dendrites. In this region the ribosomes, pale mitochondria and other constituents of the cytoplasm become more peripherally placed and well-marked neurotubules, parallel with the long axis of the dendrite, appear.

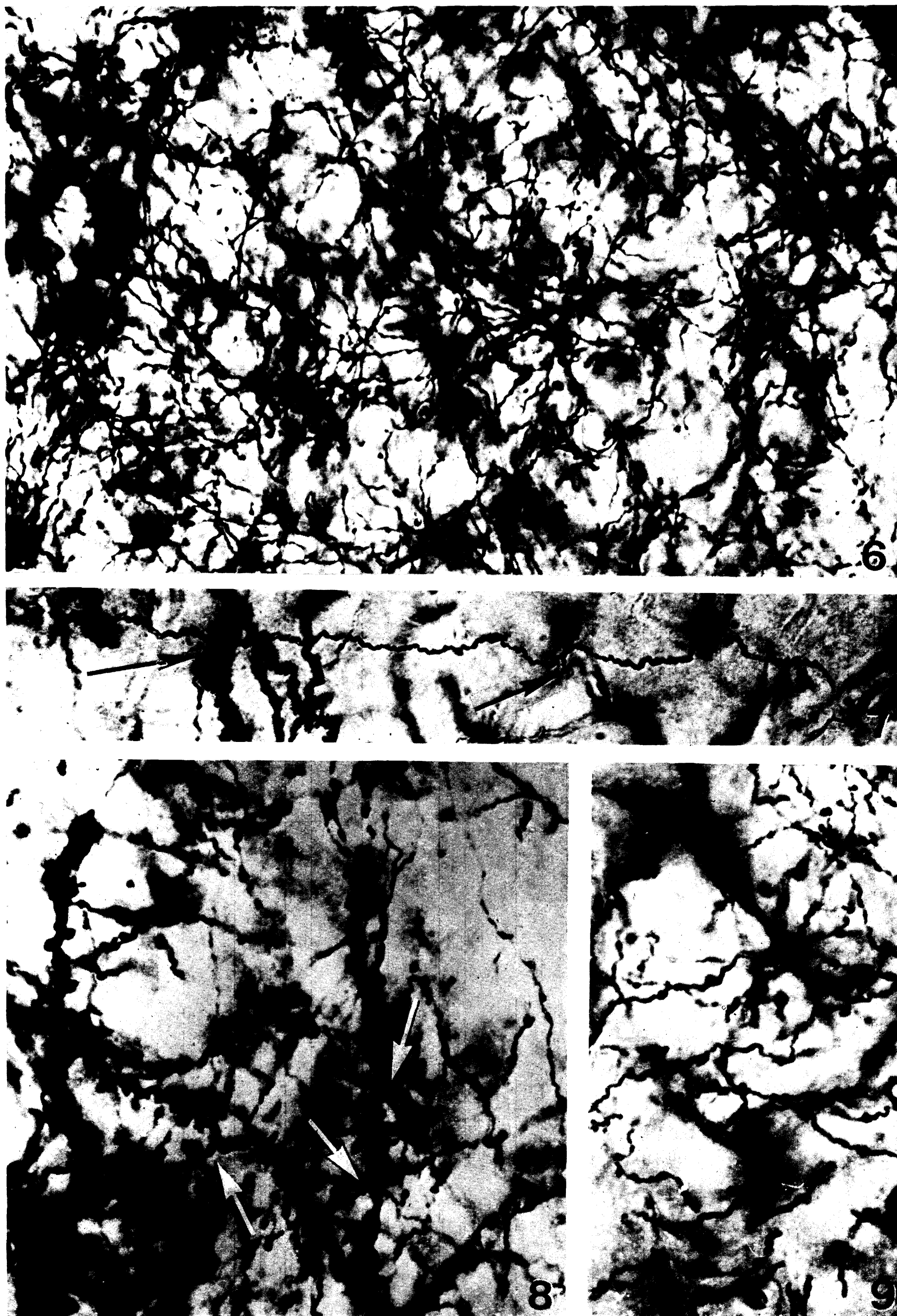
Several varieties of medium-sized cells can be differentiated on the basis of cytoplasmic constituents and the appearance of the nucleus. The most common type, in the middle of the size range, has a spherical, unindented nucleus and a moderate amount of pale cytoplasm with relatively few inclusions (figure 14, plate 56). Units of granular endoplasmic reticulum are scattered round the nucleus but do not form definite Nissl bodies. There are few cisternae of Golgi apparatus and these are usually at the bases of dendrites. The concentration of mitochondria and ribosomes falls sharply in the main stem dendrites which also contain rather poorly defined neurotubules, and though most of these run longitudinally in the dendrite a few may be oblique. Some cells, very similar to these, may be distinguished from them by their indented nuclei and slightly larger size (figure 18, plate 58). It is quite possible that the indentation in the nucleus of these cells is not always sectioned so that they could be confused with the first variety in this group; however, the number of cells with round nuclei is greater than those of similar appearance, but with indented nuclei, by more than 20 to 1 so it is likely that they form two distinct groups. The third variety of cell in this size group is very similar to the large type described first. The nucleus is indented and pronounced Nissl bodies are present, but the cells are distinctly smaller, being between 15 and 20 μm in diameter, and the mitochondria are dark with many cristae (figure 20, plate 59). The main stem dendrites are also similar to those of the large cells in that the neurotubules are distinct and invariably parallel. The final variety of medium-sized cell is slightly smaller than average and has numerous deep indentations in the nucleus (figure 22, plate 60). There are no pronounced Nissl bodies but there are frequently several groups of Golgi cisternae, often in complex elongated stacks, which tend to be

concentrated at the bases of the dendrites near the nucleus with further groups in the main stem dendrites.

The final class of cell, the smallest and least common, has a distinctive nucleus, usually with a single large indentation but occasionally with several small additional ones, and a dark rim formed by a concentration of chromatin granules (figure 21, plate 59). The narrow surrounding area of cytoplasm has few mitochondria, only scattered cisternae of granular endoplasmic reticulum and little Golgi apparatus, but it often appears dark because of the high concentration of ribosomes, both free and in rosettes. Very small somatic spines are also common and the cell body often has a very irregular appearance near the origin of the main stem dendrites. Unlike the main stem dendrites of the other cell types those of the small cell have an irregular course from their point of origin. They have very granular cytoplasm and patches where there are numbers of short neurotubules. Short branches arise from them at intervals, and they also give rise to small spines within a few micrometres of the cell body.

The cell somata in the caudate nucleus have the kind of specializations which have been described in the nerve cells in other regions of the brain. Subsurface cisternae, similar to those observed by Rosenbluth (1962) and Siegesmund (1968), are quite frequent. Alveolate vesicles (Palay 1963) are seen in association with the Golgi apparatus and multivesicular bodies are fairly common. Lysosomes are also commonly present. Somatic spines are rare, except on the small cells, and have a short stalk, cytoplasm which is more floccular than that of the cell soma and they contain small cisternae, which probably represent spine apparatus. Cilia are even more uncommon.

Several types of the peripheral branches of dendrites can be recognized but, with three possible exceptions, it has not been possible to relate them to any cell class. The most outstanding feature of the commonest variety of dendrite is the large number of spines which arise from it; the cytoplasm of the dendrite is very pale, often with a reticular appearance, and contains neurotubules which are poorly developed and often oblique to one another (figures 15 and 19, plates 56 and 58). Ribosomes are very rare, but dilated cisternae, apparently not associated with any structure within or outside the profile, are common. The large number of this type of dendrite suggests that it may arise from the commonest type of cell soma of medium size with a round nucleus and pale cytoplasm. Other medium and small-sized dendrites have well-marked neurotubules which are particularly noticeable in transverse section. Some of these dendrites have mitochondria which, on average, are smaller than those of the pale dendrites described first (figure 24, plate 60). Scattered ribosomes are often seen even in the smallest profiles, and spines are also present but are less numerous than in the first variety of dendrite. Other dendrites with conspicuous neurotubules have pale mitochondria with few cristae which suggest that they may arise from the largest variety of cell which has mitochondria of similar appearance (figure 23, plate 60). Spines are rare on this type of dendrite. Some dendrites are varicose but unlike structures of this type in other regions (see Gray, 1961; Westrum & Blackstad 1962; Fox, Hillman, Siegesmund & Dutta 1967; Price & Powell 1970*a*) they have not been seen giving rise to spines (figure 17, plate 57). They can be distinguished with certainty only in longitudinal section when it can be seen that the narrow portions of the dendrites have a high concentration of neurotubules which become dispersed in the pale varicosities. The latter cannot be distinguished in transverse section from the profiles of the first type of dendrite when it has been cut between the attachment of spines. The narrow regions are very similar in transverse section to non-myelinated fibres and can only be identified if they are



All photomicrographs in figures 6 to 13 are of material from the caudate nucleus of the cat impregnated with the Golgi–Kopsch method.

FIGURE 6. Photomicrograph of the axonal plexus of the caudate nucleus. × 570.

FIGURE 7. A long axon with two branches (arrows); probably an example of an afferent fibre. × 500.

FIGURE 8. Part of the axonal plexus showing the fibres (white arrow) crossing the dendrites of a medium spiny cell. × 1000.

FIGURE 9. The axonal plexus at a higher magnification showing the beading of the axons. × 800.

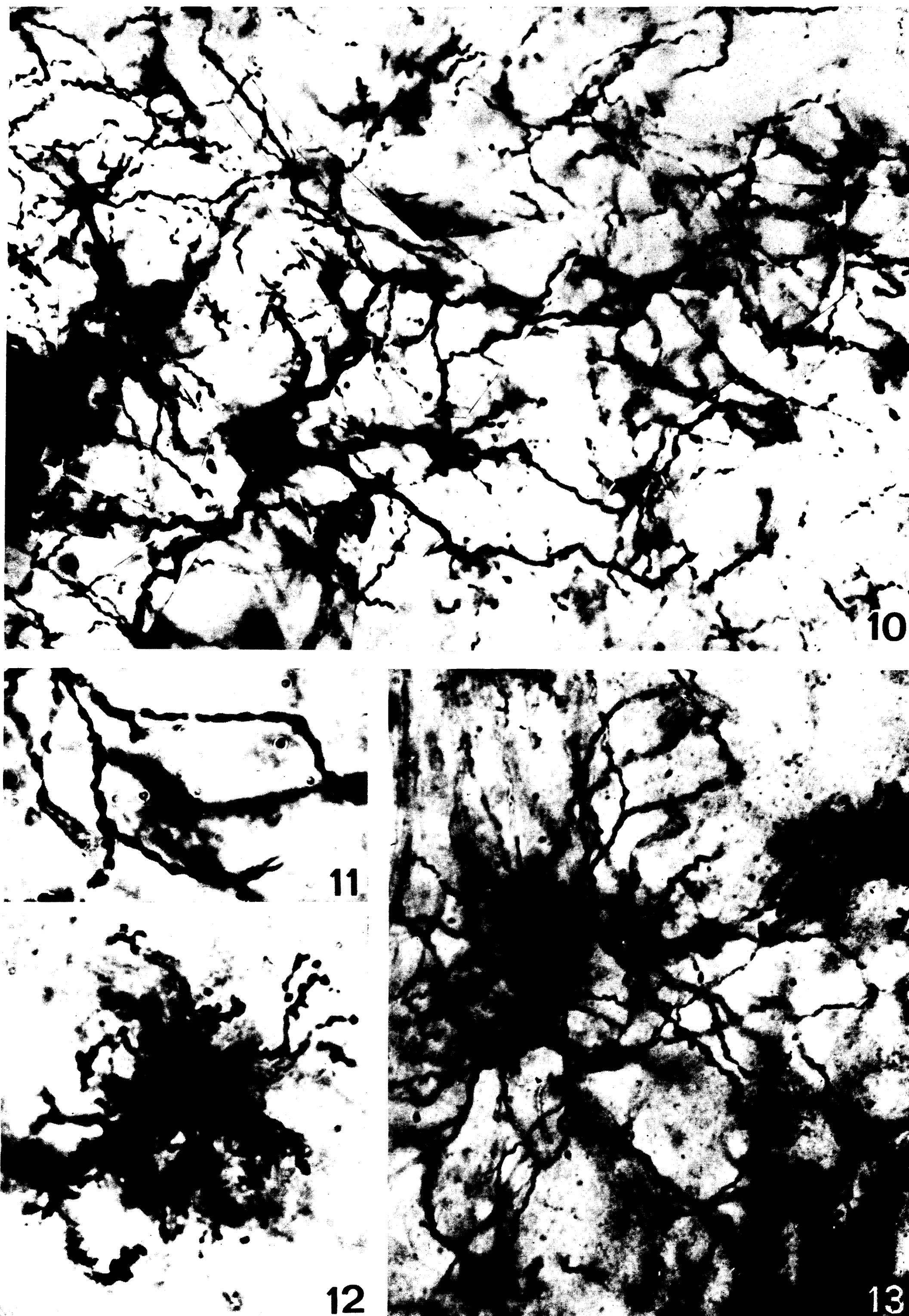


FIGURE 10. Composite photomicrograph, taken at four focal planes, of a cell with varicose dendrites showing its relationship to the fine fibres of the axonal plexus. × 870.

FIGURE 11. The dendritic varicosities of a neuron of the type shown above. × 1250.

FIGURE 12. A small cell. × 630.

FIGURE 13. Photomicrograph to show the complexity of the dendritic tree of a cell with varicose dendrites. × 1000.

