Phil. Trans. R. Soc. Lond. B. **262**, 413–427 (1971)
Printed in Great Britain

THE SITE OF TERMINATION OF AFFERENT FIBRES IN THE CAUDATE NUCLEUS

By JANET M. KEMP and T. P. S. POWELL
Department of Human Anatomy, University of Oxford

(*Communicated by G. W. Harris, F.R.S.—Received* 13 *April* 1971)

[Plates 67 to 75]

An electron microscopic study has been made of the axon terminal degeneration in the caudate nucleus in the cat after lesions in either the cerebral cortex, the thalamus, the cerebral cortex and the thalamus, the midbrain or within the caudate nucleus. Degenerating axon terminals can be recognized after a survival period of 4 days as dark, shrunken profiles with indistinct vesicles. After shorter survival periods the degenerating terminals contain swollen vesicles and have pale cytoplasm. After lesions in all the above sites there is degeneration of fine myelinated and nonmyelinated fibres. The degenerating terminals of all the afferent fibres to the caudate nucleus have asymmetrical membrane thickenings and end mainly on dendritic spines with a small proportion in contact with peripheral dendrites; after damage of the cerebral cortex or thalamus a few of the degenerating terminals also end upon main stem dendrites and cell bodies. The projection from the ipsilateral cerebral cortex is greater than that from the thalamus, which in turn is heavier than that from the contralateral cortex or midbrain. After lesions within the caudate nucleus degenerating terminals with symmetrical membrane thickenings are found in a region extending approximately 450 μm from the damaged part of the nucleus. These terminals make contact with nerve cell somata, main stem and peripheral dendrites and the initial segments of axons. After such a lesion of the caudate nucleus degenerating axon terminals with symmetrical membrane thickenings are also seen in the globus pallidus and the substantia nigra.

Introduction

The study of normal material of the caudate nucleus has shown that six cell types are present, and, of these, one forms over 95 % of the total number of cells. It is also possible with the electron microscope to recognize four varieties of axon terminal, but in normal material the origin of these cannot be determined. From previous light microscopic investigations with axonal degeneration methods it is known that the striatum receives fibres from two main sources, the cerebral cortex (Webster 1961, 1965; Carman, Cowan & Powell 1963; Kemp & Powell 1970) and the thalamus (Droogleever-Fortuyn 1953; Powell & Cowan 1954; Mehler 1966), as well as smaller projections from the midbrain (Nauta & Kuypers 1957; Nauta & Mehler 1969) and contralateral cortex (Carman, Cowan, Powell & Webster 1965). As the axons of most of the intrinsic cells of the caudate nucleus give off collateral branches which terminate within the nucleus some, if not all, of the varieties of axon terminal must arise from more than one source. Degeneration of axonal terminals can be recognized with the electron microscope, and the study of experimental material with selective lesions in the appropriate regions of the brain should therefore enable one to differentiate the types of terminal according to their origin (Kemp 1968). Furthermore, this material should show the part of the neuron which is being influenced by the fibres of a particular afferent pathway.

Material and methods

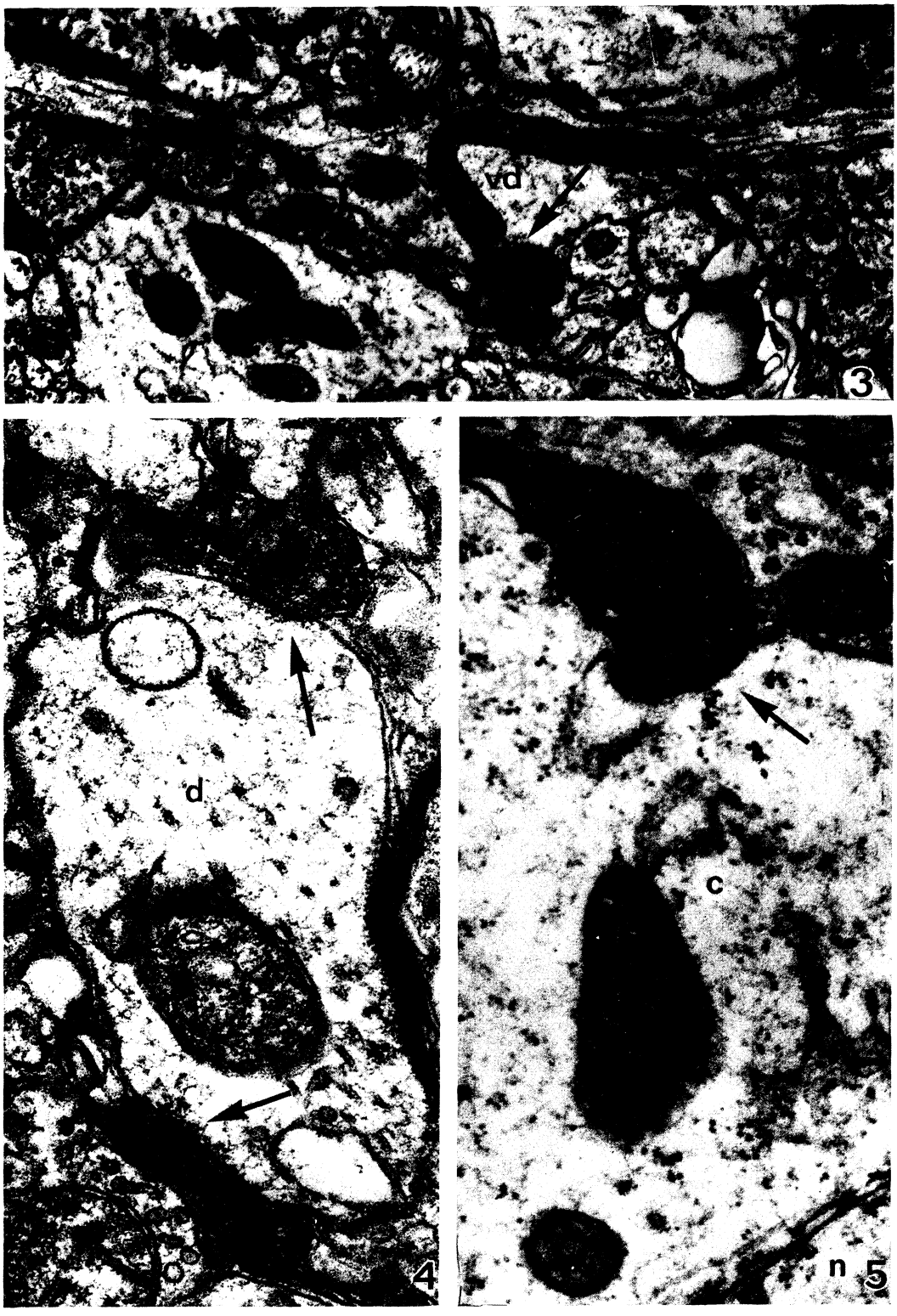
Most of the observations to be described were made on material taken from the brains of 24 adult cats which were allowed to survive for short periods, varying between 2 and 8 days, after the placement of a lesion. Under Nembutal anaesthesia and with aseptic precautions lesions were placed in different parts of the brain, and the experiments can be divided into five groups according to the site of the damage: in the cerebral cortex (7), in the thalamus (8), removal of the cortex together with a lesion in the thalamus of the same hemisphere (3), in the midbrain (3), a small lesion within the head of the caudate nucleus (3). Extensive lesions of the cerebral cortex were made by suction and involved removal of most of the cortex on the lateral and medial surfaces of the rostral half of the hemisphere. The lesions in the thalamus, caudate nucleus and midbrain were electrolytic and were made stereotaxically, those in the first two structures by a vertical approach and those in the midbrain by a horizontal approach from behind and laterally with the electrode passing behind the tentorium and below and in front of the cerebellum, with usually only minor damage to the latter. The damage in the thalamus and midbrain was made sufficiently large to interrupt most, if not all, of the afferent fibres to the striatum from these regions.

The animals were perfused, under hypothermia, with a balanced salt solution followed by a mixture of 4% formaldehyde and 1% glutaraldehyde. After removal from the skull the brain was stored in the perfusion mixture before small blocks were taken from most parts of the head of the caudate nucleus on the side of the lesion, and the blocks were numbered so that it was known from which parts of the nucleus they were taken. In order to study the contralateral cortico-striate projection, blocks were similarly taken from the caudate nucleus on the side contralateral to the cortical removal. In some experiments blocks of the putamen were also removed, and in the brains in which the lesion had been placed within the caudate nucleus blocks were also taken from the globus pallidus and substantia nigra.

In addition to this material from experiments with short survival periods similar small blocks were taken from the caudate nucleus of cats in which comparable lesions of the cortex and thalamus had been placed, but in these experiments the survival periods were much longer, between 13 and 52 weeks. These experiments with longer survival periods were done primarily for a study of the changes in dendritic spines in Golgi impregnated material (Kemp & Powell 1971*b*).

The blocks of tissue for electron microscopy were processed and sections were cut and stained as described in detail in a preceding paper (Kemp & Powell 1971*a*). In addition to the two sizes of sections which were used in the studies of normal material, large sections approximately 1 mm by 0.2 mm were cut from the blocks of the caudate nucleus in which a lesion had been placed within this nucleus; they were taken from the tissue immediately adjoining the lesion and were used to make 'maps' of the distribution of the degenerating terminals according to the method described by Alksne, Blackstad, Walberg & White (1966).

In all experiments in which lesions had been placed in the thalamus or midbrain the part of the brain containing the lesion was embedded in paraffin wax and cut coronally at 15 μm. A 1 in 20 series of sections was mounted and stained with thionin in order to determine the site and extent of the lesion.



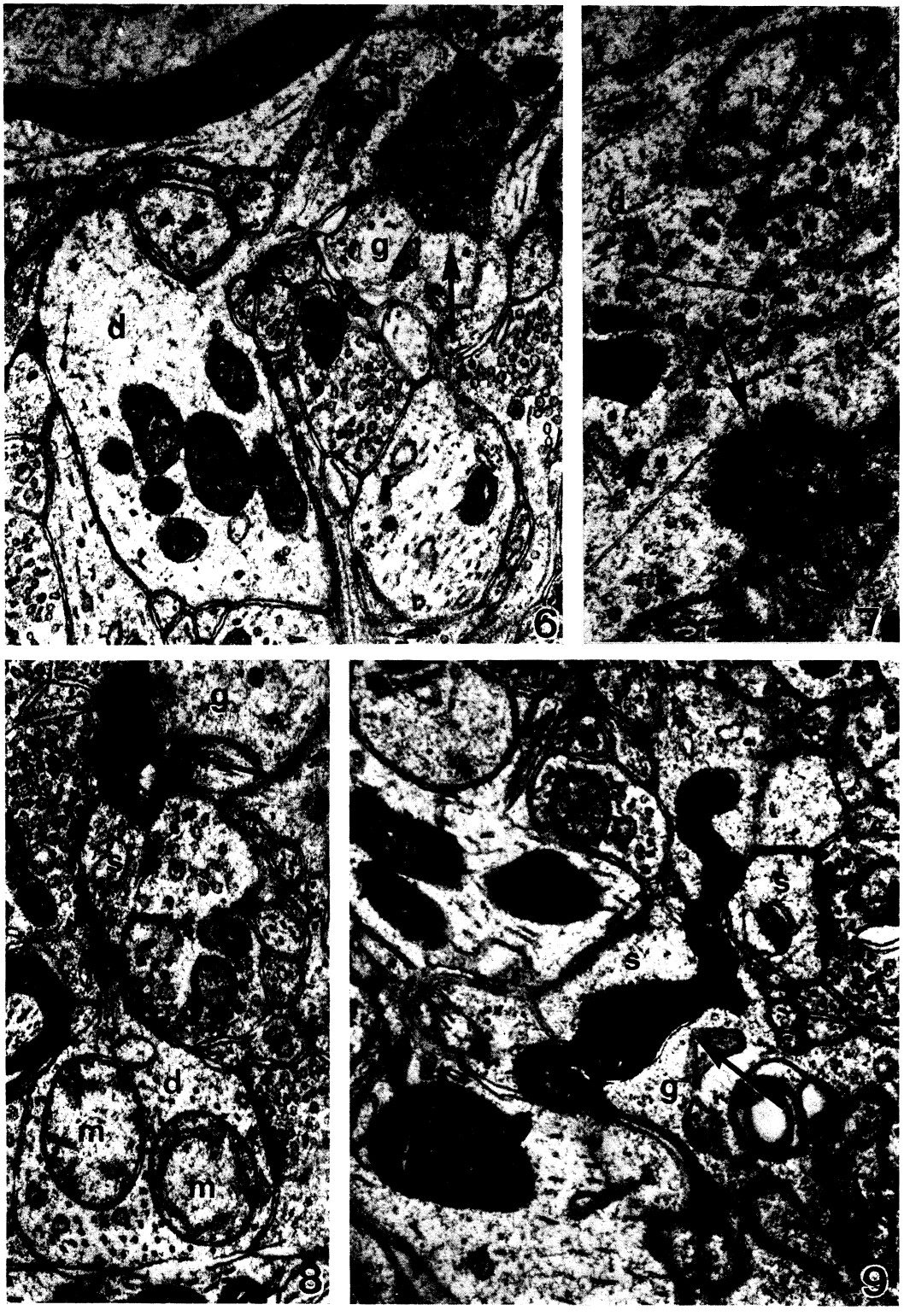
FIGURES 3 to 5. Some of the types of profiles contacted by degenerating terminals (arrows) after a lesion in the cerebral cortex.