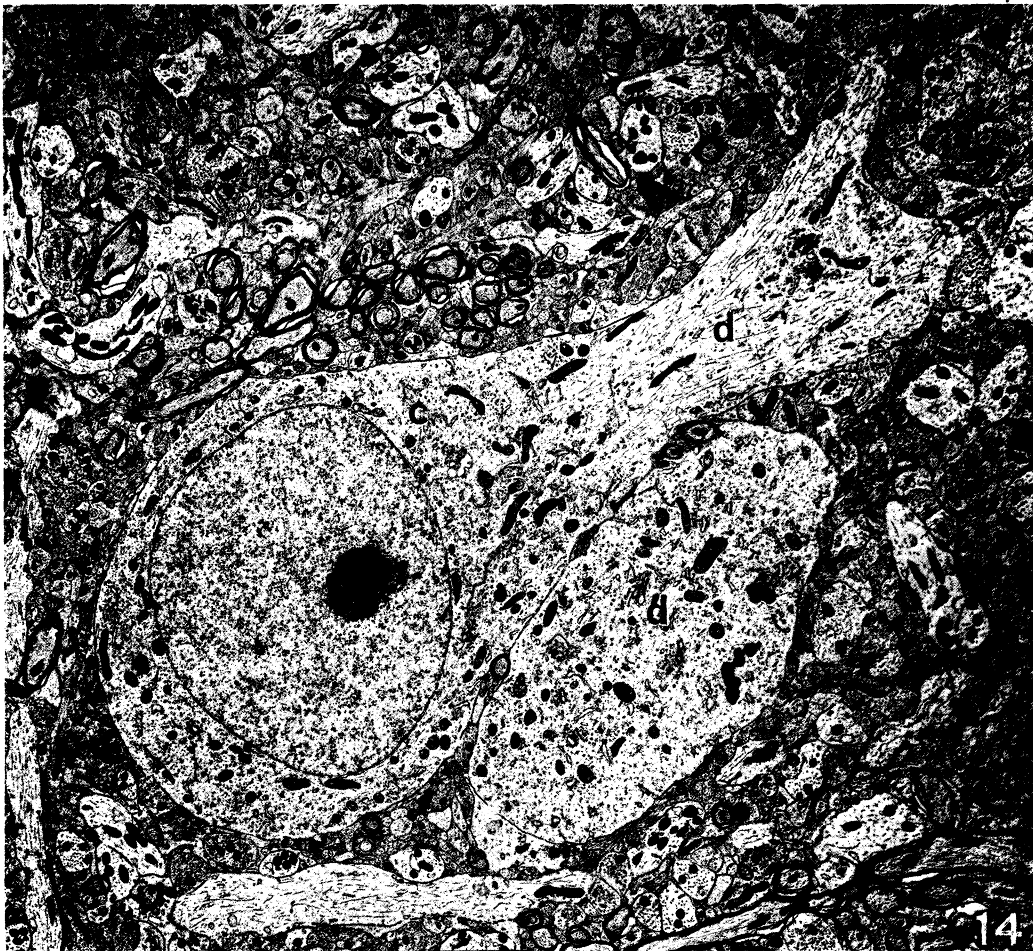


FIGURE 14. Electron micrograph of a medium spiny cell (c) with a branching main stem dendrite (d). The closely apposed profile is probably the basal dendrite of another similar cell. The appearance of the surrounding tissue is typical of the neuropil of the caudate nucleus. × 5000.

FIGURE 15. Peripheral dendrite (d) of a medium spiny cell. Note the obliqueness of some of the neurotubules. × 23000. s, spine.

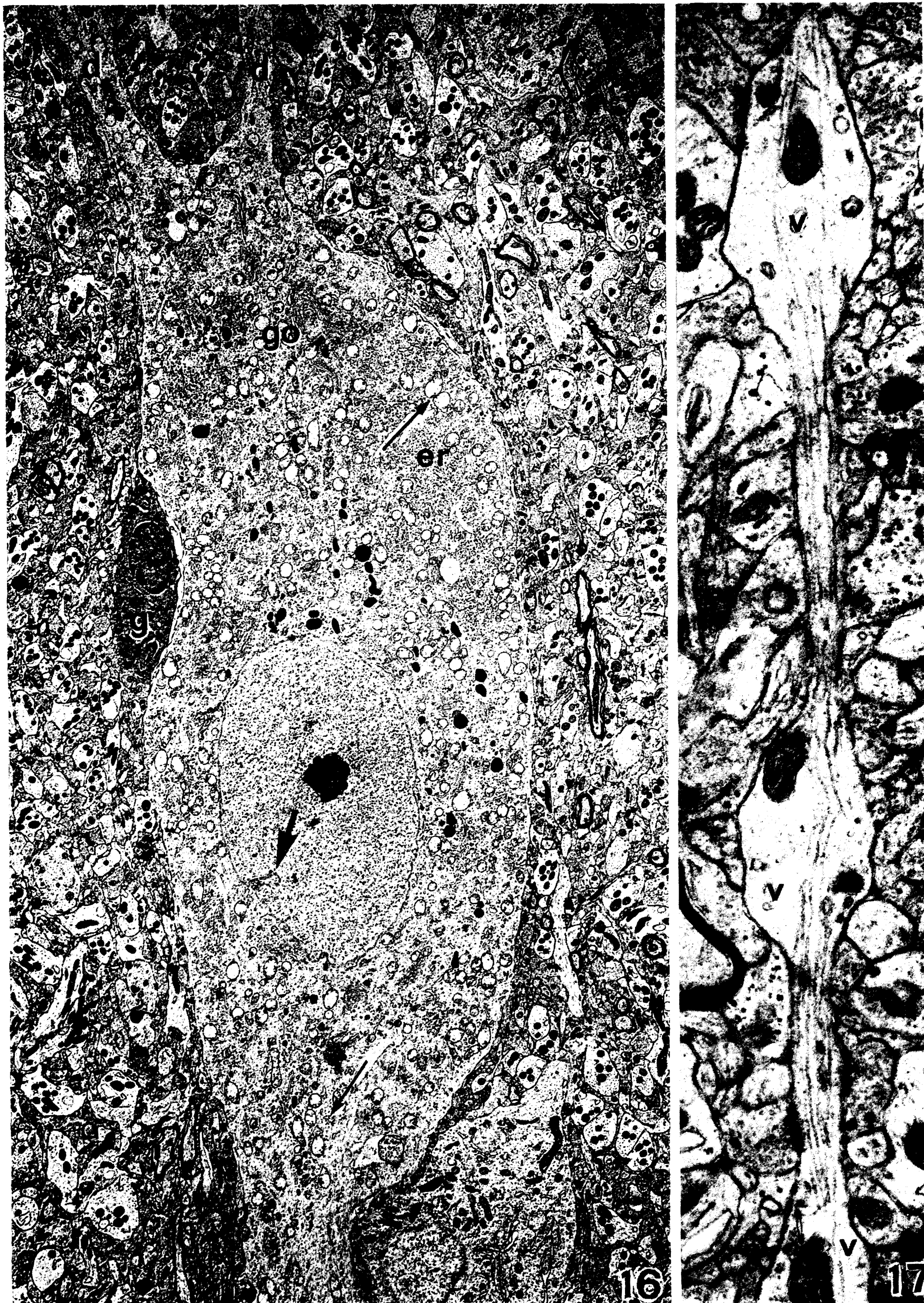
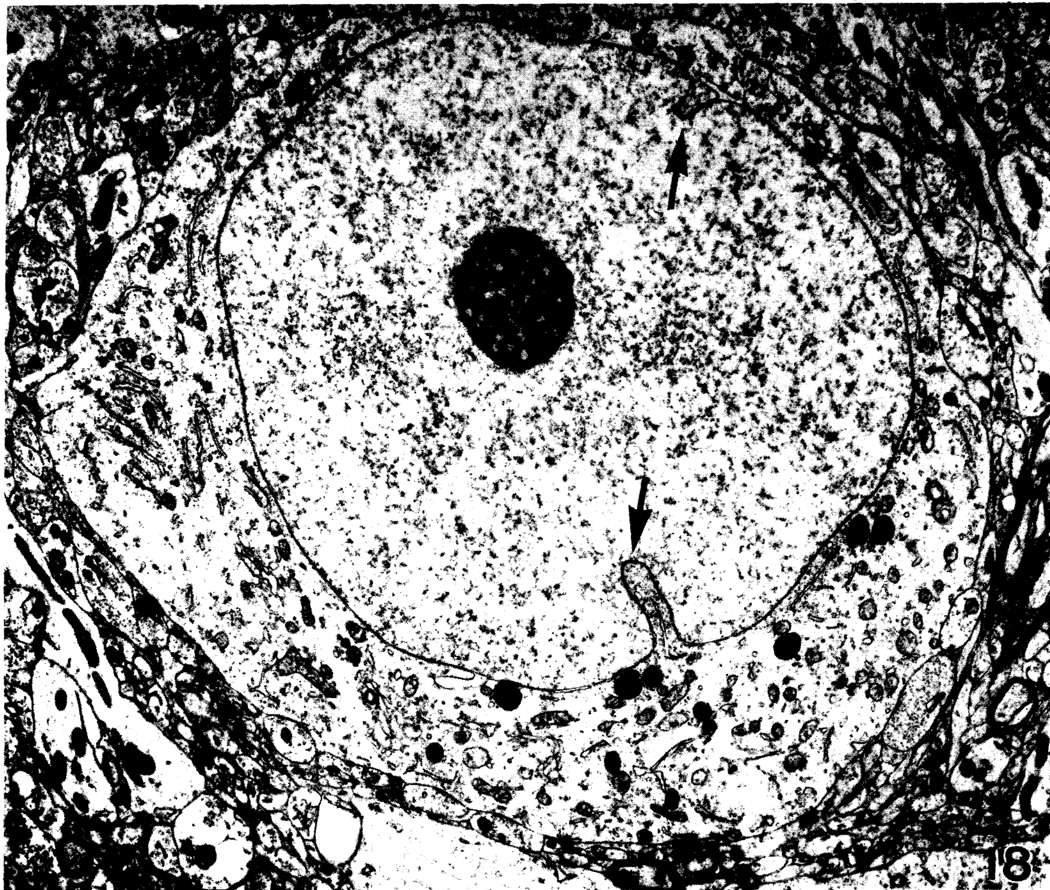


FIGURE 16. Electron micrograph of a giant cell showing the indented nucleus (large arrow), pale mitochondria (small arrows) and pronounced granular endoplasmic reticulum (er). The numerous lysosomes are commonly seen in cells of the caudate nucleus. The small satellite cell (g) may be microglia. × 4500, d. dendrite; go, Golgi apparatus.

FIGURE 17. Varicose dendrite with three varicosities (v). × 13000.



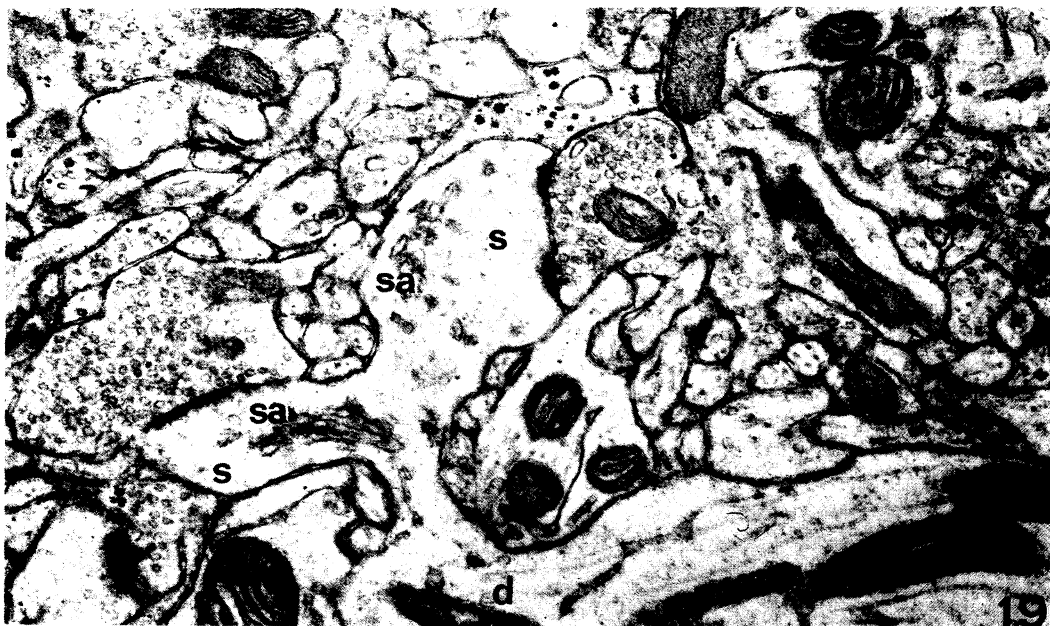
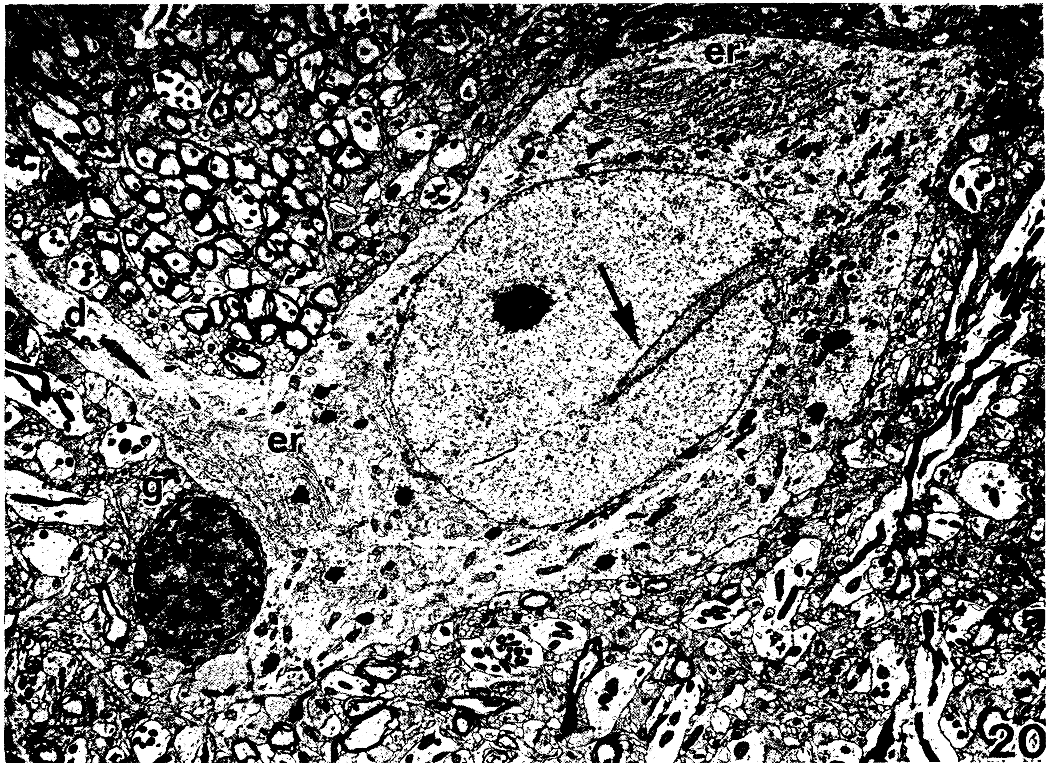


FIGURE 18. Medium-sized cell, similar to the medium spiny cell but with an indented nucleus (arrows). × 7000.

FIGURE 19. Branched spine (s) from the dendrite (d) of a medium spiny cell. Note the separate groups of spine apparatus (sa.). × 30000.



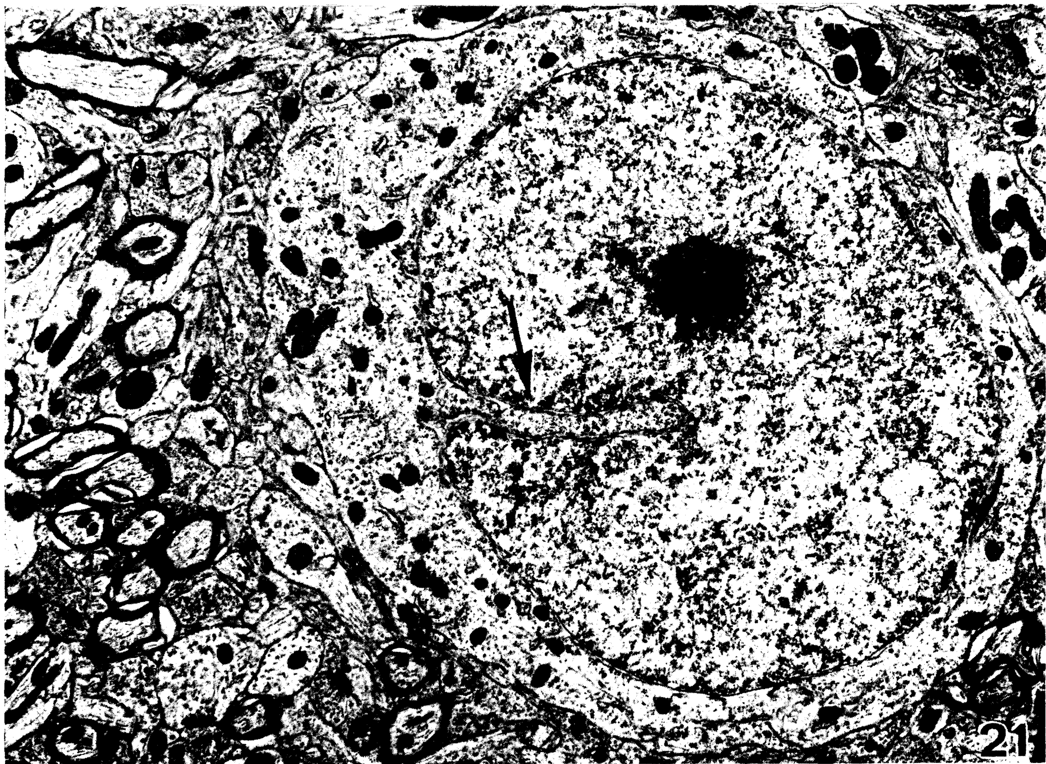
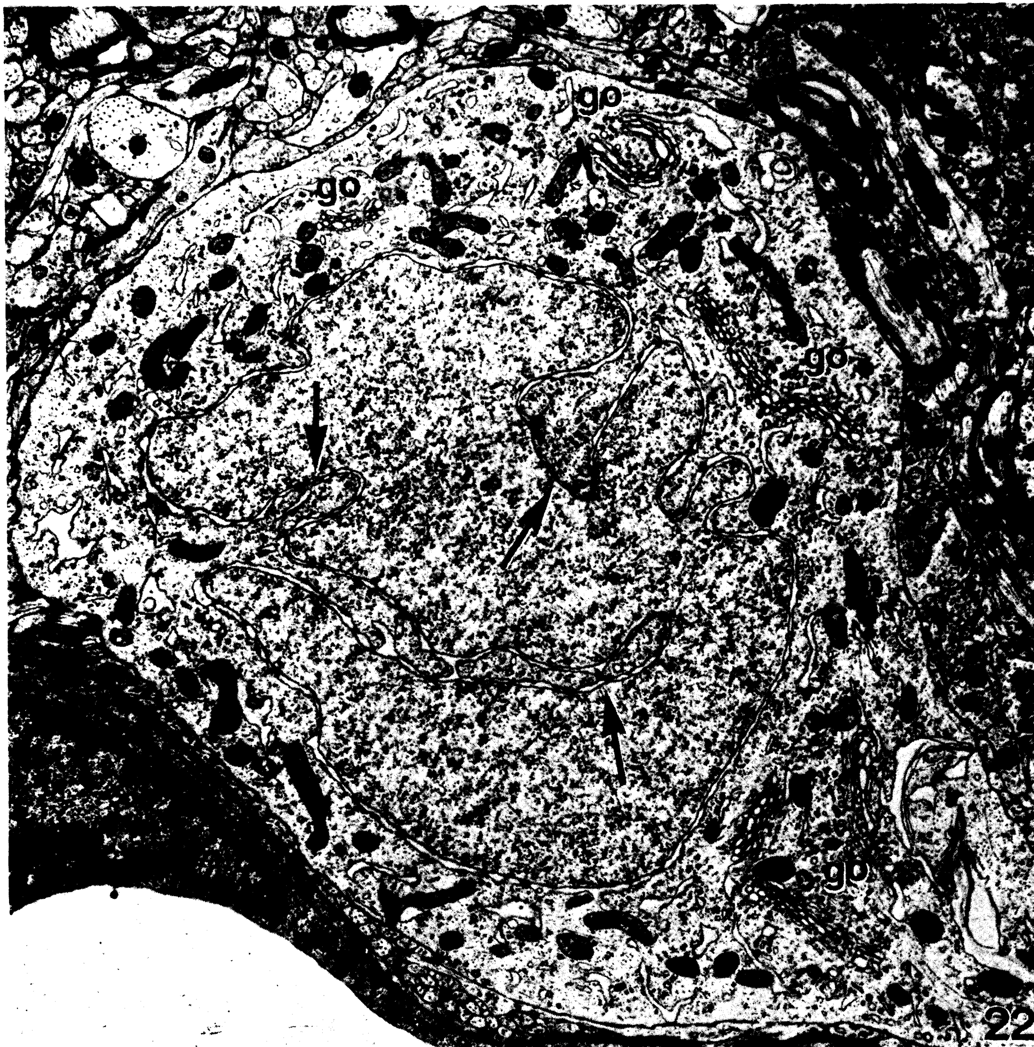


FIGURE 20. Medium-sized cell with deeply indented nucleus (arrow) and stacks of granular endoplasmic reticulum (er). Note the satellite glial cell (g) and the group of myelinated nerve fibres. × 5000.

FIGURE 21. Small cell with indented nucleus (arrow), a dark rim around the periphery of the nucleus and many ribosomes in the cytoplasm. × 9000.



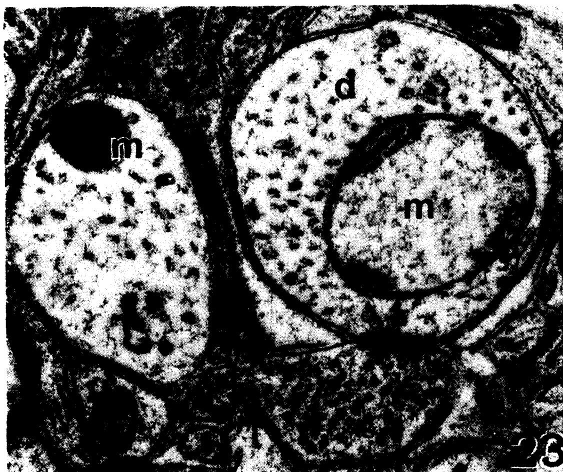
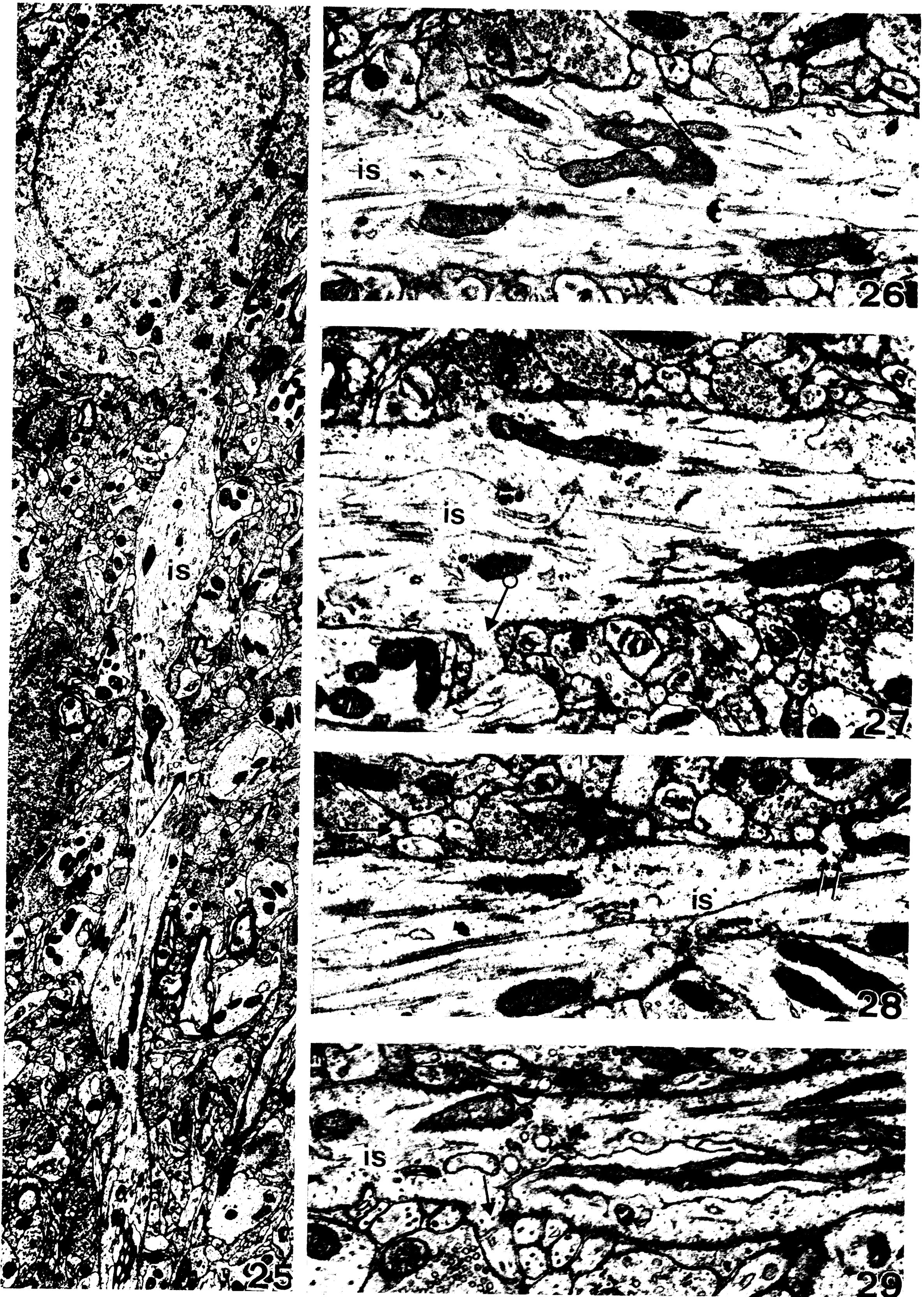


FIGURE 22. Medium cell with many deep nuclear indentations (arrows). Note the four stacks of complex Golgi apparatus (go). × 7000.

FIGURE 23. Peripheral dendrite (d) with conspicuous neurotubules and a large pale mitochondrion (m). × 23000.

FIGURE 24. Small dendrite (d) with prominent neurotubules, a small dark mitochondrion and a spine (s). × 23000.



Figures 25–29. For legend see facing page

postsynaptic. The majority of varicose dendrites are medium or small but large, varicose main stem dendrites have been seen in continuity with the medium cells with deeply indented nuclei and complex Golgi apparatus.