FIGURE 3. Varicose dendrite (vd). × 25000.

FIGURE 4. Dendrite of a medium spiny cell (d). × 80000.

FIGURE 5. Cell soma (c). × 50000. n, nucleus.

(*Facing p.* 414)



FIGURES 6 to 9. Varieties of profile contacted by degenerating terminals (arrows) after a lesion in the thalamus.

FIGURE 6. Spine (s) from the dendrite (d) of a medium spiny cell. × 30000. g, glia.

FIGURE 7. Main stem dendrite (d) of a giant cell containing pale mitochondria (m). × 40000.

FIGURE 8. Spine (s) arising from the peripheral dendrite (d) of a giant cell. Note the pale mitochondria (m). × 40,000. g, glia.

FIGURE 9. Degenerating terminal 'en passant' in contact with a spine (s). × 30000. g, glia.

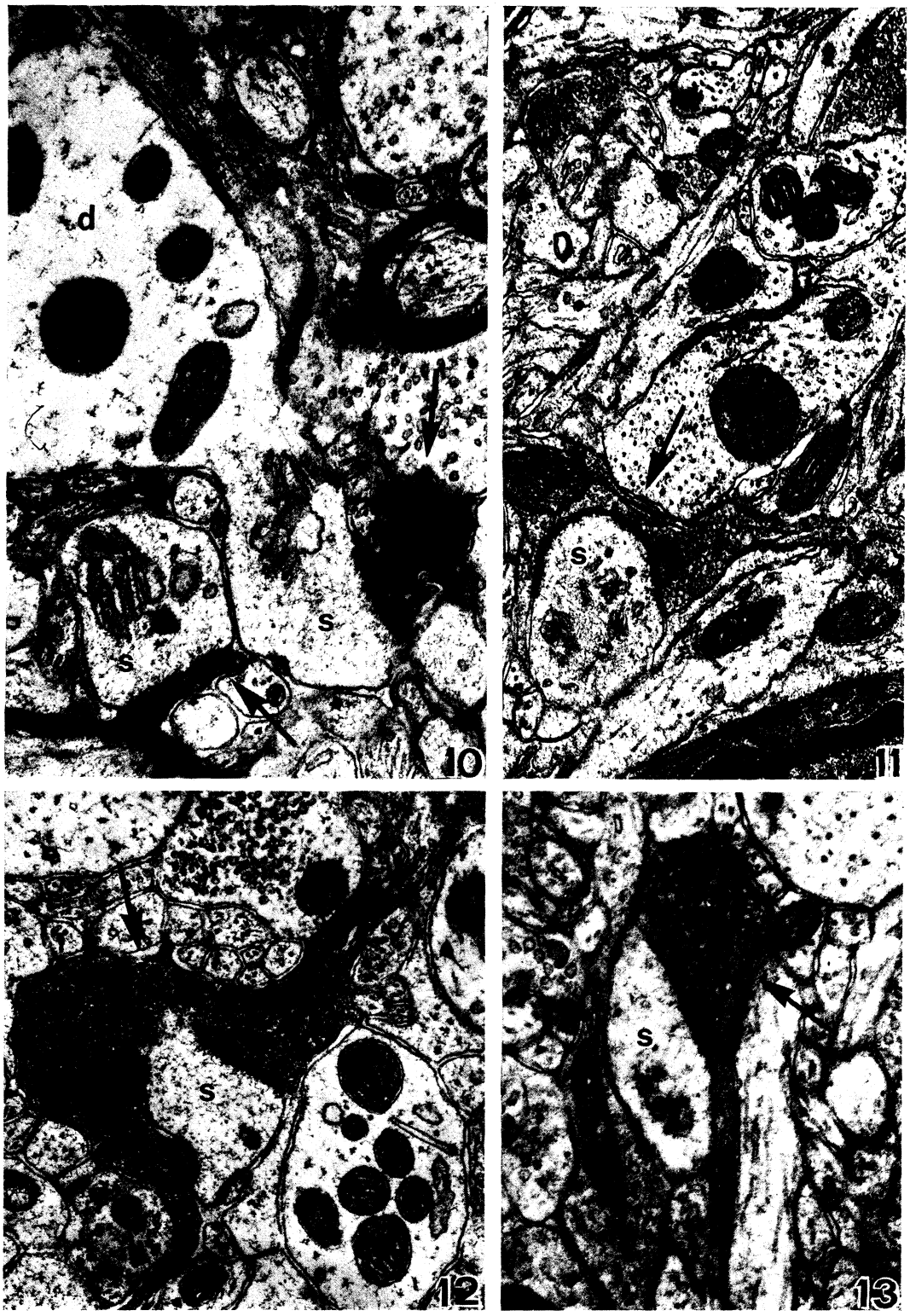
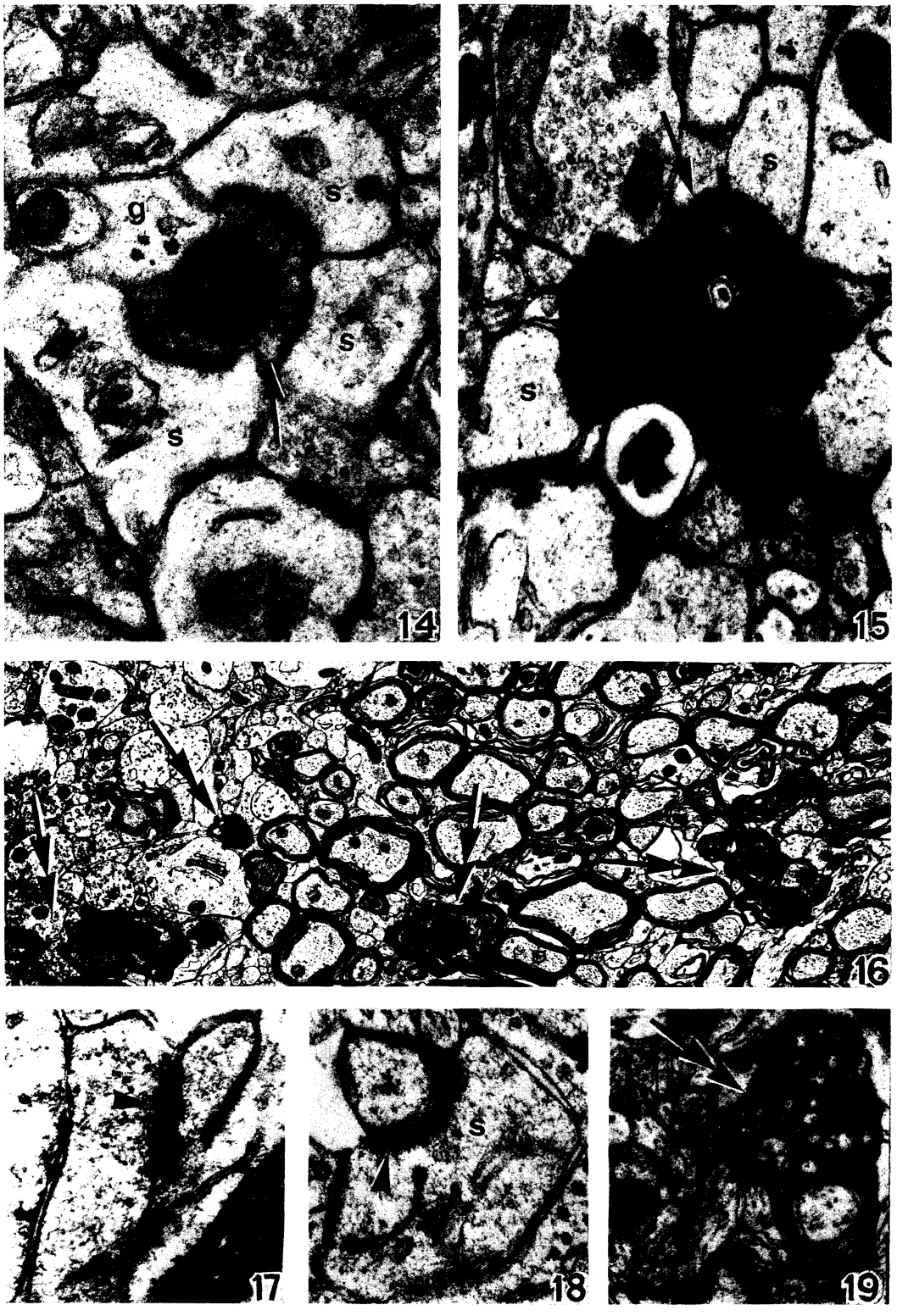


FIGURE 10. Two degenerating terminals (arrows) in contact with spines (s) after a lesion in the contralateral cerebral cortex. × 40000.

FIGURE 11. Terminal *en passant* (arrow) showing early degenerative changes after a lesion in the midbrain. × 25000.

FIGURE 12. Degenerating terminal *en passant* (arrow) in contact with a spine (s) after a lesion in the contralateral cerebral cortex. × 25000.

FIGURE 13. Degenerating terminal (arrow) in contact with a spine (s) after a lesion in the midbrain. × 30000.