The spines arising from the two common types of spiny peripheral dendrite show no apparent differences. Most consist of a dilated head on a narrow stalk of varying length though some are sessile, some have branched stalks with two heads and others have branched heads (figure19, plate 58). One of the most distinguishing features of spines is the floccular cytoplasm which makes them appear considerably greyer than the dendrites. This feature is so striking that spine tips isolated from the dendrite and lacking spine apparatus can be identified with almost complete certainty. The spine apparatus, the other characteristic feature, is composed of elongated cisternae with interposed dense material as described by Gray (1959) (figures 19 and 24, plates 58 and 60). Usually the cisternae are irregularly arranged and, in larger spines, the system often has many small sacs and appears to be quite complex. A spine apparatus is most often seen in the enlarged head of the spine but may extend into the stalk where this is large and wide. There is usually only one spine apparatus in a spine and where two separate groups of cisternae are present they may represent branches of the same stack, but in bifid spines, where the heads are clearly separated, there may be two distinct units of spine apparatus (figure 19, plate 58). The stalks of the spines vary in length and there seems to be no relationship between the size of the spine, the length of the stalk and the size of the parent dendrite. An expanded cisterna is often seen in the dendrite at the origin of the stalk of the spine and may pass into it for a short distance, but this cannot be confused with a spine apparatus as there is no associated dense material; a spine apparatus may occupy a similar position in spines which are branched, have wide short stalks or are sessile. Spines may contain ribosomes, multivesicular bodies and neurofilaments which pass up the stalk from the dendrite. Mitochondria have not been seen in the spine heads or stalks of these types of spines and in sessile spines, where the only demarcation between the spine and the dendrite is the floccular cytoplasm, they lie in the clear dendritic region. Spines associated with the main stem dendrites of small cells have a less well-developed spine apparatus than that already described, consisting of a few dilated cisternae. Ribosomes are very common and these spines occasionally contain a mitochondrion.

Axon hillocks and the initial segments of axons can be recognized by the groupings of neurotubules and the layer of dense material beneath the membrane (Palay, Sotelo, Peters & Orkand

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Description of plate 61

Figures 25 to 28 are micrographs of serial sections of the same axon initial segment.

Figure 25. Initial segment (is) in continuity with cell soma and showing small protuberance or spine (arrow). ×8500.

Figure 26. Portion of same initial segment as in figure 25, four serial sections away and still showing same protuberance (arrow) as in that figure. ×26000.

Figure 27. Same initial segment a further two serial sections away. The first protuberance has been traced to a small profile (arrow) separate from the axon, and a second protuberance has appeared on the opposite side (ringed arrow). ×26000.

Figure 28. Same initial segment a further two serial sections away. A third protuberance (double arrows) has now appeared and there is a synapse on to this. The profile continuous with the first protuberance is still present (arrow) and on an adjoining part of this section (not shown) the second protuberance can be seen to be separating from the axon. ×26000.

Figure 29. Initial segment from another neuron showing a protuberance (arrow). ×36000.

Note the alveolate vesicles in continuity with the plasma membrane in figures 28 and 29.

1968). Axons can arise from cell bodies or basal dendrites and, in the latter situation, part of the profile has the grouping of neurotubules seen in the axon initial segment while the remaining portion is typical of a dendrite. Though several descriptions of axon hillocks and initial segments have been published (e.g. Palay *et al.* 1968; Peters, Proskauer & Kaiserman-Abramov 1968; Jones & Powell 1969*a*; Westrum 1970) some features seen in the initial segments of axons in the caudate nucleus can be emphasized. Cisternal organs (Peters *et al.* 1968), which are very similar to spine apparatus, are prominent and very frequently associated with synapses (see following paper, Kemp & Powell 1971). It seems highly likely that the cisternal organ is invariably present in axon initial segments, for while individual profiles of initial segments may not contain the structure, those which have been studied in detail in serial sections have always contained one or more cisternal organs. These cisternae may lie in a bulge on the side of the initial segment forming a unit very similar to a sessile spine, and there is often an increase in the floccularity of the cytoplasm in this region (see following paper Kemp & Powell 1971). Small, but definite, protuberances or appendages of up to 0.3 μm diameter are also present on the initial segment. It is difficult to give an accurate estimate of the length of these processes as they can only be traced with certainty, because of their small size, over a few serial sections after they have lost continuity with the axon. Serial sections (figures 26, 27 and 28, plate 61) show that at least three such processes may come off the same initial segment within a few sections of each other. They have been found to arise from the initial segment within 20 μm of its origin. At first, at least, they lack neurotubules but the dense undercoating of the membrane of the initial segment usually extends into them for some distance. Axon terminals synapse on to these appendages and, like those on the initial segment itself, the membrane thickenings are of the symmetrical type (figure 28, plate 61). In some cases it has been possible to trace the processes to small, vesicle-containing profiles, but no synapse polarized away from them has been seen. We have not observed such appendages or spines on the axons impregnated in the Golgi material as Westrum did (1970), but this failure to find them with light microscopy is probably because of the small diameter of the axons (and appendages) in the caudate nucleus.

Discussion

This study has shown that the caudate nucleus is more complex than might have been anticipated in view of its apparently homogeneous structure. The nucleus is indeed homogeneous in that samples from one part do not differ essentially from those from another part. Two striking features which are apparent with both the light and electron microscopes are the dense axonal plexus and the great predominance of one cell type. It is possible to correlate these and other observations from the light microscopical examination of Nissl-stained and Golgi-impregnated material with the findings made at the higher magnifications of the electron microscope. The discussion will attempt this synthesis.

The cells can be classified into three groups according to size. Light microscopy shows that these are scattered in an irregular and apparently random manner throughout the nucleus. It is clear from either light or electron microscopy that the small and the large cells comprise a very small proportion of the total number of cells, the majority being medium sized of between 10 and 18 μm diameter. In Golgi impregnated material and with the electron microscope the latter group can be divided into four subtypes and, in most instances, correlation of these is possible. The commonest type of cell, representing over 95 % of the total in Golgi

impregnated material, has dendrites which are densely covered with spines. These, on the basis of number alone, can be correlated with the pale cell with the round nucleus seen with the electron microscope, and it seems likely that the pale dendrites with few neurotubules and many spines arise from this cell. Cells with varicose dendrites are apparent at the light microscope level and can be directly related to a cell seen with the electron microscope which has a very indented nucleus, complex Golgi apparatus and varicose main stem dendrites. Correlation of the other two cell types can only be tentative, but it seems probable that the cell which in

TABLE 1. CORRELATION OF THE CELL TYPES IN THE CAUDATE NUCLEUS SEEN IN GOLGI IMPREGNATED MATERIAL AND WITH THE ELECTRON MICROSCOPE

cell type	%	Golgi	electron microscope
medium spiny	96	12–18 μm diameter, 5–6 medium length dendrites, many spines, short axon, many collaterals	10–20 μm diameter, nucleus not indented, little granular endoplasmic reticulum
medium long axon	3	16–18 μm diameter, 4–6 medium length dendrites, few spines, long axon, few collaterals	10–20 μm diameter, indented nucleus, some stacks granular endoplasmic reticulum
medium smooth		16–18 μm diameter, 4–5 long dendrites, very few spines, short axon, many collaterals	10–20 μm diameter, indented nucleus, little granular endoplasmic reticulum
varicose dendrite		12–14 μm diameter, many short dendrites, varicose, no spines, short axon, many collaterals	10–20 μm diameter, very indented nucleus, much complex Golgi apparatus
giant	< 1	22–30 μm diameter, few long dendrites, few spines, long axon, few collaterals	22–30 μm diameter, indented nucleus, granular endoplasmic reticulum in stacks, pale open mitochondria
small	<1	5–9 μm diameter, many very short dendrites, few spines, axon?	5–9 μm diameter, indented nucleus with dark rim, many ribosomes

Golgi material is rather larger, has straight dendrites with a moderate number of spines and a long axon is the same as the cell which with the electron microscope appears at the upper end of the size range for this group, has fairly pronounced Nissl bodies and main stem dendrites with a conspicuous neurotubular system. These correlations are summarized in table 1.

The small cells with short dendrites seen in the Golgi impregnated material have not been described by Cajal (1911) or Leontovich (1954). This may be due to the fact that they do not often impregnate well and may, in some instances, be confused with glial cells. However, well-stained examples show short, relatively stout dendrite-like processes, and cells of this size group can be found in sections stained by the Nissl method and with the electron microscope. In the first case they can be distinguished from glia by their nuclear properties, and in the second by the presence of axosomatic synapses. Striking correlation is also seen between the shape of the cell body and dendrites in Golgi impregnated material, and the shape of the cell body and main stem dendrites seen with the electron microscope. Axons have not been seen arising from these cells in Golgi impregnated material and initial segments have not been identified with the electron microscope. This does not necessarily mean that the cell is without an axon, for the number examined with either technique has been small.

One of the main criteria used for differentiating the different types of cell in the caudate

nucleus has been the presence of an indentation in the nucleus. Such indentations have been noticed in neurons from a number of areas (for example: Dowling & Boycott 1966; Peters & Palay 1966), but it is not possible to make any suggestions about their functional significance.

Cajal (1911) stated that the very large cells and some larger varieties of the medium cells give rise to the efferent fibres from the nucleus. This material has not yielded any definite information on this point, but the only two cells which seem likely candidates are the giant cells and the large type of medium cell, as these are the only cell varieties in Golgi impregnated material with axons of large diameter passing any distance beyond the dendritic field of the parent cell. On the other hand, there was no evidence to support the statement of Leontovich (1954) that the majority of small cells have long axons which pass outside the confines of the nucleus. Quite close correlation of the cell types described by Cajal (1911), Leontovich (1954)

Table 2. Correlation of cell types in the caudate nucleus in Golgi impregnated material with the findings of other authors

present study, cat	Cajal (1911) rabbit and human	Leontovich (1954) dog and human
large cell, long axon	giant cell (Fig. 325C), long axon	large (Figs. 3, 4; b_1, b_2)
medium spiny, short axon	large or medium, spiny, short axon (Fig. 325A)	medium spiny, long axon (Figs. 3, 4; A_1, A_2)
medium, long axon	medium, long axon (Fig. 325B, G)	
medium, varicose dendrite, short axon	dwarf, short axon (Fig. 325D, E)	short axon (Figs. 3, 4; B_1, B_2)
medium smooth long dendrites, short axon	medium (Fig. 325F)?	
small		

and those found in the present material is possible, if slight differences in species and interpretation, and possible variations in impregnation, particularly of the peripheral parts of dendrites, are taken into account (table 2).

The morphology of the spines in the caudate nucleus seen with the electron microscope is as varied as in the cerebral cortex (Jones & Powell 1969*b*; Peters & Kaiserman-Abramof 1970) and this variation is also apparent with the light microscope. Careful examination with either method has failed to reveal any relationship between the size of the spine head or the length of the stalk to the position on the dendrite in any type of cell having dendritic spines. In this respect the caudate nucleus differs from the cerebral cortex where the smaller, more peripheral, dendrites tend to have spines with larger heads and longer stalks. A further difference is apparent when considering the type of cell having the most numerous spines. Globus & Scheibel (1967) suggested that a large number of spines is characteristic of long axon cells and that interneurons have few or none of these dendritic appendages. The evidence presented here suggests that in the caudate nucleus the converse is true, the short axon, interneuronal cells having the most spines. Another exception to the generalization of Globus & Scheibel is found in the olfactory bulb where the granule cell, an undoubted interneuron, has quite a large number of spines while the mitral cell, which is the source of the long efferent axon has none (Price & Powell 1970*a*, *b*). It is possible that the correlation between the high density of dendritic spines and a long axon is true only in cortical structures since two of the cells for which it appears to be so are the pyramidal cell of the cerebral cortex and the Purkinje cell of the cerebellum.

A striking feature of the caudate nucleus in Golgi impregnated material and with the electron microscope is the dense network of fine axons. The identification of the source of these fibres in normal material is not possible, but it is clear that they may be either afferent or intrinsic fibres. Large numbers of non-myelinated fibres are sometimes present amongst myelinated fibres, and quite frequently non-myelinated fibres have been seen to arise as branches from myelinated fibres. In the latter case they may be collaterals of axons of intrinsic cells which have become myelinated. Since these are likely to be axons of long axon cells which form only a small proportion of the total, more of the non-myelinated fibres must arise from other sources. The Golgi impregnated material shows that a significant number of the fine fibres of the axonal plexus are the collateral axons of the intrinsic cells, and that most of the cells of origin of these fibres lie in the medium-sized cell group. Because of the similarity of the appearance of the collaterals it is not possible to identify their cell of origin unless there is continuity between the two. The problem still remains of identifying the afferent fibres, and with one exception the Golgi impregnated material does not yield unequivocal evidence on this point. The one type of identified afferent fibre is very similar to that described by Cajal (1911) as an ascending afferent, both in diameter and form of branching, and if this correlation is correct, this fibre could come from the thalamus or mid-brain. Collateral branches of fibres in the internal capsule, clearly arising at right angles from the parent axon, have been seen entering the nucleus and axons of similar diameter, but not in continuity with them, branch within the nucleus forming a network of fine fibres indistinguishable from the other components of the axonal plexus. Cajal (1911) and Webster (1961) identified such collaterals as branches of descending cortical fibres, but this type of Golgi impregnated material, with the axons so far from their origin, cannot show whether the parent axon in the internal capsule is ascending or descending. The other possible afferent fibre crosses between the internal capsule and the nucleus in a bundle which then disperses in the neuropil. Similar fibres in bundles in the mouse brain were considered by Cajal (1911) to be branches of fibres of passage, but in a species like the cat, with a definite internal capsule, this interpretation seems unlikely.

The small protuberances arising from the initial segments of the neurons of the caudate nucleus are similar to those coming off the initial segments of neurons of the neocortex, and which were called branches (Jones & Powell 1969*a*), and to those identified as axonic spines in neurons of the pyriform cortex by Westrum (1970). The features of these appendages have been described in detail by Westrum (1970), and the present observations are in close agreement except that most of the appendages we have found in the caudate nucleus appear to be smaller than those in the pyriform cortex. Some initial segments have at least three such processes, as was also found by Westrum (1970), and it is possible that further study with serial sections may show that a larger number may arise from a single axon and also that more initial segments have such appendages. Perhaps the important point to determine is whether all these processes arising from initial segments are axonic spines as proposed by Westrum (1970) or whether some of them are collateral branches ending in axon terminals. The presence of vesicles in some of them is by no means conclusive, and so far none of them have been found to make a synapse on to another profile; the appearance of the vesicle-filled process arising from an initial segment of a thalamic neuron (Jones & Powell 1969*c*), however, is suggestive of an axon terminal.

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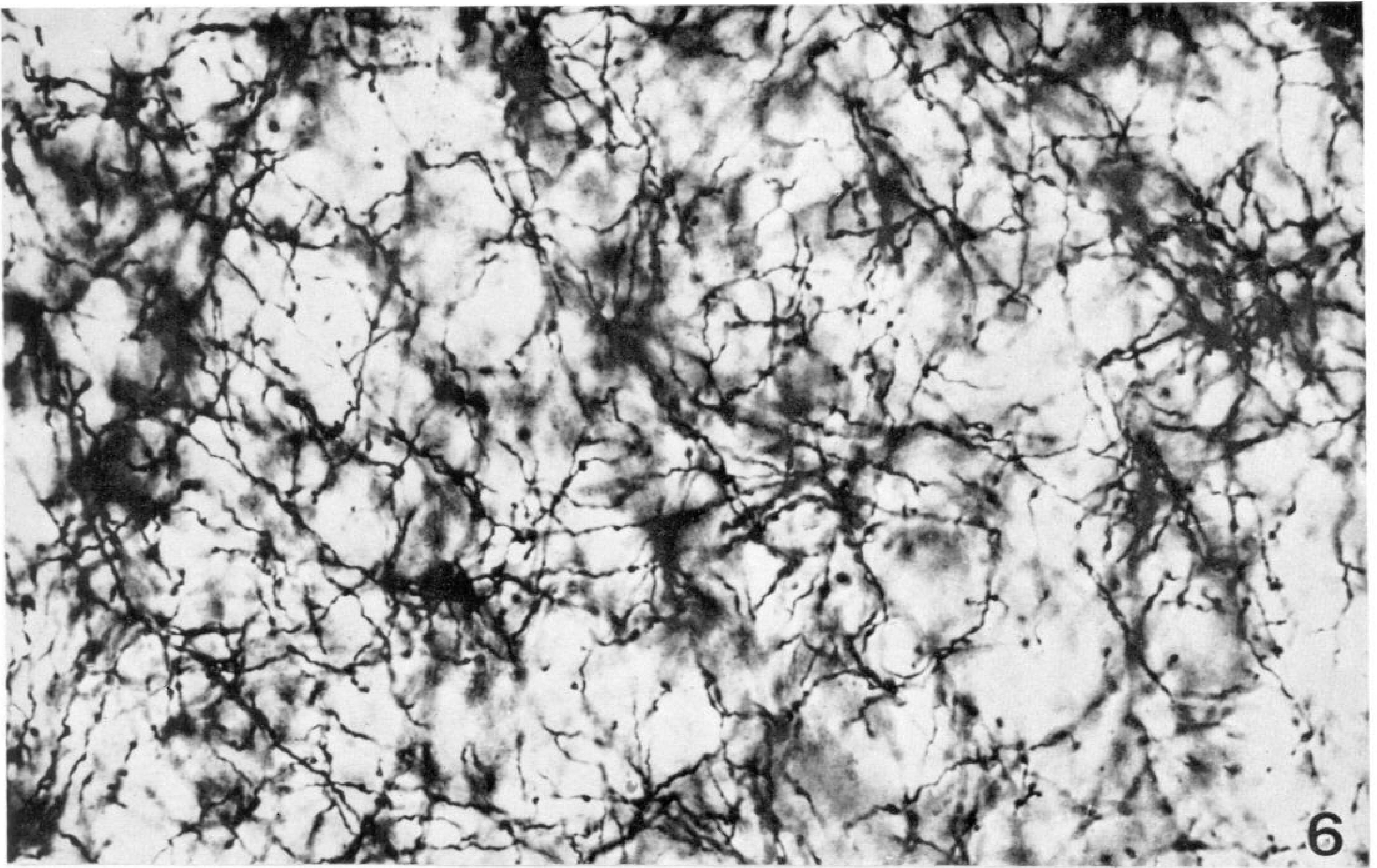
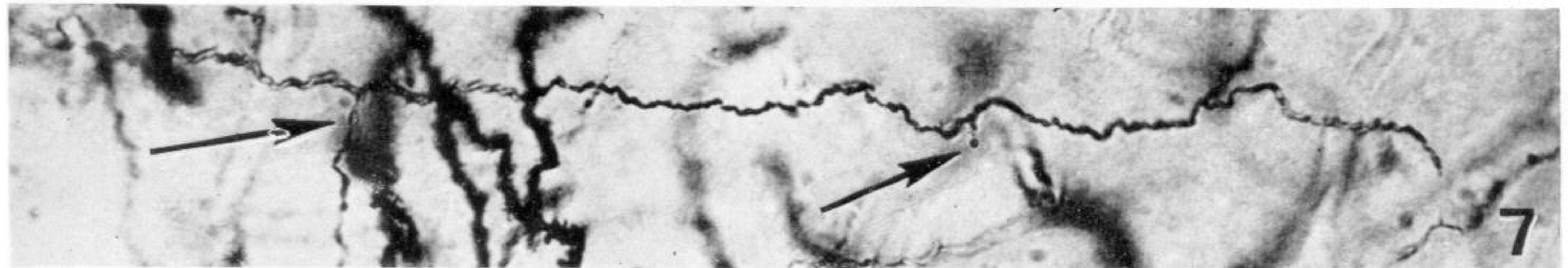
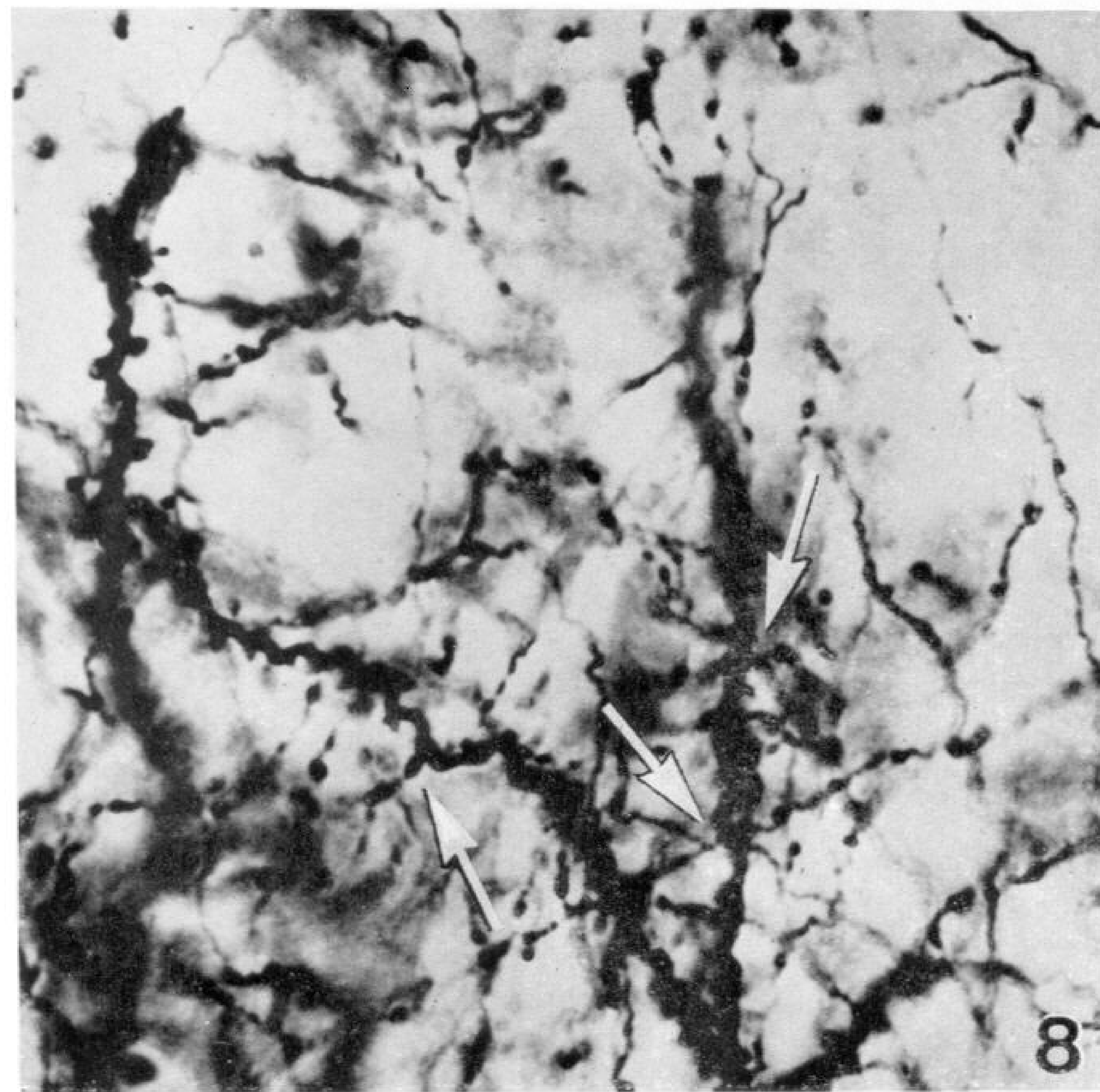






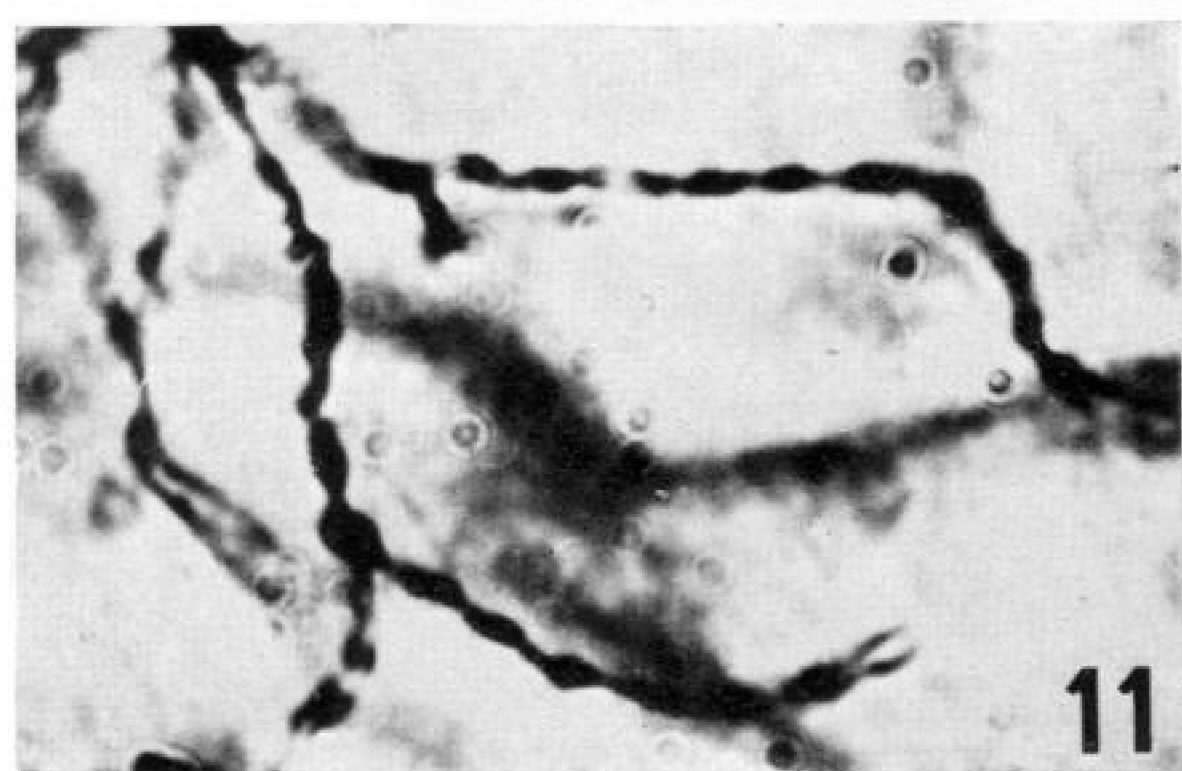
All photomicrographs in figures 6 to 13 are of material from the caudate nucleus of the cat impregnated with the Golgi–Kopsch method.