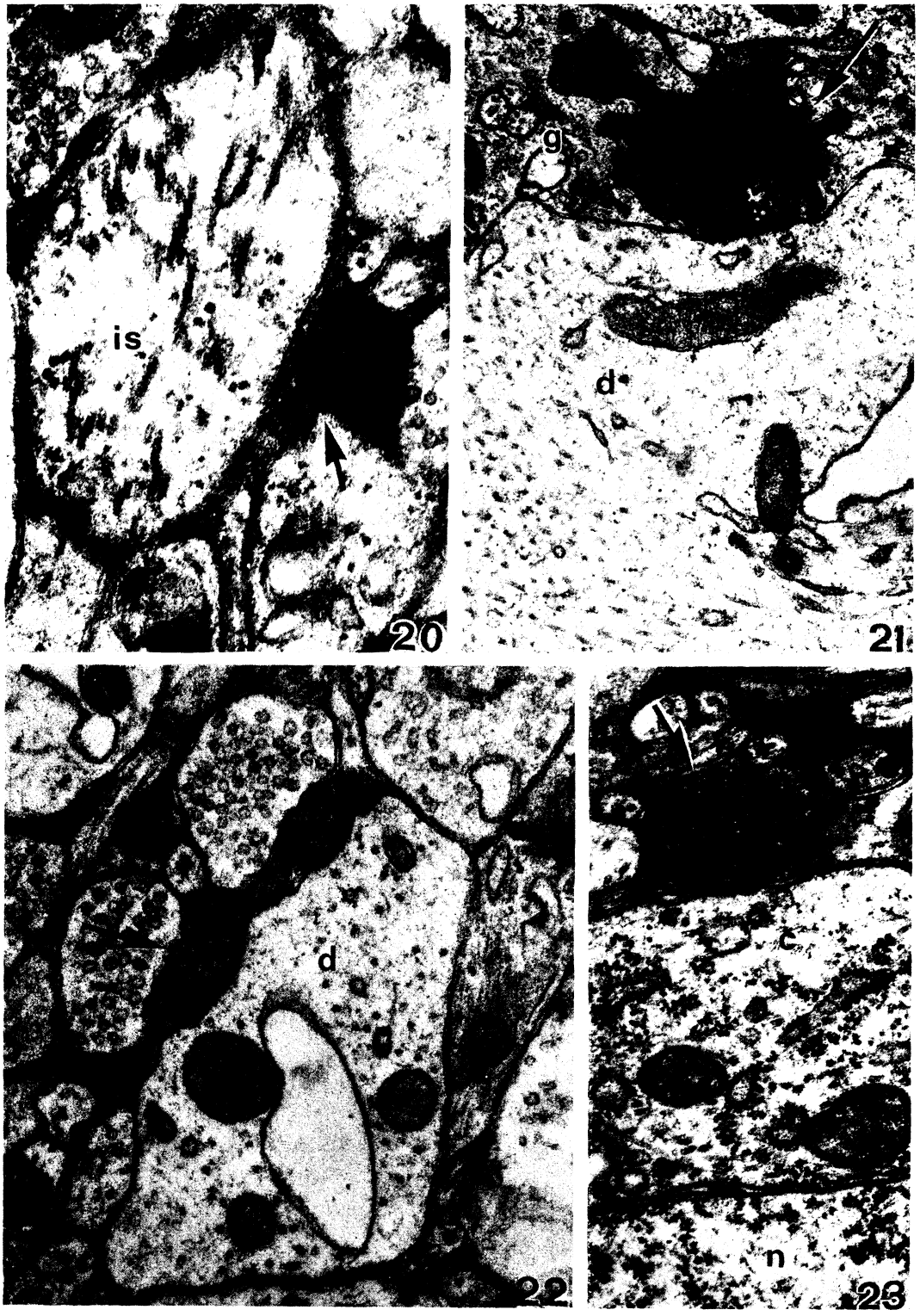


FIGURES 14, 15. Large degenerating terminals (arrows), after a combined lesion of the cerebral cortex and thalamus, each forming synaptic contacts with more than one spine (s). g, glia. 14, × 45000; 15, × 40000.

FIGURE 16. Part of a bundle of myelinated fibres some of which are degenerating (double arrows) after a lesion in the thalamus. × 7000.

FIGURES 17, 18. Exposed postsynaptic membrane thickenings (arrow heads) in the caudate nucleus 112 days after a combined lesion in the cerebral cortex and thalamus. × 80000. s, spine.

FIGURE 19. Degenerating myelinated nerve fibre (double arrow) after a lesion in the midbrain. × 30000.



FIGURES 20 to 23. Varieties of processes of caudate neurons contacted by degenerating terminals (arrows) with symmetrical membrane thickenings after a lesion in the caudate nucleus.

FIGURE 20. The initial segment of an axon (is). Note the grouped neurotubules and undercoating of the axon membrane. × 80000.

FIGURE 21. Large dendrite (d). × 30000. g, glia.

FIGURE 22. Peripheral dendrite (d). × 48000

FIGURE 23. Cell soma (c). × 40000. n, nucleus.

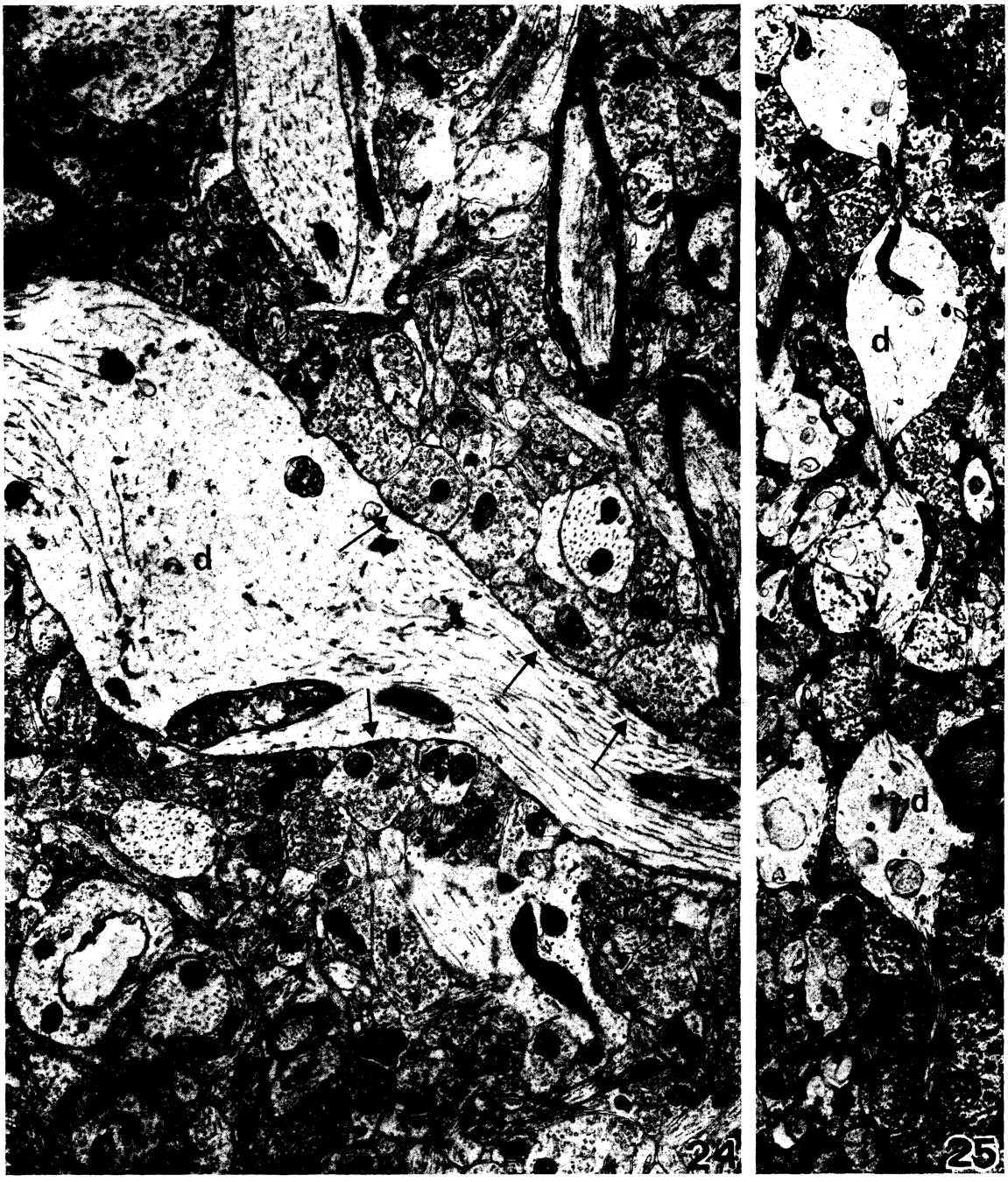


FIGURE 24. Dendrite (d) of the globus pallidus covered with axon terminals many of which are making synaptic contact (arrows) with it. × 9500.

FIGURE 25. Varicose dendrite (d) of the globus pallidus receiving many synapses. × 7000.

FIGURE 27. Serial synapse in the substantia nigra. The first synapse is asymmetrical and is from terminal t1 to terminal t2, and the second synapse is symmetrical from terminal t2 to a dendrite (d). Arrows indicate degenerating preterminal axons. × 27000. Note the difference in size of the vesicles in the three terminals shown here; the polymorphic vesicles in t2 are smaller than those in the most common type of terminal in the substantia nigra (on left of t2), and those in t1 (associated with an asymmetrical synapse) are the smallest.

FIGURE 28. A *possible* example of a similar serial synapse in the globus pallidus if the terminal t2 which *receives* an asymmetrical synapse from terminal t1, makes a definite synapse, on an adjoining section, with the dendrite (d). × 26000.

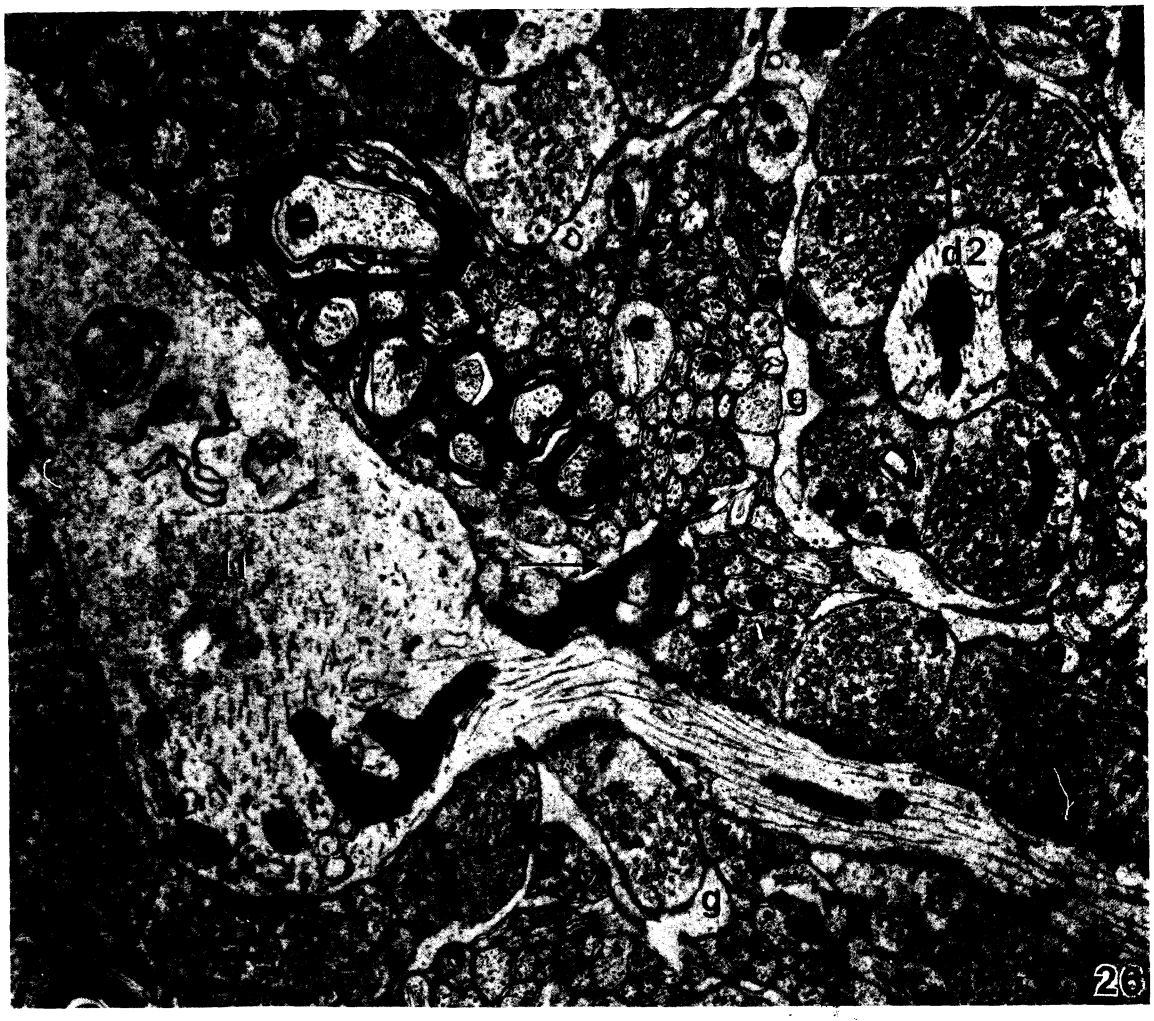


FIGURE 26. Two dendrites of the substantia nigra, one cut longitudinally (d 1) and the other transversely (d 2); both are in synaptic contact with numerous axon terminals, and the complex thus formed is ensheathed with glia (g). Arrow indicates a degenerating preterminal axon. × 21 500. Note the similarity in the structure and synaptic organization shown in this electron micrograph of the substantia nigra with that of the globus pallidus shown in figure 24.