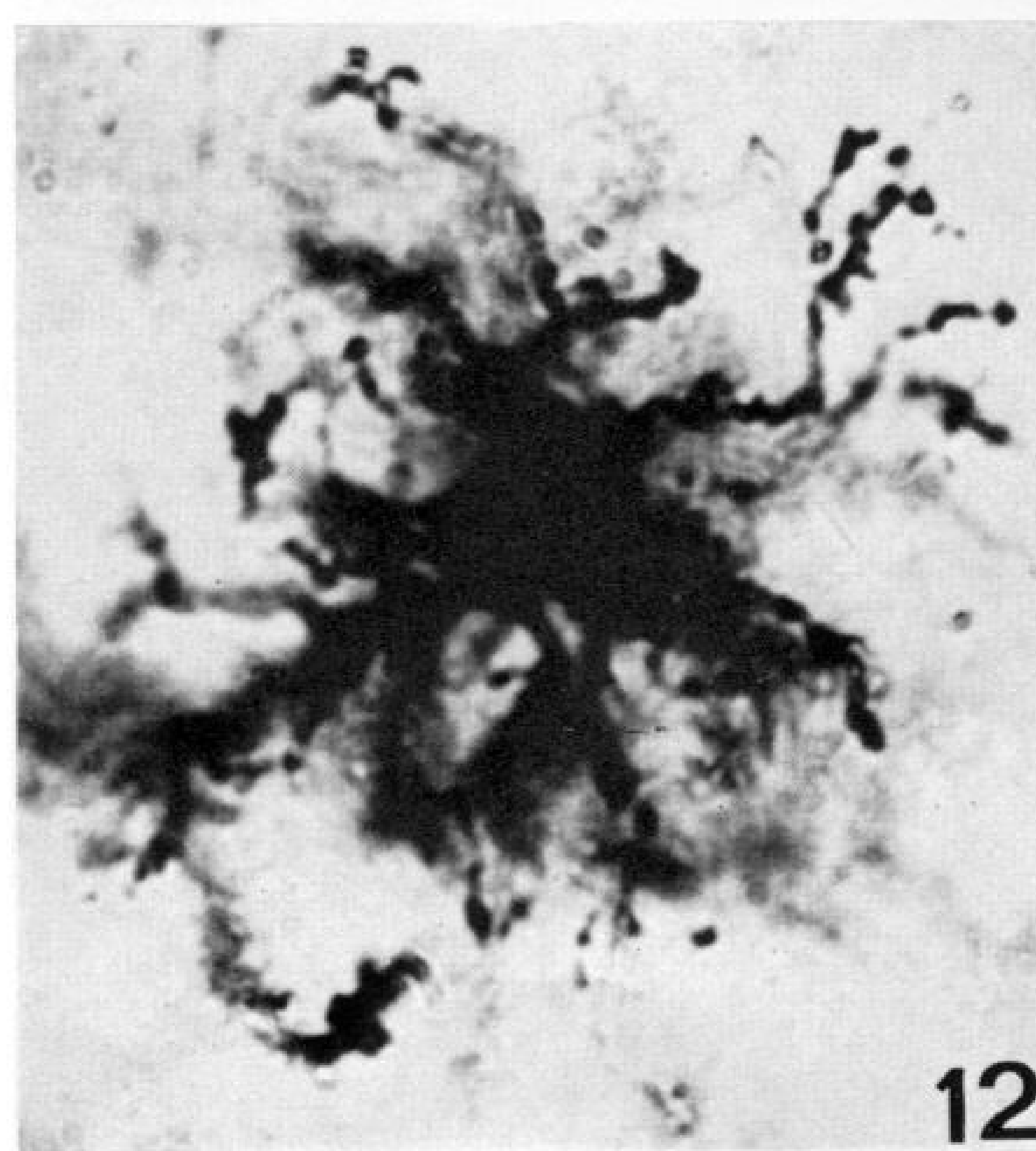
FIGURE 6. Photomicrograph of the axonal plexus of the caudate nucleus. ×570.

FIGURE 7. A long axon with two branches (arrows); probably an example of an afferent fibre. ×500.

FIGURE 8. Part of the axonal plexus showing the fibres (white arrow) crossing the dendrites of a medium spiny cell. ×1000.

FIGURE 9. The axonal plexus at a higher magnification showing the beading of the axons. ×800.





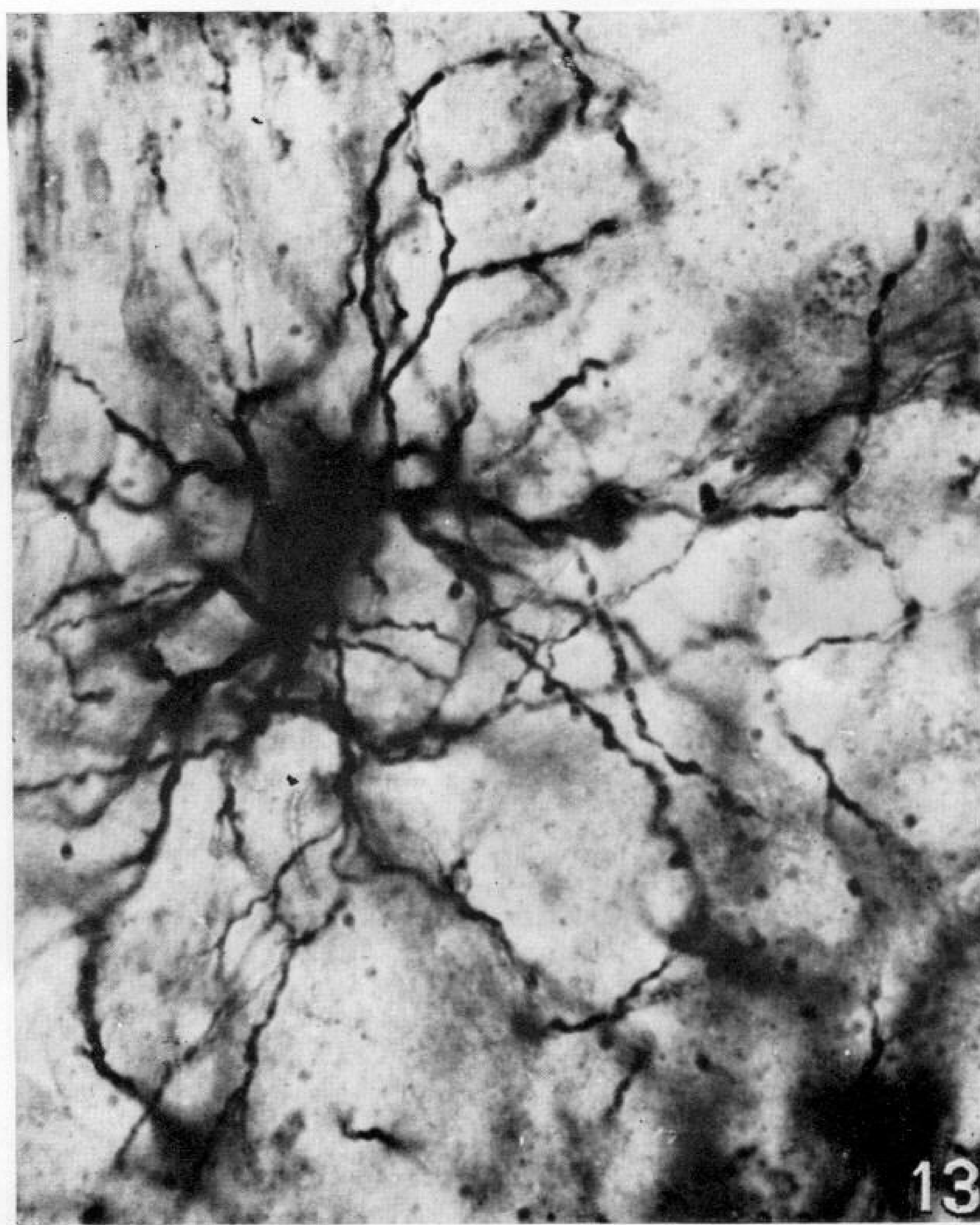


FIGURE 10. Composite photomicrograph, taken at four focal planes, of a cell with varicose dendrites showing its relationship to the fine fibres of the axonal plexus. × 870.

FIGURE 11. The dendritic varicosities of a neuron of the type shown above. × 1250.

FIGURE 12. A small cell. × 630.

FIGURE 13. Photomicrograph to show the complexity of the dendritic tree of a cell with varicose dendrites. × 1000.

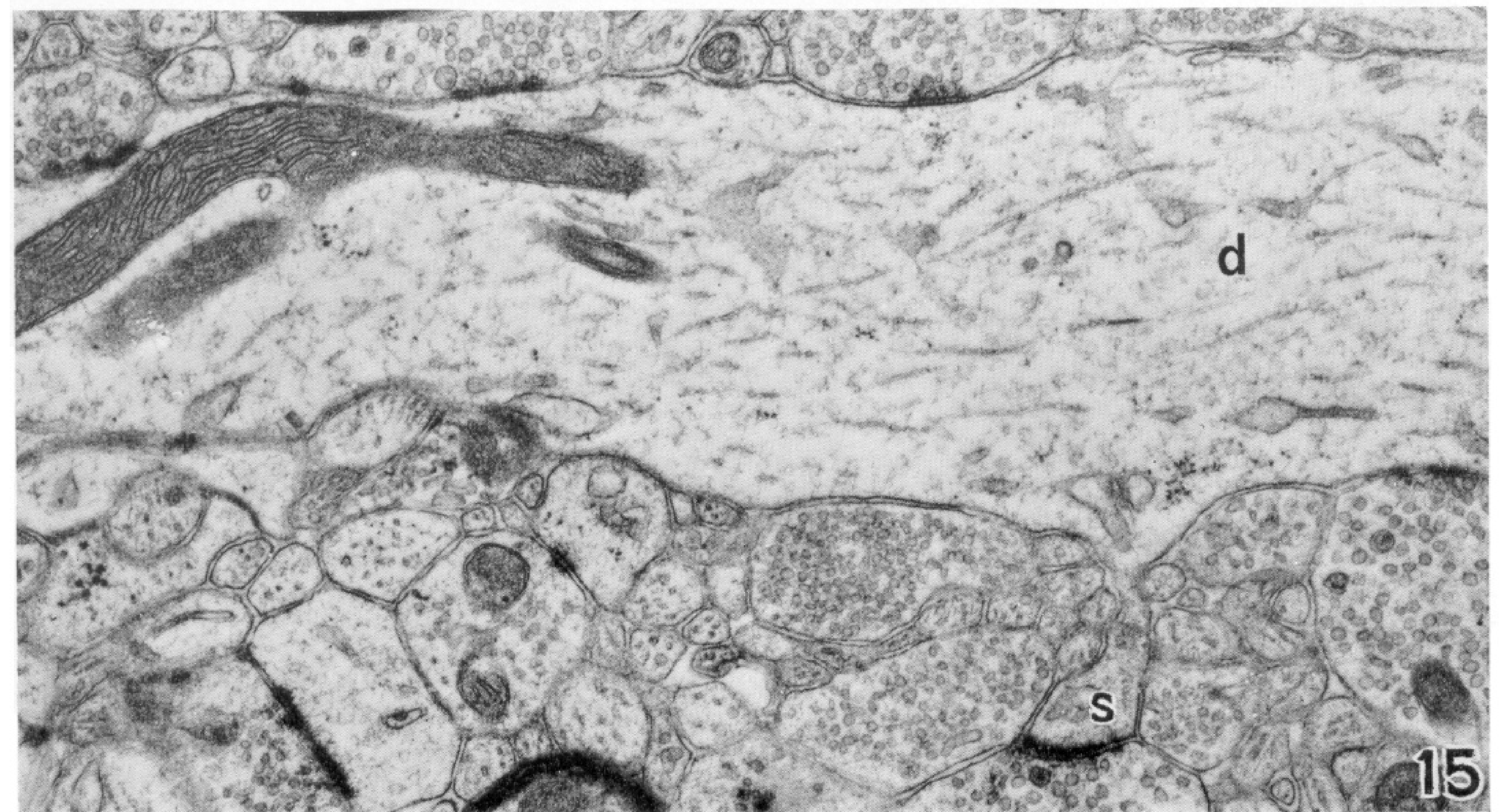


FIGURE 14. Electron micrograph of a medium spiny cell (c) with a branching main stem dendrite (d). The closely apposed profile is probably the basal dendrite of another similar cell. The appearance of the surrounding tissue is typical of the neuropil of the caudate nucleus. × 5000.

FIGURE 15. Peripheral dendrite (d) of a medium spiny cell. Note the obliqueness of some of the neurotubules. × 23000. s, spine.

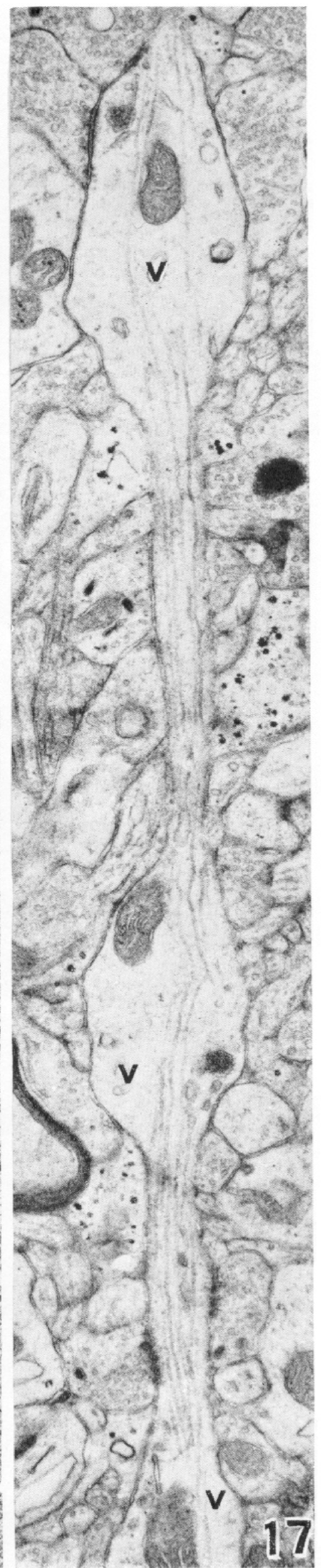


FIGURE 16. Electron micrograph of a giant cell showing the indented nucleus (large arrow), pale mitochondria (small arrows) and pronounced granular endoplasmic reticulum (er). The numerous lysosomes are commonly seen in cells of the caudate nucleus. The small satellite cell (g) may be microglia. ×4500, d. dendrite; go, Golgi apparatus.

FIGURE 17. Varicose dendrite with three varicosities (v). ×13000.

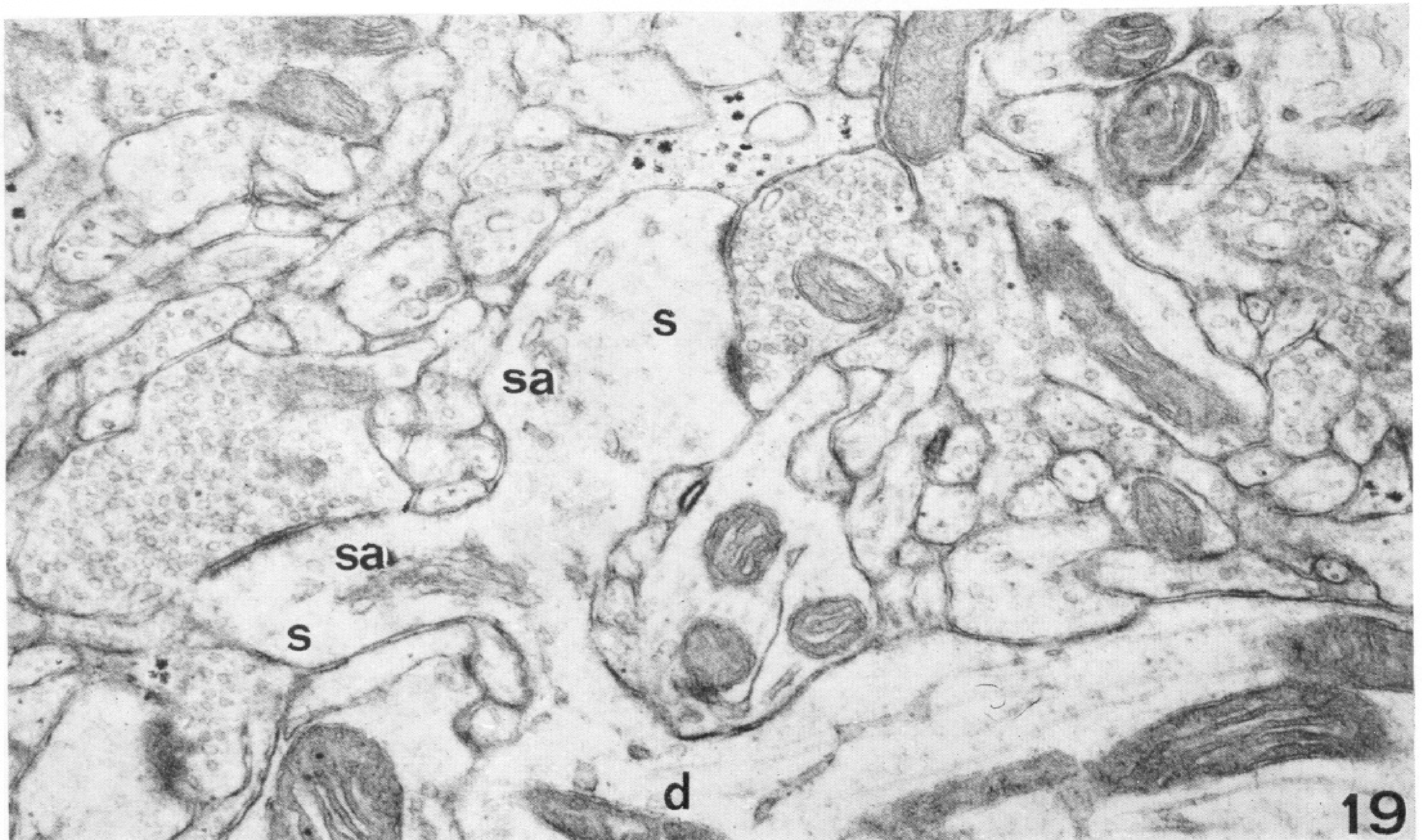
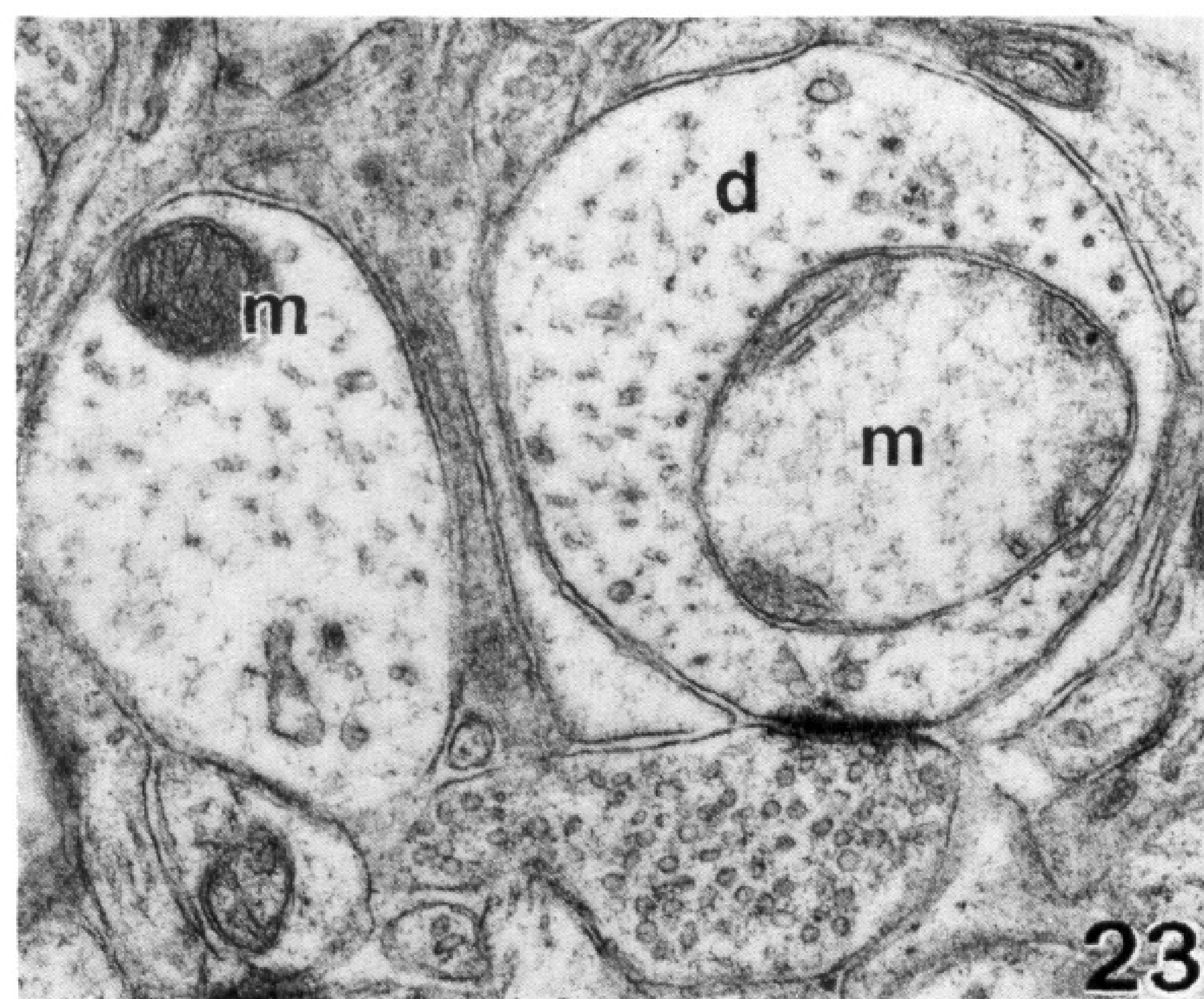


FIGURE 18. Medium-sized cell, similar to the medium spiny cell but with an indented nucleus (arrows). × 7000.

FIGURE 19. Branched spine (s) from the dendrite (d) of a medium spiny cell. Note the separate groups of spine apparatus (sa.). × 30000.

FIGURE 20. Medium-sized cell with deeply indented nucleus (arrow) and stacks of granular endoplasmic reticulum (er). Note the satellite glial cell (g) and the group of myelinated nerve fibres. $\times 5000$.

FIGURE 21. Small cell with indented nucleus (arrow), a dark rim around the periphery of the nucleus and many ribosomes in the cytoplasm. $\times 9000$.



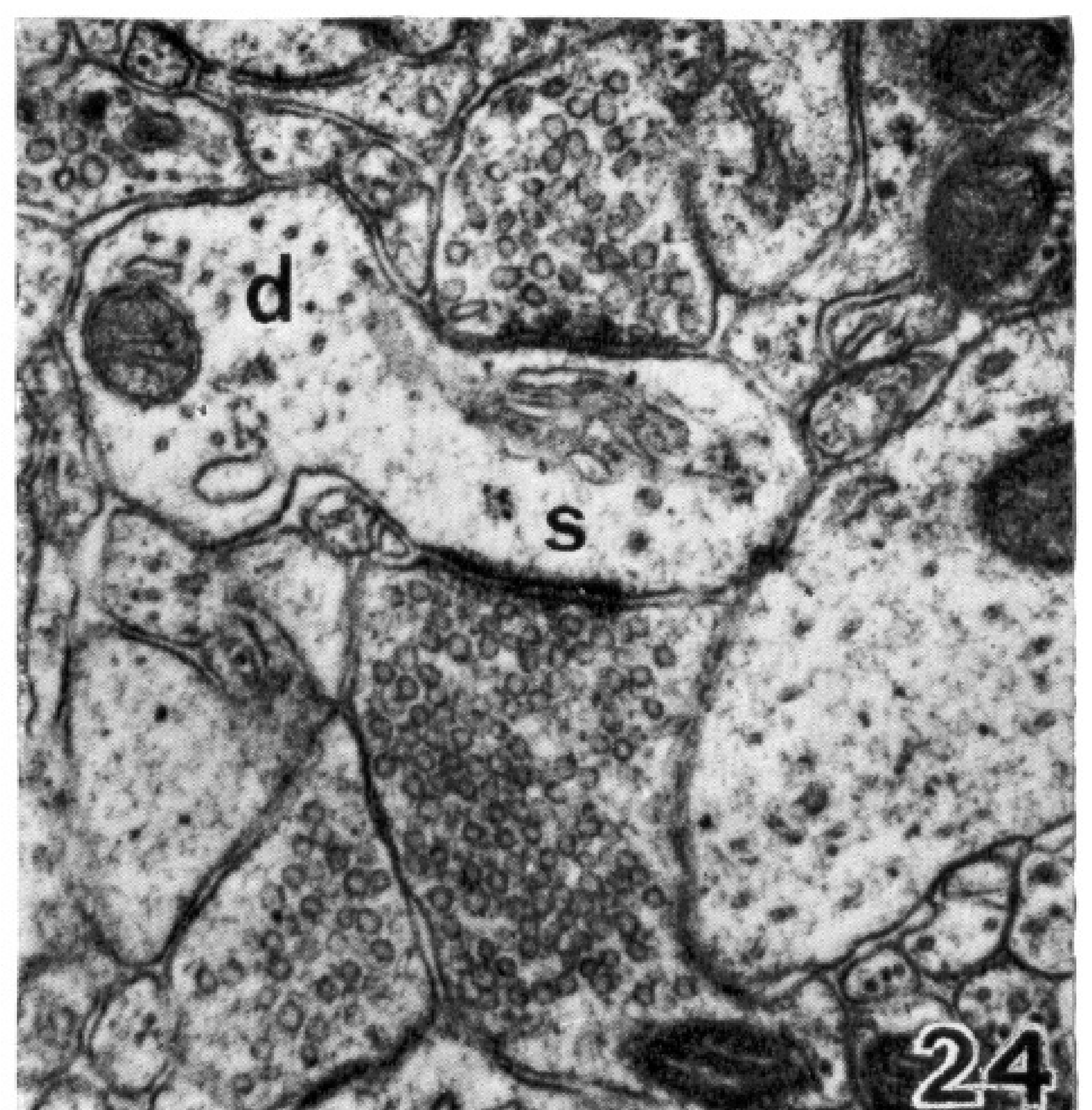
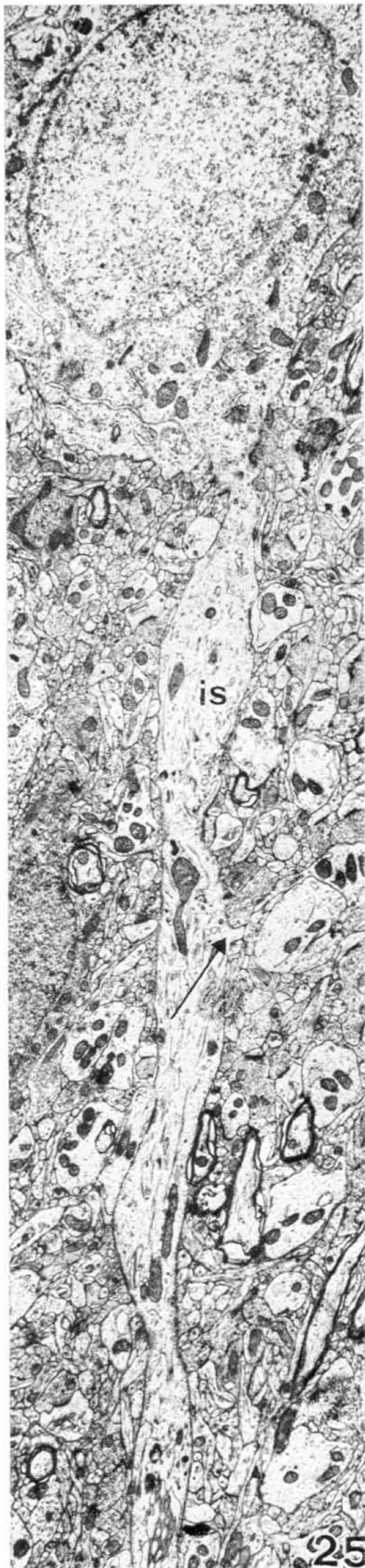
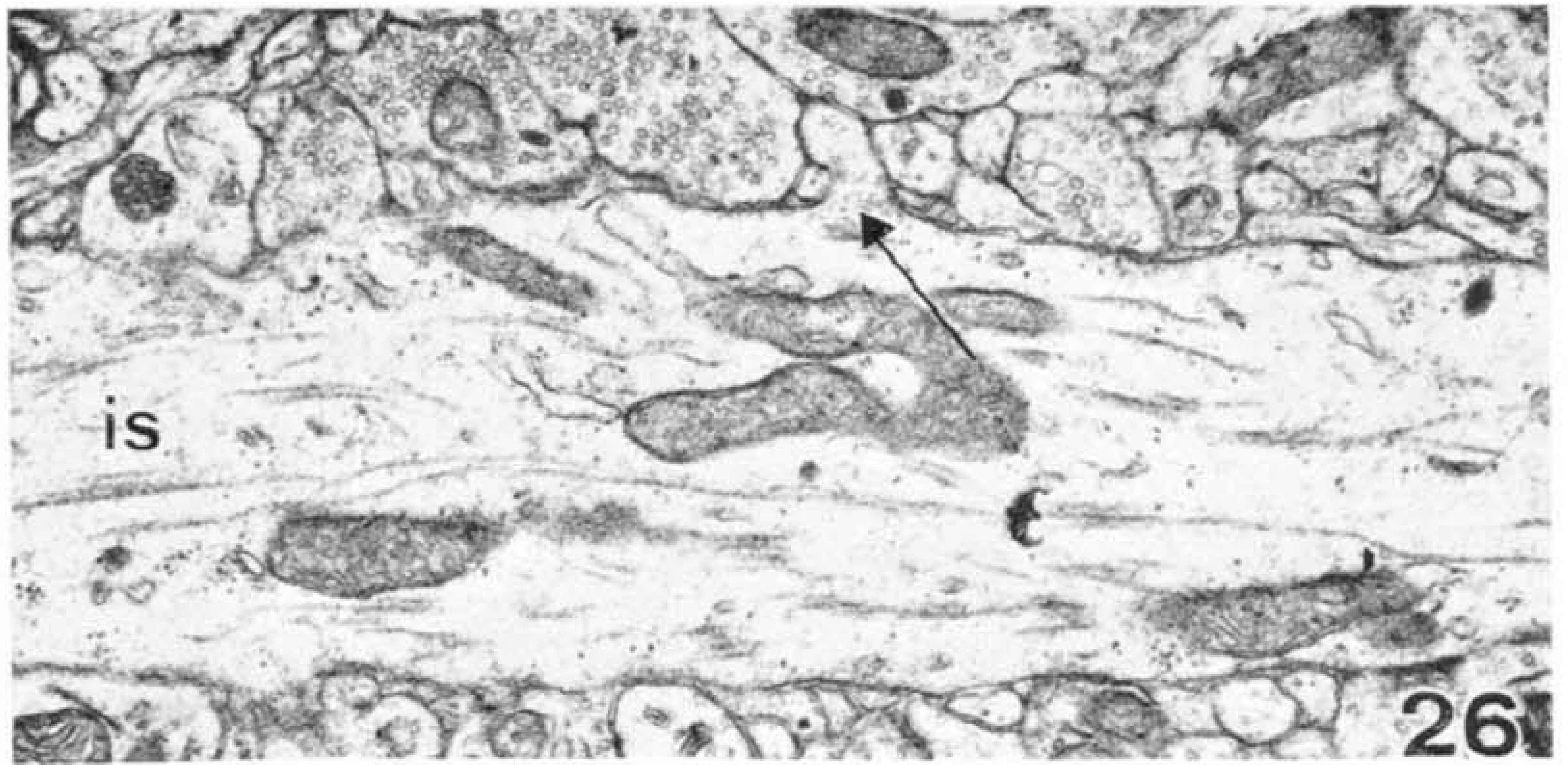