FIGURES 27 and 28. For legends see facing page.

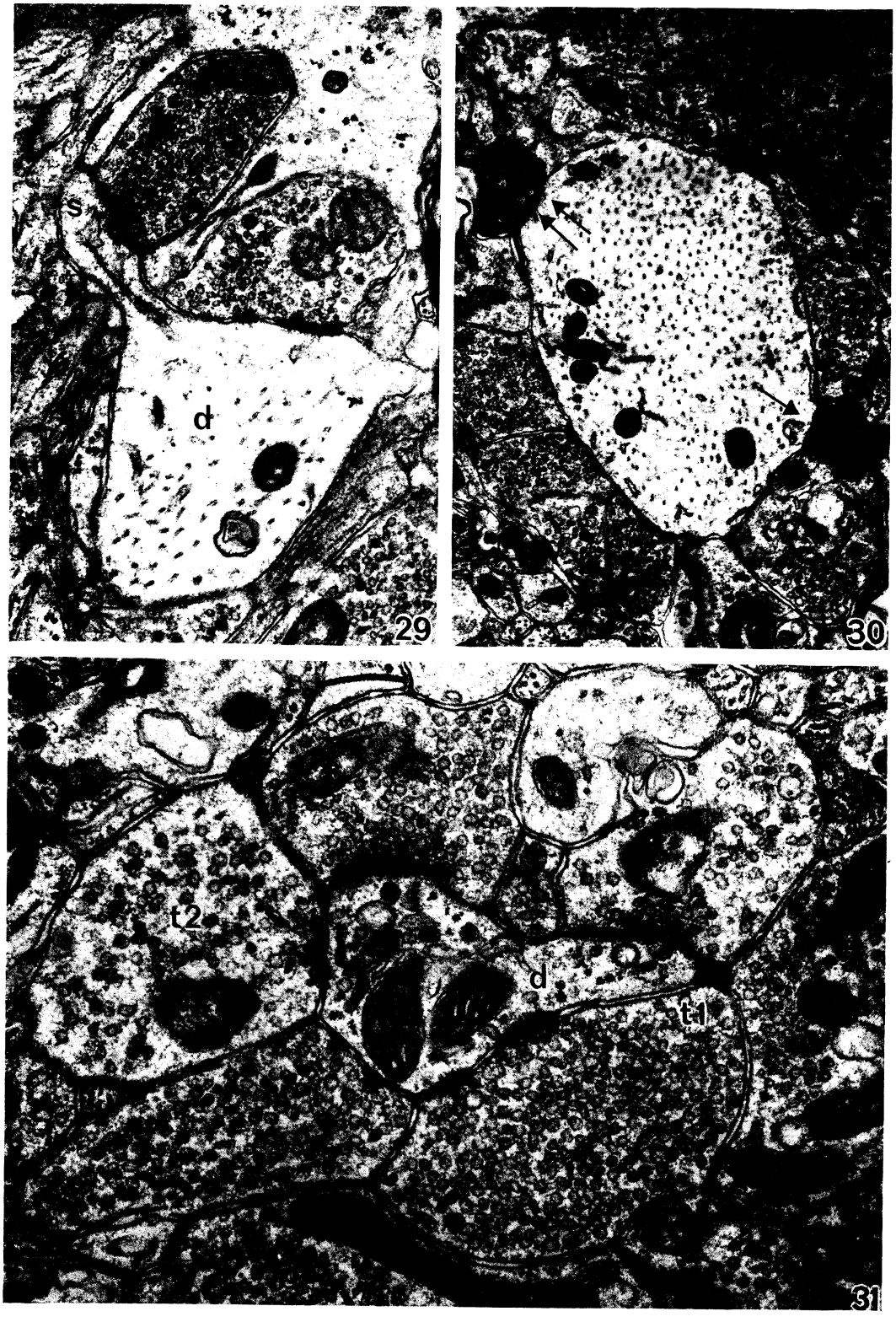


FIGURE 29. A dendritic spine (s) on a dendrite (d) of the globus pallidus. Axon terminals make asymmetrical synapses on to the spine and adjoining part of the dendrite. × 20000.

FIGURE 30. Degeneration of axon terminals (double arrows) and preterminal axons (arrow) in the substantia nigra 4 days after a lesion in the caudate nucleus. × 17000.

FIGURE 31. Dendrite of the substantia nigra (d) upon which an axon terminal (t1) makes an asymmetrical synapse and another (t2) makes a symmetrical synapse. × 43000.

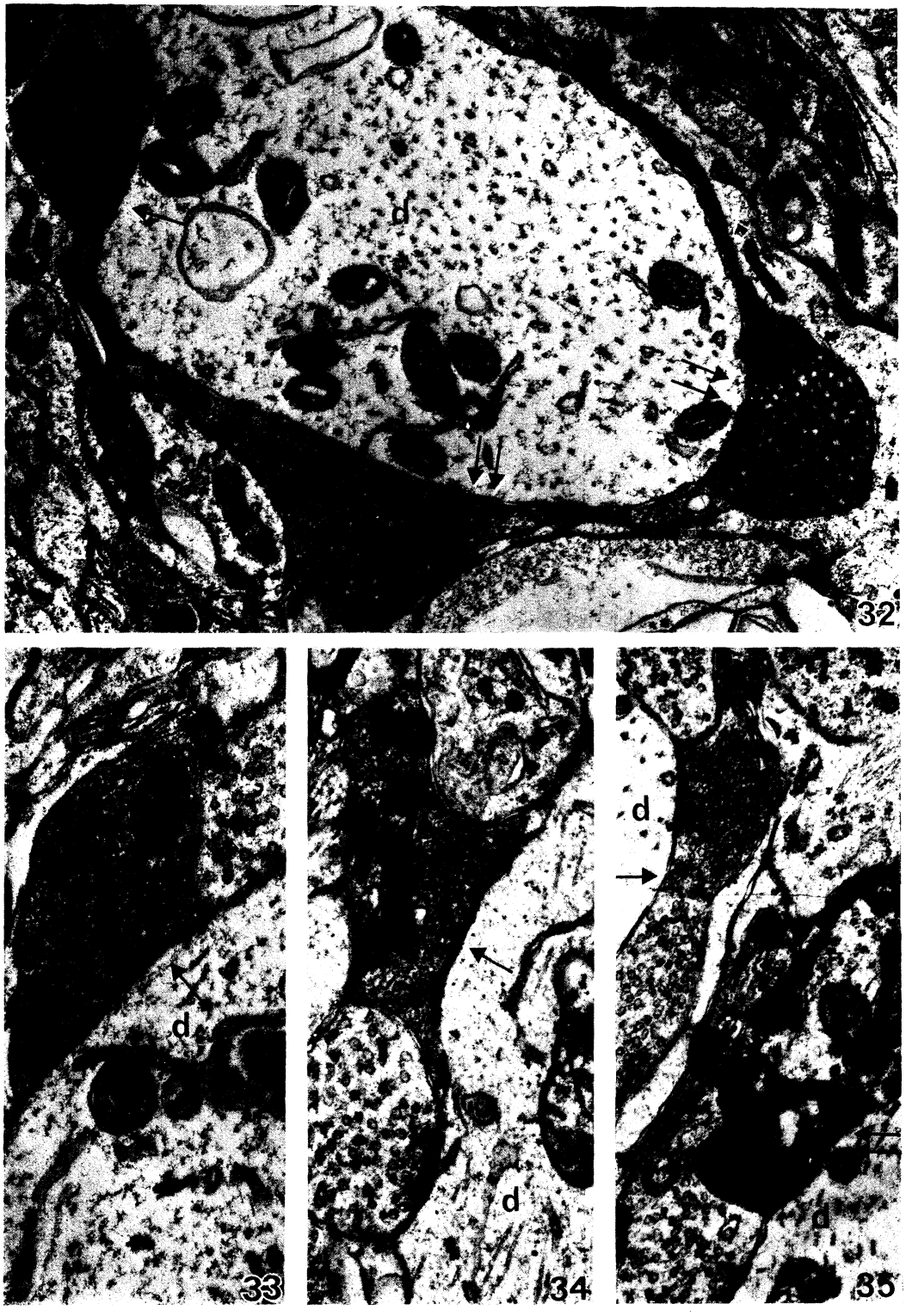


FIGURE 32. Axon terminals (double arrows) and preterminal axon (arrow) in the substantia nigra at different stages of degeneration 4 days after a lesion in the caudate nucleus. d, dendrite. × 29000.

FIGURE 33. Axon terminal (arrow) which is making a symmetrical axodendritic synapse in the substantia nigra in an early stage of degeneration 4 days after a lesion in the caudate nucleus. d, dendrite. × 37000.

FIGURE 34. Degenerating axon terminal (arrow) in symmetrical synaptic contact with a dendrite in the globus pallidus; 4 days after a lesion in the caudate nucleus. d, dendrite. × 30000.

FIGURE 35. Two axon terminals making axodendritic synapses in the globus pallidus and at different stages of degeneration 4 days after a lesion in the caudate nucleus. The one above (arrow) is at a very early stage of degeneration and is darker than the normal terminals on either side of it; the terminal below (double arrow) is at a later stage and is much darker and distorted. d, dendrite. × 21000.

Results

The appearance of the degenerating axons and terminals which are present in the caudate nucleus following lesions in the cerebral cortex, contralateral cerebral cortex or thalamus is very similar. Since the process of degeneration in this region does not seem to differ essentially from that in other parts of the brain (e.g. Colonnier & Gray 1962; Walberg 1964; Westrum 1966; Jones & Powell 1970) only a brief description will be given. After a survival of 2 days some terminals are a little paler than normal and a proportion of the synaptic vesicles within them are swollen (Pinching 1969; Cuénod, Sandri & Akert 1970); glycogen-like granules are commonly present. A very few terminals are seen whose cytoplasm is darkened and in which the swollen vesicles are crowded together. Four days survival is the earliest at which degenerating myelinated and nonmyelinated fibres are seen in any number. After this time most of the altered terminals contain very dark cytoplasm, vesicles are not clearly seen and the profile is distorted and shrunken (Walberg 1964; Westrum 1966) (figures 4 and 7, plates 67 and 68); at this survival period many of the terminals have glial processes close to them (figures 6 and 8, plate 68). A slightly earlier stage is also seen where the cytoplasm is moderately dark and the vesicles uniformly swollen and tightly packed together (figures 11 and 13, plate 69). Any mitochondria present are distorted or broken up at both these stages (figure 15, plate 70). Endings at an advanced stage of degeneration become progressively more common after 6 or 8 days survival and here the glial processes invade the degenerating terminals and engulf them (Jones & Powell 1970) (figure 9, plate 68). The number of degenerating terminals found after lesions in the cerebral cortex or thalamus is greatest 6 days following placement of the lesion. After 4 days survival the degeneration is half as dense, while increasing the survival period to 8 days does not increase the density compared with the 6-day survival. After long survivals of 16 weeks the degenerating terminals are no longer evident, but exposed postsynaptic membrane thickenings on spines and dendrites apposed by glial or neural processes are seen (Pinching 1969) (figures 17 and 18, plate 70). This brief description of the appearance of the degeneration also applies to that seen in the nucleus after a lesion in the midbrain except that in this case the changes take longer to occur, the degeneration still being at a fairly early stage after a survival of 5 days (figures 11 and 13, plate 69).