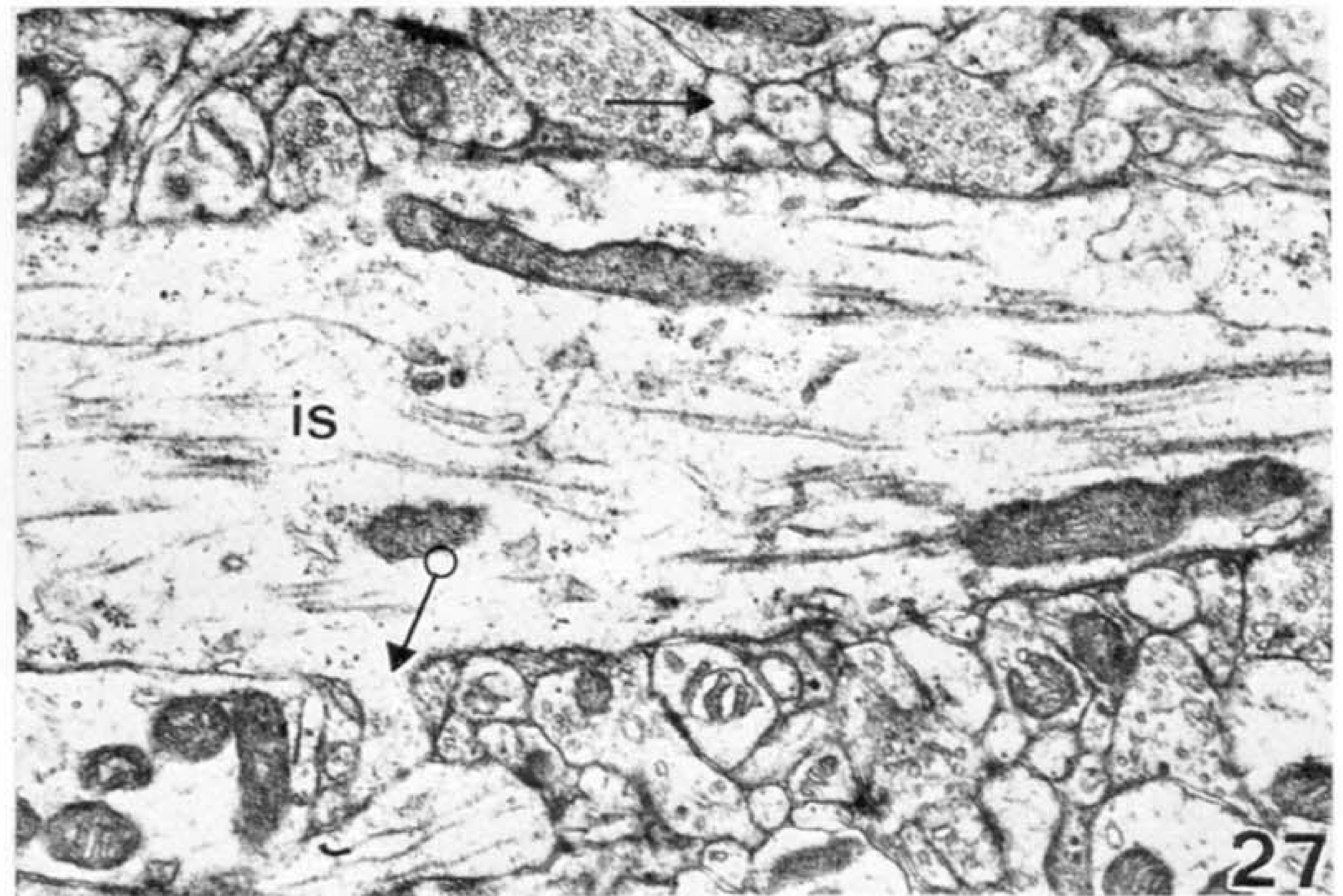
FIGURE 22. Medium cell with many deep nuclear indentations (arrows). Note the four stacks of complex Golgi apparatus (go). × 7000.

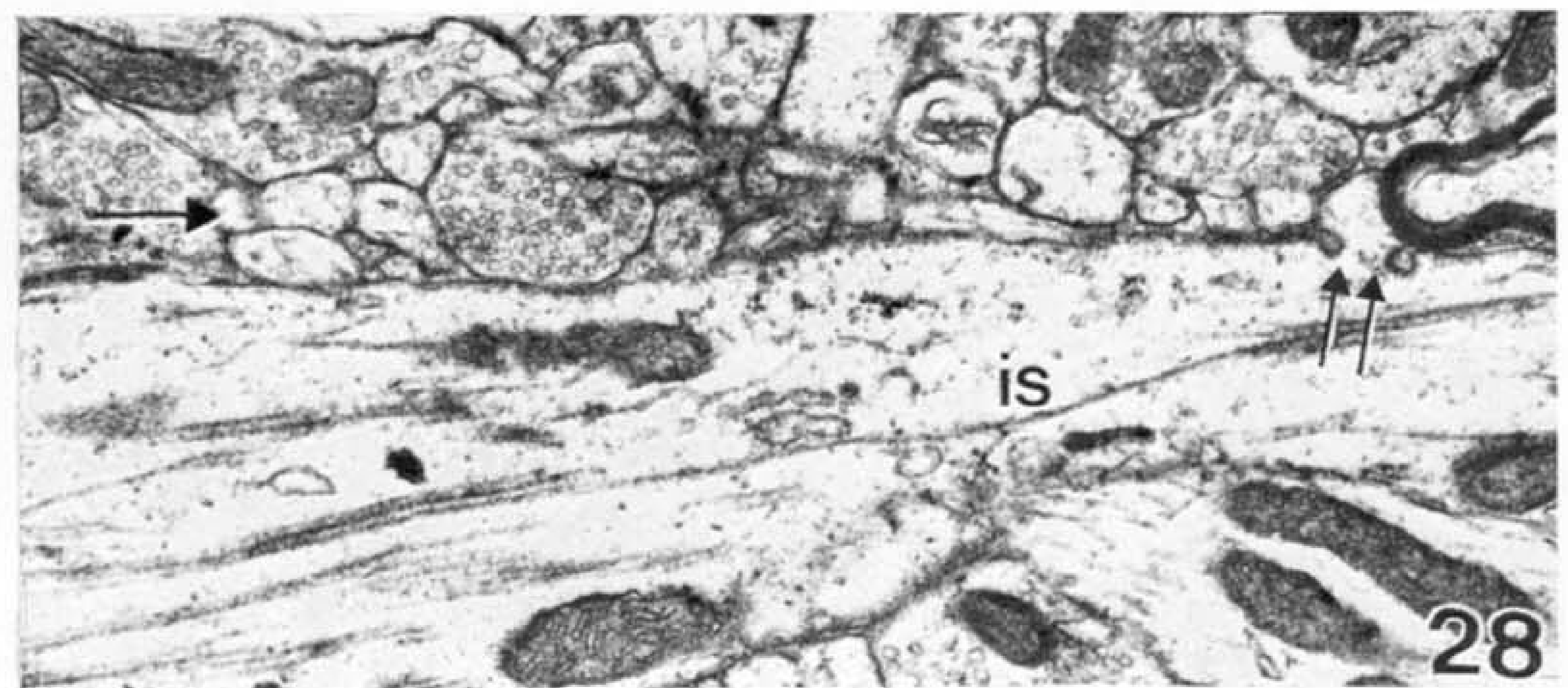
FIGURE 23. Peripheral dendrite (d) with conspicuous neurotubules and a large pale mitochondrion (m). × 23000.

FIGURE 24. Small dendrite (d) with prominent neurotubules, a small dark mitochondrion and a spine (s). × 23000.









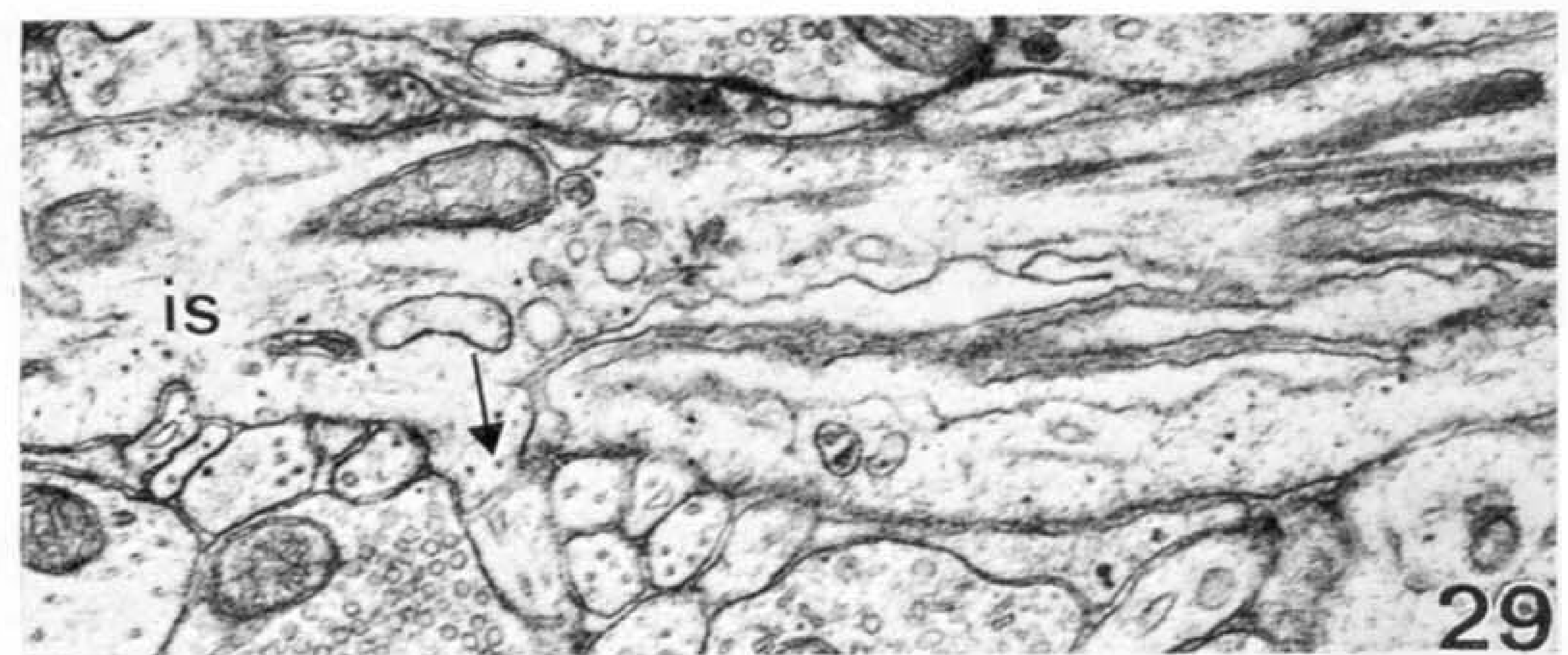


FIGURE 25–29. For legends see facing page.