Lesions in the cerebral cortex

A lesion in the cerebral cortex involving most of the lateral and medial surfaces of the hemisphere gives rise to degeneration of thinly myelinated nerve fibres of 0.6 to 2 μm close to the internal capsule and scattered in the neuropil; they are also present in the fibre bundle which lies beneath the ependymal layer. The number of degenerating axons seen in the bundles of fibres is very variable and an estimate of the proportion degenerating is not possible. Scattered degenerating non-myelinated fibres are also present sometimes close to degenerating terminals. These all form synapses with asymmetrical membrane thickenings and are, most probably, the small terminals with round vesicles which can be seen in the normal nucleus; occasionally the terminals are *en passant*. Most of the degenerating terminals contact spines which arise from medium or small dendrites of medium spiny cells or the dendrites with conspicuous neurotubules and small mitochondria. A degenerating and a normal terminal, both of which form synapses with asymmetrical membrane thickenings, have not been seen contacting one spine though a second normal terminal with symmetrical membrane thickenings

may be present. Other degenerating terminals form synapses with the shafts of the peripheral dendrites from which the spines arise (figure 4, plate 67) and occasionally with varicose dendrites (figure 3, plate 67) and the dendrites of giant cells. A degenerating terminal is found more rarely in contact with main stem dendrites and cell somata of medium spiny cells (figure 5, plate 67) and small cells.

There is evidence of grouping of terminals so that adjacent parts of a section may have very different densities of degeneration. A large cortical lesion may result in the degeneration of about 50 % of the terminals forming synapses with asymmetrical membrane thickenings within an area which is severely affected; in view of the clustering, however, it is probable that a more realistic estimate of the numbers of terminals from the cerebral cortex to the caudate nucleus as a whole would be between 30 and 40 % of the terminals of this one type.

Lesions in the thalamus

The lesions in the thalamus were large and were so placed that most of the efferent fibres from the intralaminar nuclei were almost certainly interrupted. In the majority of the brains most of the mediolateral extent of at least the ventral half of the thalamus was destroyed at the level of the anterior end of the mediodorsal nucleus. It should be noted that there was no evidence in the thionin-stained sections of either direct or ischaemic involvement of the body of the caudate nucleus or of the globus pallidus, and that there was no suggestion of ischaemic necrosis in the thin sections of the head of the caudate nucleus examined with the electron microscope.

After such a lesion in the thalamus there is degeneration of thinly myelinated nerve fibres in the head of the caudate nucleus; they are between 0.5 and 2.5 μm diameter (figure 16, plate 70) and are similar to those seen after a lesion in the cerebral cortex. These and degenerating non-myelinated fibres are distributed widely throughout the nucleus and in the subependymal layer. All the degenerating terminals form synapses with asymmetrical membrane thickenings and are again probably the small terminals with round vesicles; some may be *en passant* (figure 9, plate 68). Most of the degenerating terminals are in contact with spines arising from medium spiny cells (figure 6, plate 68), from dendrites with conspicuous neurotubules and small mitochondria and more rarely with the spines of giant cells (figure 8, plate 68). Very occasionally a second normal terminal with an asymmetrical contact region forms a synapse with the same spine, but more commonly the second terminal has a symmetrical contact region. Degenerating terminals also form synapses with the shafts of the peripheral dendrites of medium spiny cells and of the dendrites with well-marked neurotubules and small mitochondria, but they are less common than after a lesion in the cerebral cortex. The fibres from the thalamus have also been seen ending upon main stem dendrites and cell bodies of medium spiny cells and giant cells (figure 7, plate 68).

There is some evidence that the fibres from the thalamus are arranged in groups in the caudate nucleus in the same manner as the afferent fibres from the cerebral cortex and consequently there is a similar difficulty in estimating the number of thalamic terminals in the nucleus. Furthermore, there seem to be two phases of degeneration. After 3 days survival there are only a few degenerating terminals and these are at a more advanced stage of degeneration than those after a cortical lesion of the same survival, almost all being surrounded by glia. After 6 days survival the density of degeneration is about four times greater and most of the darkened profiles are still clearly recognizable as terminals. If these factors are taken into account a reasonable

estimate of the number of terminals arising from the thalamus is probably between 20 and 25 % of the total number of terminals with asymmetrical membrane thickenings. This is considerably less than the number which arise from the cerebral cortex and though the number of degenerating endings on spines does not appear to be very different the cortical fibres also terminate more frequently on the shafts of dendrites.

Combined lesions in the cerebral cortex and thalamus

As would be expected, the number of degenerating myelinated fibres seen in the caudate nucleus after lesions in the cerebral cortex *and* thalamus is greater than after either lesion alone. There are also more degenerating terminals with asymmetrical membrane thickenings after the combined lesion, though normal endings still remain with both types of membrane thickening. The degenerating endings do not seem to form the distinct clusters seen after a lesion in either the cerebral cortex or thalamus, but whether or not there are smaller variations in the density of the degeneration is difficult to determine. After such a combined lesion an occasional darkened terminal is seen, which may contain the remains of several mitochondria and which is in contact with a number of spines (figures 14 and 15, plate 70). Such a relationship is characteristic of the large terminals, with round vesicles, which form contacts with asymmetrical membrane thickenings and which were identified in normal material; exact identification is impossible as the degenerating profiles are shrunken. Terminals making multiple axospinous synaptic contacts have not been seen after lesions in the cerebral cortex or thalamus alone. However, these large terminals are rare and may be confused with small terminals unless they are sectioned across their widest point and so, though present, may not have been identified after the selective lesions.

Lesions in the contralateral cerebral cortex

In accord with the earlier evidence from light microscopical examination of experimental material (Carman *et al.* 1965) the degeneration in the caudate nucleus after a lesion in the contralateral cerebral cortex is limited to the dorsolateral quadrant of the head of the nucleus and is considerably less dense than after either of the other lesions. Degenerating myelinated and non-myelinated fibres are present as well as degenerating axon terminals. The latter have contact regions with asymmetrical membrane thickenings. The degenerating terminals contact spines of medium spiny cells (figure 10, plate 69) and of dendrites with conspicuous neurotubules and small mitochondria. There are few degenerating axodendritic endings, and these may be in contact with medium spiny dendrites and dendrites with well-marked neurotubules and small mitochondria. Any of these degenerating terminals may be *en passant* (figure 12, plate 69). Though isolated degenerating terminals are found they are also commonly seen in small widely separated groups. Each of the groups may contain two or three darkened processes in close proximity to one another (figure 10, plate 69), Such groups are more obvious than after either of the other lesions and this may be due to the sparseness of the degeneration.

Lesions in the midbrain

The lesions in the midbrain were large and varied in extent and position in different experiments. In the antero-posterior dimension they were situated between the posterior end of the inferior colliculus and the anterior third of the superior colliculus. Mediolaterally they involved principally either the midbrain tegmentum, red nucleus and the ventral part of the

substantia nigra, or, more laterally, the dorsolateral part of the substantia nigra, the brachium of the inferior colliculus and the adjoining medial geniculate nucleus. In several experiments an attempt was made to place a *large* lesion confined within the limits of the substantia nigra. Although the direct electrolytic damage in these brains was found to be restricted to the substantia nigra there was also a variable extent of ischaemic necrosis of the overlying tegmentum due to involvement of the blood vessels which traverse the site of damage. It is certainly possible to place *small* lesions within the substantia nigra, suitable for light microscopical axonal degeneration studies, but, because of the small amount of degeneration in the thin sections of the striatum used for electron microscopy it was not considered practicable to search for degeneration after such lesions. For these reasons no attempt has been made in the present investigation to differentiate between a projection to the striatum from the midbrain tegmentum or from the substantia nigra.

The degeneration resulting from these large lesions of the midbrain is very sparse and though fairly widespread in the caudate nucleus tends to be a little more dense near the ventrolateral margins. Degenerating thinly myelinated fibres of about 0.75 to 2 μm in diameter (figure 19, plate 70) are present, but there are many fewer than after any of the lesions previously described. The degenerating terminals all form synapses with asymmetrical membrane thickenings and some of the terminals are *en passant* (figure 11, plate 69). These terminals are most commonly found in contact with spines (figures 11 and 13, plate 69) though whether these arise from medium spiny cells alone or from cells of other types is not known as the spines have not been seen in continuity with identifiable dendrites. Some degenerating terminals are in contact with the dendrites of medium spiny cells. There is no evidence of grouping of degenerating terminals after damage to the midbrain in contrast to the arrangement seen after the other lesions.

Lesions in the caudate nucleus

As all the known extrinsic fibres to the caudate nucleus terminate with asymmetrical membrane thickenings and the normal nucleus contains a significant proportion of terminals with symmetrical membrane thickenings the latter, by inference, should be intrinsic. In order to confirm this hypothesis, small lesions were placed in the caudate nucleus, and tissue immediately adjacent and 2 and 3 mm away from the lesion was examined.

An important and novel feature of the degeneration after an intrinsic lesion of the caudate nucleus is the presence of degenerating terminals with symmetrical membrane thickenings as well as some with asymmetrical contact regions. The majority of the darkened endings with symmetrical membrane thickenings are in contact with the shafts of dendrites of medium spiny cells and dendrites with conspicuous neurotubules and small mitochondria (figure 22, plate 71), though some also contact the spines arising from these dendrites, main stem dendrites (figure 21, plate 71) and cell somata (figure 23, plate 71). They are also present on the initial segments of axons (figure 20, plate 71). The total density of the degeneration is similar to that seen after a lesion in the cerebral cortex.

Sections have been taken which are about 1 mm long and include a small part of the lesion at one end together with an undamaged part of the nucleus. The distribution of the terminals with symmetrical and asymmetrical membrane thickenings was plotted on a map of the section (figure 1). While the dark endings with asymmetrical membrane thickenings are distributed throughout the section, those with symmetrical contact regions are found only within a distance of about 450 μm of the damaged part of the nucleus. These endings show some evidence of

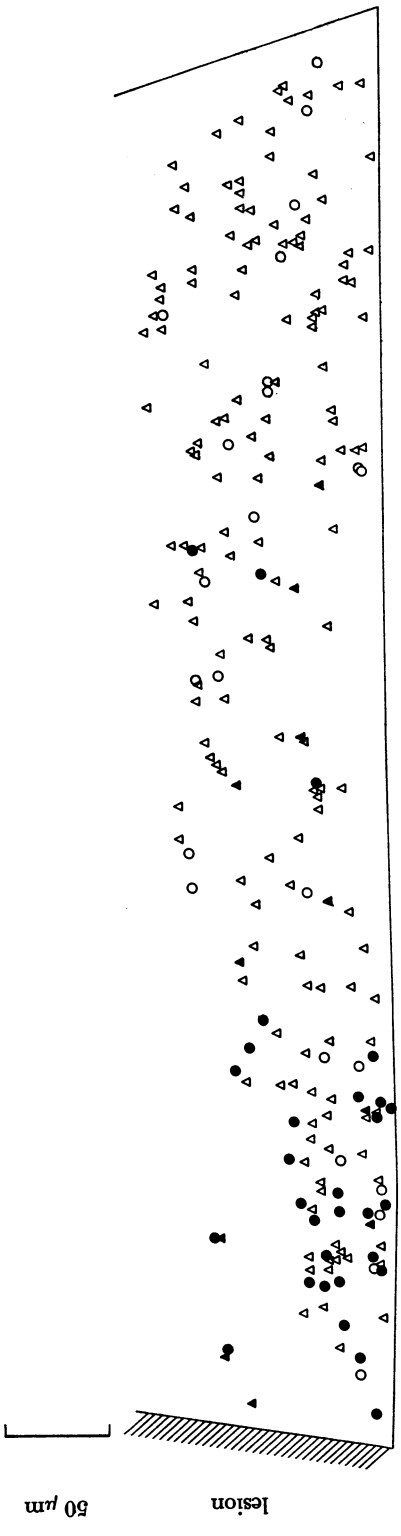


FIGURE 1. Map of the distribution of degenerating axon terminals of different types over a distance of 1 mm from a small lesion within the head of the caudate nucleus. △, axospinous asymmetrical; ○, axodendritic and axosomatic asymmetrical; ▲, axospinous symmetrical; ●, axodendritic and axosomatic symmetrical.

forming clusters (figure 1). The site of termination of endings with asymmetrical membrane thickenings did not seem to differ from that seen after any of the extrinsic lesions.

The globus pallidus and substantia nigra were also examined after lesions in the caudate nucleus in an attempt to determine the mode of termination of the efferent fibres from the caudate nucleus. A systematic study of the structure and connexions of the globus pallidus and substantia nigra has not been done as part of this investigation, and only those findings relevant to the interpretation of the observations upon the intrinsic organization of the striatum will be mentioned. Several brief reports of certain aspects of the ultrastructure of the globus pallidus and substantia nigra have already appeared (Fox, Hillman, Siegesmund & Sether 1966; Mori 1965, 1966; Bak 1967; Adinolfi 1969*a*, *b*; Rinvik & Walberg 1969; Schwyn & Fox 1969; Kemp 1970) and recently a detailed account of the substantia nigra by Rinvik & Grofová (1970); the present account is in essential agreement with these.

Neither of the regions has many neurons, the dendrites have few spines (figure 29, plate 74) and some of them are distinctly varicose (figure 25, plate 70). The dendrites are, however, studded with axon terminals making synaptic contact (figures 24 and 26, plates 72 and 73), and the whole complex is ensheathed with glia. The majority of the terminals contain vesicles which are smaller than the large polymorphic ones in the caudate nucleus which are associated with symmetrical membrane thickenings but are not flattened like the small ones in the caudate nucleus. A few of the endings with symmetrical membrane thickenings contain smaller vesicles, but the size difference between these and the larger ones is not as striking as between the large and small vesicles in terminals with symmetrical membrane thickenings in the caudate nucleus. A small proportion of the axon terminals contain round vesicles and their synaptic thickenings are asymmetrical (figure 31, plate 74). Dense core vesicles of around 100 nm are commonly found in all types of terminal. In both the substantia nigra and the globus pallidus a few examples of serial synapses have been seen (figures 27 and 28, plate 73). In both these regions the first synapse has asymmetrical membrane thickenings and the second has a symmetrical thickening associated with polymorphic vesicles which are smaller than those in the majority of terminals with this type of synaptic thickening.

After a lesion in the caudate nucleus severe degeneration is found in both the globus pallidus and the substantia nigra. After a survival period of 4 days there is a great range in the appearance of the degeneration (figure 32, plate 75); the majority of the degenerating terminals are dark but are not very shrunken and the vesicles can still be seen within them (figures 32 to 35, plate 75); some are at an earlier stage while others are more advanced and are grossly shrunken, with the vesicles not discernible, and are partially engulfed in glia. The degeneration in the globus pallidus is particularly dense and several degenerating terminals can be seen in contact with dendrites both in longitudinal and transverse section (figure 35, plate 75). In both structures the dark terminals form symmetrical synaptic thickenings in contact with dendrites and cell bodies. In one brain in which white matter had been involved by the lesion there is an occasional ending with asymmetrical membrane thickenings.

Discussion

The appearance of the degeneration in the caudate nucleus after lesions involving different pathways, or damage to the nucleus itself, does not seem to be different from that seen in a number of other regions of the brain (Colonnier & Gray 1962; Walberg 1964; Westrum 1966; Alksne *et al.*

1966; Jones & Powell 1970). Though the degenerative change is quite advanced after 4 days survival many more degenerating profiles are seen after 6 days, but at this stage the degenerating terminals are either so dark or attenuated that it is difficult to distinguish certain terminals from preterminal fragments. After shorter survivals very few terminals are seen showing the early stages, suggesting that the onset of the visible changes is rapid. The enlargement of the vesicles appears to be an important criterion in the establishment of early degeneration and confirms the observations of other workers (Pinching 1969; Cuénod *et al.* 1970).

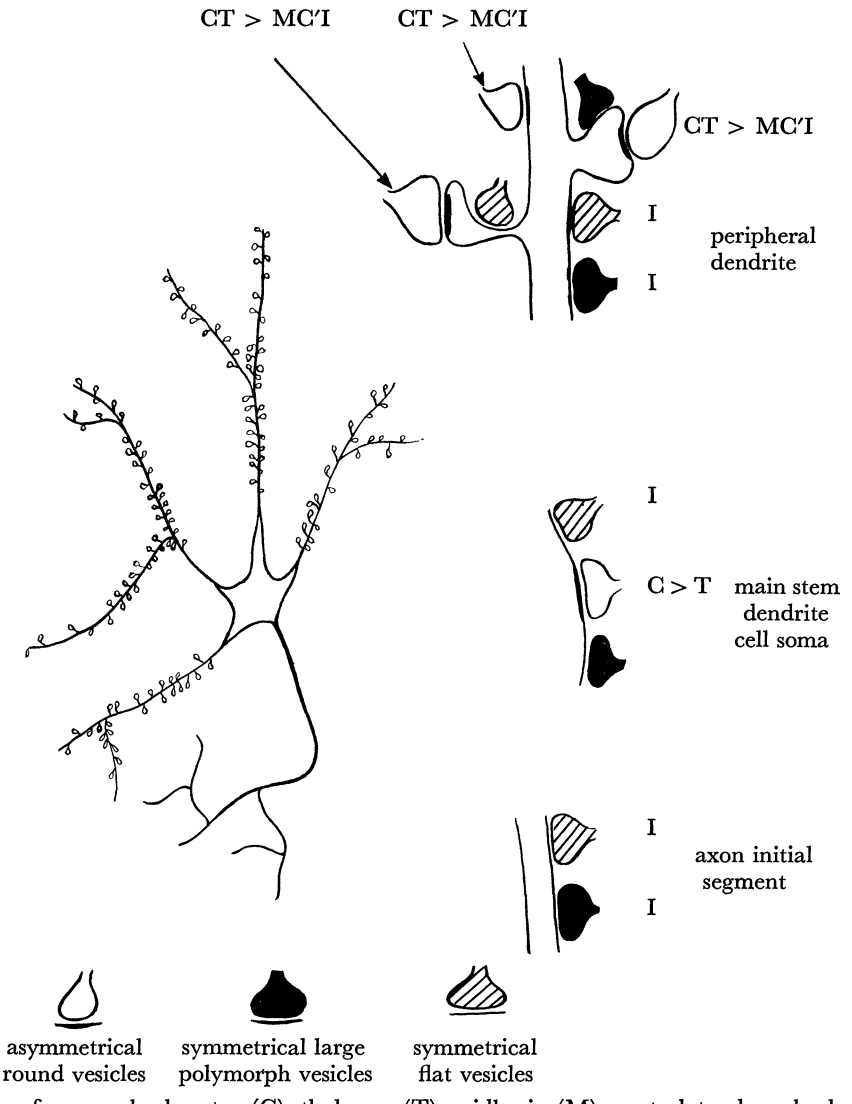
Estimates of the percentage of terminals degenerating after lesions in the cerebral cortex and thalamus were attempted but the results were considered to be unreliable. In the first place it is not possible to be certain that all the fibres from either area have been interrupted, and this is particularly so in regard to the fibres from the thalamus to the striatum. Further difficulty arises from the spread in the time course of the degeneration as discussed above. Finally, terminals from both areas are in groups so that in order to obtain a reliable estimate of the size of the projection to the caudate nucleus from either source very extensive counts would be required.

Comparison of the density of the degeneration after damage to the different pathways to the striatum indicates that the largest projection probably arises from the cerebral cortex, is less from the thalamus and is small from the contralateral cerebral cortex and midbrain (figure 2). Bearing in mind the qualifications mentioned in the previous paragraph, about 30 to 40 % of the terminals with asymmetrical membrane thickenings could arise in the cerebral cortex and about 20 to 25 % in the thalamus. The projections from the contralateral cerebral cortex and midbrain almost certainly represent only a few per cent of the total asymmetrical contacts. This suggests that slightly less than half of the asymmetrical contacts in the caudate nucleus may arise from the intrinsic cells of the nucleus. A direct estimate of the number of these is not possible as lesions within the caudate nucleus inevitably interrupt fibres entering from the internal capsule or subcallosal fasciculus and which are passing to regions beyond the damaged area.

Most of the degenerating terminals with asymmetrical synapses seem to be of the small variety. Identification of the large type of terminal is difficult, as the affected profiles shrink, but they can be recognized with reasonable certainty if they contact a number of spines. Degenerating terminals of this type have been seen after a combined lesion of the cerebral cortex and thalamus indicating that such terminals arise from cells outside the caudate nucleus in either or both of these areas. In normal material the number of large terminals is not sufficient to account for the entire projection from either the cerebral cortex or the thalamus and so the small terminals must certainly arise from cells in both areas. One possible origin for the large terminals could be a different variety of cell situated in either region. On the other hand, it is possible that they might originate from the same cells as the small terminals. There is some evidence from Golgi impregnated material and from electron microscopy that all small terminals may be *en passant* and such terminals have been seen degenerating after lesions in the cortex or thalamus. Large terminals may also be *en passant* and so could lie in series with small terminals along the same non-myelinated axon.

Following lesions in the thalamus two phases of degeneration with apparently the same region of termination seemed to be present in the caudate nucleus. One of these was past its peak at 3 days survival while the other was approaching a similar stage 6 days after the operation. If this difference in the rate of degeneration is a reflexion of two groups of fibres it would suggest that there may either be two regions in the thalamus projecting to the same site within the

caudate nucleus or that the projection from the intralaminar nuclei is both by direct fibres and collateral branches. Another explanation is possible in view of the recent report of Miledi & Slater (1970) that the rate of degeneration of the nerve terminals at muscle endplates in the rat diaphragm is directly related to the length of the degenerating peripheral nerve stump. The intralaminar nuclei extend over a large part of the antero-posterior extent of the thalamus and



Terminals of fibres from cerebral cortex (C), thalamus (T), midbrain (M), contralateral cerebral cortex (C'), intrinsic cells (I).

FIGURE 2. Schematic figure to show the site and mode of termination, and the relative proportions, of the main afferent and intrinsic fibres of the caudate nucleus upon the medium spiny cell of this nucleus.

therefore the fibres from the more anterior of these nuclei are shorter than those from the more posteriorly placed. If the rate of degeneration in the central nervous system is similar to that in the periphery the terminals of the fibres from the anterior parts of the intralaminar system may degenerate more rapidly than the remainder.

Degeneration of terminals with symmetrical membrane thickenings is seen only after a lesion in the caudate nucleus and clearly indicates that both types of symmetrical terminal arise from

cells within the nucleus. The fact that the terminals in the globus pallidus and substantia nigra, which arise from the caudate nucleus, also have symmetrical contacts indicates that one or both of the cells in the caudate nucleus with long axons are the source of some, if not all, of the terminals of this type within the nucleus. Since the long axon cells of the caudate nucleus have collateral branches terminating within the nucleus, it is surprising that the vesicles in the terminals with symmetrical contacts in the caudate and terminals with this type of contact in the globus pallidus and substantia nigra in the same brains are not similar; the majority of the terminals in the substantia nigra and globus pallidus have vesicles which are slightly smaller than the large polymorphic vesicles in the caudate nucleus. This may be due to a difference in the site of the nuclei and the effect of a difference in diffusion times of the fixative to the more deeply situated structures.

It seems unlikely that the giant cell and the medium-sized long axon cell, which are probably the origin of the fibres to the globus pallidus and substantia nigra, are the only source of terminals with symmetrical contacts which form as much as 10 % of the total number of terminals in the caudate nucleus, for the collateral branches associated with these cells are not profuse. Furthermore, these cells form a very small proportion of the total. It has not been possible to identify the terminals of any other cell type even with this degree of certainty.

A further problem is the identification of the cell of origin of those intrinsic fibres of the caudate nucleus which terminate with asymmetrical membrane thickenings. That such fibres exist is indicated by the findings in experiments with combined lesions of the cerebral cortex and thalamus that a considerable number of terminals with asymmetrical membrane thickenings persist unchanged, and that these cannot be accounted for by projections from the contralateral cerebral cortex and midbrain. Furthermore, it is probable that these asymmetrical terminals of intrinsic fibres are greater in number than the terminals with symmetrical membrane thickenings. It would appear, on the basis of the available evidence, that the common medium spiny cell is a likely candidate as this cell is the most numerous type and has a profuse collateral plexus.

Though the maps showing the distribution of the symmetrical contacts in relation to a lesion in the nucleus show that the degeneration has a limited distribution, it is rather more widespread than might have been expected, extending about 450 μm from the lesion. Study of normal Golgi impregnated material has shown that the collateral plexus of most cell types does not extend beyond the dendritic field of the parent cell, which is about 250 to 300 μm from the cell body. One possible explanation for the discrepancy may be that the measurements have been made on two kinds of material which, though fixed by the same procedure, subsequently received different treatment. Another possibility is that in the Golgi material the terminal parts of very fine axons are not readily impregnated, and consequently the full extent of the collateral branches of the intrinsic cells is not seen. Furthermore, some of the very fine fibres may arise as branches from the nodal regions of the myelinated fibres of long axon cells.

The suggested correlation between round vesicles in terminals with asymmetrical membrane thickenings and excitation and flat vesicles in terminals with symmetrical membrane thickenings with inhibition has some support from electrophysiological studies made on the caudate nucleus. Both intracellular and extracellular recordings from units in the caudate nucleus after stimulation of the cerebral cortex or thalamus (Rocha-Miranda 1965; Sedgwick & Williams 1967; Purpura & Malliani 1957; Vernon, Hull, Bernardi & Buchwald 1969) have shown that the earliest response is frequently excitatory in the form of an EPSP, which may or may not have

superimposed spikes. These observations can be related to those in the present study, which show that the afferent fibres from these sources terminate with asymmetrical membrane thickenings, which, by reference to the normal, contain round vesicles. The latencies of these responses suggest that the fibres are of fine calibre and conduct at approximately 2 m/s (Rocha-Miranda 1965; Sedgwick & Williams 1967) which is supported by the anatomical findings that the degenerating fibres after extrinsic lesions are of the order of 0.5 to 2 μm in diameter. Inhibitory responses have also been shown after stimulation of the cerebral cortex (Rocha-Miranda 1965) by a decrease in the frequency of the spikes or by long-lasting hyper-polarization of the neurons (Vernon *et al.* 1969) which follows the EPSP. A sequence of an EPSP followed by an IPSP is also seen after stimulation of the thalamus (Purpura & Malliani 1967; Vernon *et al.* 1969). These longer latency inhibitory effects could be due to activation of neurons situated within the nucleus which have an inhibitory effect on the cells from which the recording is being made. It is significant that neurons giving rise to axons with terminals which have flat vesicles or large polymorphic vesicles, both of which are associated with symmetrical membrane thickenings, are known to be present in the caudate nucleus in contact with all cell types and they may be the basis of the inhibitory effects.

The available evidence suggests that there may be two pathways to the striatum from the midbrain, from the substantia nigra (Andén *et al.* 1964; Frigyesi & Purpura 1967; Connor 1968; Hökfelt & Ungerstadt 1969) and the midbrain tegmentum (Nauta & Kuypers 1957). The present study has not differentiated between these two projections; that from the midbrain tegmentum has certainly been involved and possibly also the projection from the substantia nigra. It is interesting that all the degenerating endings found after large lesions in the midbrain terminated with asymmetrical membrane thickenings so that if fibres from both regions were interrupted it seems likely that they would have similar effects upon striatal neurons. The results of stimulating the substantia nigra and recording from units in the caudate nucleus have been equivocal (Frigyesi & Purpura 1967; Connor 1968). Frigyesi & Purpura recorded long latency excitatory effects while Connor found predominantly inhibitory effects, though he also found a few units with shorter latency which were facilitated by nigral stimulation. Further work is required, however, to clarify the anatomical problems associated with the projection of the midbrain upon the striatum (see Mettler 1970).

Though the strio-pallidal (Kemp 1970) and strio-nigral (Kemp 1970; Grofová & Rinvik 1970) fibres terminate with symmetrical contacts, correlation with the physiological findings is less easy. Malliani & Purpura (1967) found predominantly inhibitory effects on cells of the entopeduncular nucleus of the cat following stimulation of the caudate nucleus. Similar, but longer latency, effects were noticed after stimulation of the thalamus and presumably arose through the activation of the cells of the caudate which in turn send their axons to the entopeduncular nucleus. On the other hand, Frigyesi & Purpura (1967) found predominantly excitatory influence on the cells of the substantia nigra from the caudate nucleus. Since the globus pallidus and substantia nigra both receive axons which end in symmetrical membrane thickenings it is surprising that the efferent fibres to these two regions have apparently different effects. Whether these findings are evidence of a failure of the correlation of the morphology of the axon terminal with its functional effects or that the recordings were made from an area of the substantia nigra which does not receive a direct projection from the striatum cannot be ascertained. However, if the correlation of morphology and function should be correct, that terminals with symmetrical membrane thickenings have inhibitory effects, the

finding that the strio-pallidal and strio-nigral fibres end with this type of thickening would be further evidence to that for the Purkinje cell (Eccles, Ito & Szentagothai 1967) and the vestibulospinal projection (Wilson & Yoshida 1969) that neurons with long axons may be inhibitory.

The fibres of the collateral plexus of the caudate nucleus are arranged so that the axons cross from one dendrite to another and do not lie parallel to them. The afferent fibres to the nucleus, which form part of this plexus, are therefore arranged in a very different way from those in the globus pallidus. Fox *et al.* (1966) have shown that the long pallidal dendrites are ensheathed in axons which lie parallel to them and electron microscopy shows that the dendrites are studded with terminals (Fox *et al.* 1966; Adinolfi 1969*a*; Kemp 1970). Many of these terminals arise from the same source for some pallidal dendrites are surrounded by degenerating terminals after lesions in the caudate nucleus. This comparison of the arrangement of the terminals in the caudate nucleus and globus pallidus may be considered further. Although in both nuclei there is clearly convergence of afferent fibres onto relatively few cells, it would appear that there are distinct differences in the internal organization of the constituent cells of these structures. Thus in the caudate nucleus afferent fibres from sources as different as the neocortex, thalamus and midbrain all appear to terminate in relation to several types of cells in any particular part of the nucleus. As only a small proportion of these cells are the source of efferent fibres from the nucleus, however, it would follow that there is a considerable degree of integration by the interneurons. In the globus pallidus the available evidence suggests that the numerous afferents from adjoining parts of the striatum converge upon the same type of long axon cell, but whether there is also further interaction by interneurons, as in the caudate nucleus, remains to be investigated.

An interesting pattern has emerged from a study of the overall arrangement of the terminals from the cerebral cortex and thalamus. After lesions in either area the terminals appear to be arranged in clusters and in view of the observations made in the Golgi impregnated material on the arrangement of the afferent fibres to the nucleus (Cajal 1911; Kemp & Powell 1971*a*) it is possible that these clusters are due to the branching of the incoming fibres. After a combined lesion this clustering is not so evident which suggests either that the fibres from the two regions are influencing small and discrete, neighbouring parts of the nucleus, or that the greater amount of degeneration has blurred the clustering. When taken in conjunction with the observations to be presented in the next paper (Kemp & Powell 1971*b*) it is probable that the second alternative is correct. It must be emphasized that these clusters of endings from either the cerebral cortex or thalamus are small compared with the total size of the dendritic field of a nerve cell.

The groups of terminals seen after an intrinsic lesion may arise from the collateral axons of single cells which have been damaged. Such a lesion affects only the terminals of axons entering the area from one side and the interstices between the groups of degenerating terminals with symmetrical membrane thickenings may be filled with terminals from the adjacent undamaged parts of the nucleus.

It should be emphasized that this electron microscope study of the termination of the fibres of the major afferent pathways to the caudate nucleus has not shown any marked difference in their mode or site of termination (figure 2). In particular it has not been possible to determine whether the fibres from the cerebral cortex and the thalamus are ending upon the same or different cells. The further elucidation of this question is the subject of the following paper.

This work was supported by grants from the Medical and Science Research Councils.

References

Adinolfi, A. M. 1969*a* The fine structure of neurons and synapses in the entopeduncular nucleus of the cat. *J. comp. Neurol.* **135**, 225–248.

Adinolfi, A. M. 1969*b* Degenerative changes in the entopeduncular nucleus following lesions of the caudate nucleus: an electron microscopic study. *Expl Neurol.* **25**, 246–254.

Alksne, J. F., Blackstad, T. W., Walberg, F. & White, L. E. 1966 Electron microscopy of axon degeneration: a valuable tool in experimental neuroanatomy. *Rev. Anat. Emb. Cell Biol.* **39**, 6–32.

Andén, N-E., Carlsson, A., Dahlström, A., Fuxe, K., Hillårp, N-Å. & Larsson, K. 1964 Demonstration and mapping out of nigro-neostriatal dopamine neurons. *Life Sci.* **3**, 523–530.

Bak, I. J. 1967 The ultrastructure of the substantia nigra and caudate nucleus of mouse and the cellular localisation of catecholamines. *Expl Brain Res.* **3**, 40–57.

Cajal, S. R. 1911 *Histologie du système nerveux de l'homme et des vertébrés*, II. Paris: Maloine.

Carman, J. B., Cowan, W. M. & Powell, T. P. S. 1963 The organization of the cortico-striate connexions in the rabbit. *Brain* **86**, 525–562.

Carman, J. B., Cowan, W. M., Powell, T. P. S. & Webster, K. E. 1965 A bilateral cortico-striate projection. *J. Neurol. Neurosurg. Psychiat.* **28**, 71–77.

Colonnier, M. & Gray, E. G. 1962 Degeneration in the cerebral cortex. In *Electron microscopy* (ed. S. S. Breese), **2**, U 3. New York: Academic Press.

Connor, J. D. 1968 Caudate unit responses to nigral stimuli: evidence for a possible nigro-neostriatal pathway. *Science, N.Y.* **160**, 899–900.

Cuenod, M., Sandri, S. & Akert, K. 1970 Enlarged synaptic vesicles as an early sign of secondary degeneration in the optic nerve terminals of the pigeon. *J. Cell Sci.* **5**, 605–613.

Droogleever-Fortuyn, J. 1953 Anatomical basis of cortico-subcortical interrelationships. *Third International EEG Congress Symposia*, pp. 149–162.

Eccles, J. C., Ito, M. & Szentagothai, J. 1967 *The cerebellum as a neuronal machine.* Berlin: Springer.

Fox, C. A., Hillman, D. E., Siegesmund, K. A. & Sether, L. A. 1966 The primate globus pallidus and its feline and avian homologues: a Golgi and electron microscopic study. In *Evolution of the forebrain* (ed. R. Hassler and H. Stephan), pp. 237–248. Stuttgart: Georg Thieme Verlag.

Frigyesi, T. L. & Purpura, D. P. 1967 Electrophysiological analysis of reciprocal caudato-nigral relations. *Brain Res.* **6**, 440–456.

Grofová, I. & Rinvik, E. 1970 An experimental electron microscopic study on the striatonigral projection in the cat. *Expl Brain Res.* **11**, 249–262.

Hökfelt, T. & Ungerstadt, U. 1969 Electron and fluorescence microscopical studies on the nucleus caudatus putamen of the rat after unilateral lesions of ascending nigro-neostriatal dopamine neurons. *Acta Physiol. scand.* **75**, 415–1426.

Jones, E. G. & Powell, T. P. S. 1970 An electron microscopic study of terminal degeneration in the neocortex of the cat. *Phil. Trans. R. Soc. Lond.* B **257**, 29–43.

Kemp, J. M. 1968 An electron microscopic study of the termination of afferent fibres in the caudate nucleus. *Brain Res.* **11**, 464–467.

Kemp, J. M. 1970 The termination of strio-pallidal and strio-nigral fibres. *Brain Res.* **17**, 125–128.

Kemp, J. M. & Powell, T. P. S. 1970 The cortico-striate projection in the monkey. *Brain*, **93**, 525–546.

Kemp, J. M. & Powell, T. P. S. 1971*a* The structure of the caudate nucleus of the cat: light and electron microscopy. *Phil. Trans. R. Soc. Lond.* B **262**, 383–401.

Kemp, J. M. & Powell, T. P. S. 1971*b* The termination of fibres from the cortex and thalamus upon dendritic spines in the caudate nucleus: a study with the Golgi method. *Phil. Trans. R. Soc. Lond.* B **262**, 429–439.

Malliani, A. & Purpura, D. P. 1967 Intracellular studies of the corpus striatum. II. Patterns of synaptic activities in lenticular and entopeduncular neurons. *Brain Res.* **6**, 341–354.

Mehler, W. R. 1966 Further notes on the centre median nucleus of Luys. In *The thalamus* (ed. D. P. Purpura and M. D. Yahr). New York: Columbia University Press.

Mettler, F. A. 1970 Nigrofugal connections in the Primate brain. *J. comp. Neurol.* **138**, 291–321.

Miledi, R. & Slater, C. R. 1970 On the degeneration of rat neuromuscular junction after nerve section. *J. Physiol.* **207**,507–528.

Mori, S. 1965 The electron microscope study of the corpus striatum. *Arch. Histol. Jap.* **25**, 241–256.

Mori, S. 1966 Some observations on the fine structure of the corpus striatum of the rat brain. *Z. Zellforsch. mikrosk. Anat.* **70**, 461–488.

Nauta, W. J. H. & Kuypers, H. G. J. M. 1957 Some ascending pathways in the brain stem reticular formation. In *Reticular formation of the brain. Henry Ford Hospital Symposium*, pp. 3–30. Boston: Little Brown.

Nauta, W. J. H. & Mehler, W. R. 1969 Fiber connections of the basal ganglia. In *Psychotropic drugs and dysfunctions of the basal ganglia* (ed. G. E. Crane and R. Gardner), pp. 68–74. Public Health Service Publication 1938, Washington, D.C.: U.S. Government Printing House.

Pinching, A. J. 1969 Persistence of post-synaptic membrane thickenings after degeneration of olfactory nerves. *Brain Res.* **16**, 277–281.

Powell, T. P. S. & Cowan, W. M. 1954 The connexions of the midline and intralaminar nuclei of the thalamus of the rat. *J. Anat.* **88**, 307–319.

Purpura, D. P. & Malliani, A. 1967 Intracellular studies of the corpus striatum. I. Synaptic potentials and discharge characteristics of caudate neurons activated by thalamic stimulation. *Brain Res.* **6**, 324–340.

Rinvik, E. & Grofová, I. 1970 Observations on the fine structure of the substantia nigra in the cat. *Expl Brain Res.* **11**, 229–248.

Rinvik, E. & Walberg, F. 1969 Is there a cortico-nigral tract? A comment based on experimental electron microscopic observations in the cat. *Brain Res.* **14**, 742–744.

Rocha-Miranda, C. E. 1965 Single unit analysis of cortex-caudate connections. *Electroenceph. clin. Neurophysiol.* **19**, 237–247.

Schwyn, R. C. & Fox, C. A. 1969 A Golgi and electron microscopic study of the substantia nigra in *Macaca mulatta* and *Saimiri sciureus*. *Anat. Rec.* **163**, 342.

Sedgwick, E. M. & Williams, T. D. 1967 The response of single units in the caudate nucleus to peripheral stimulation. *J. Physiol.* **189**, 281–298.

Vernon, L., Hull, C. D., Bernardi, F. & Buchwald, N. A. 1969 Cortical and thalamic inputs to caudate neurons. *Anat. Rec.* **153**, 280.

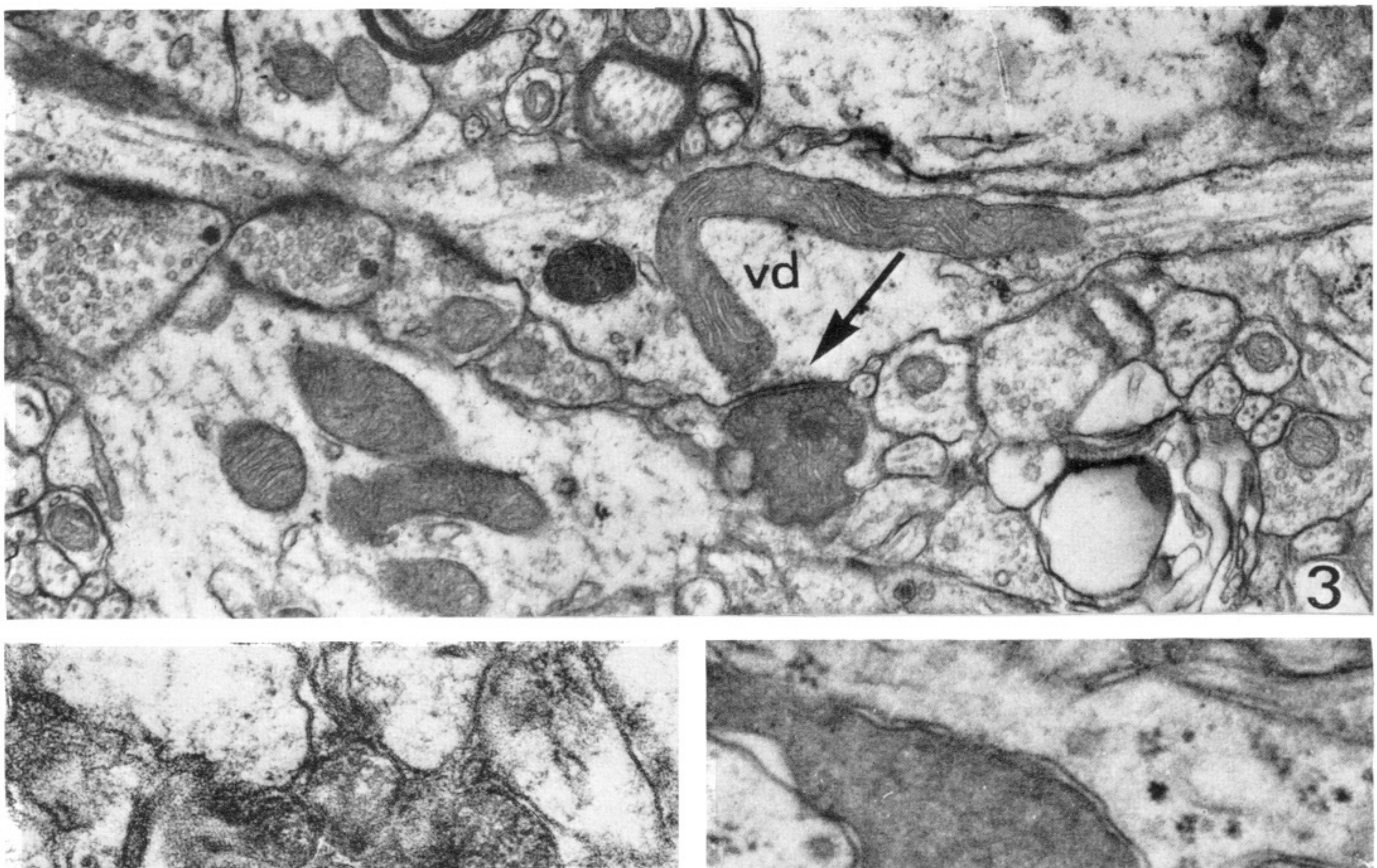
Walberg, F. 1964 The early changes in degenerating boutons and the problem of argyrophilia. Light and electron microscopic observations. *J. comp. Neurol.* **122**, 113–137.

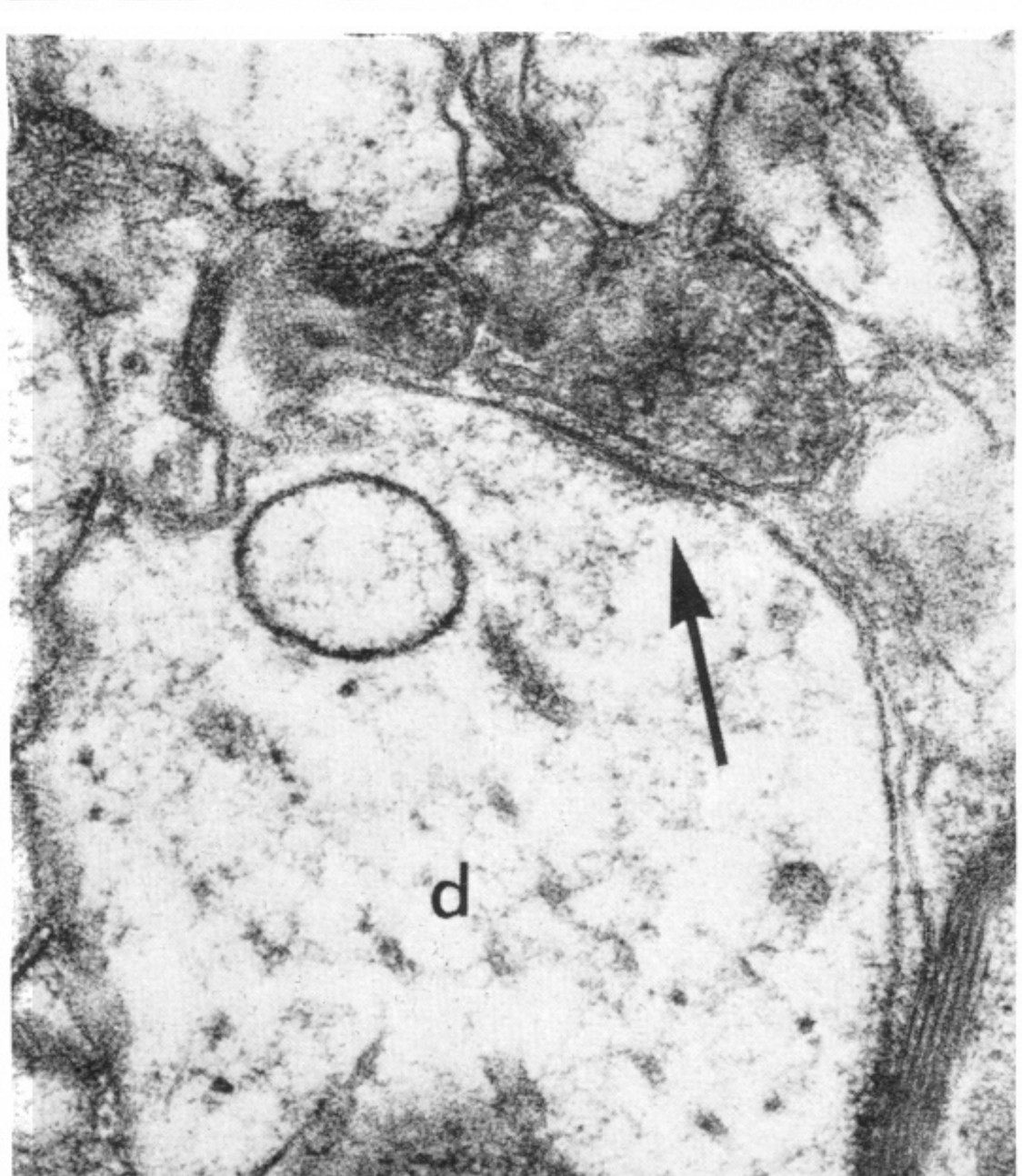
Webster, K. E. 1961 Cortico-striate interrelations in the albino rat. *J. Anat.* **95**, 532–544.

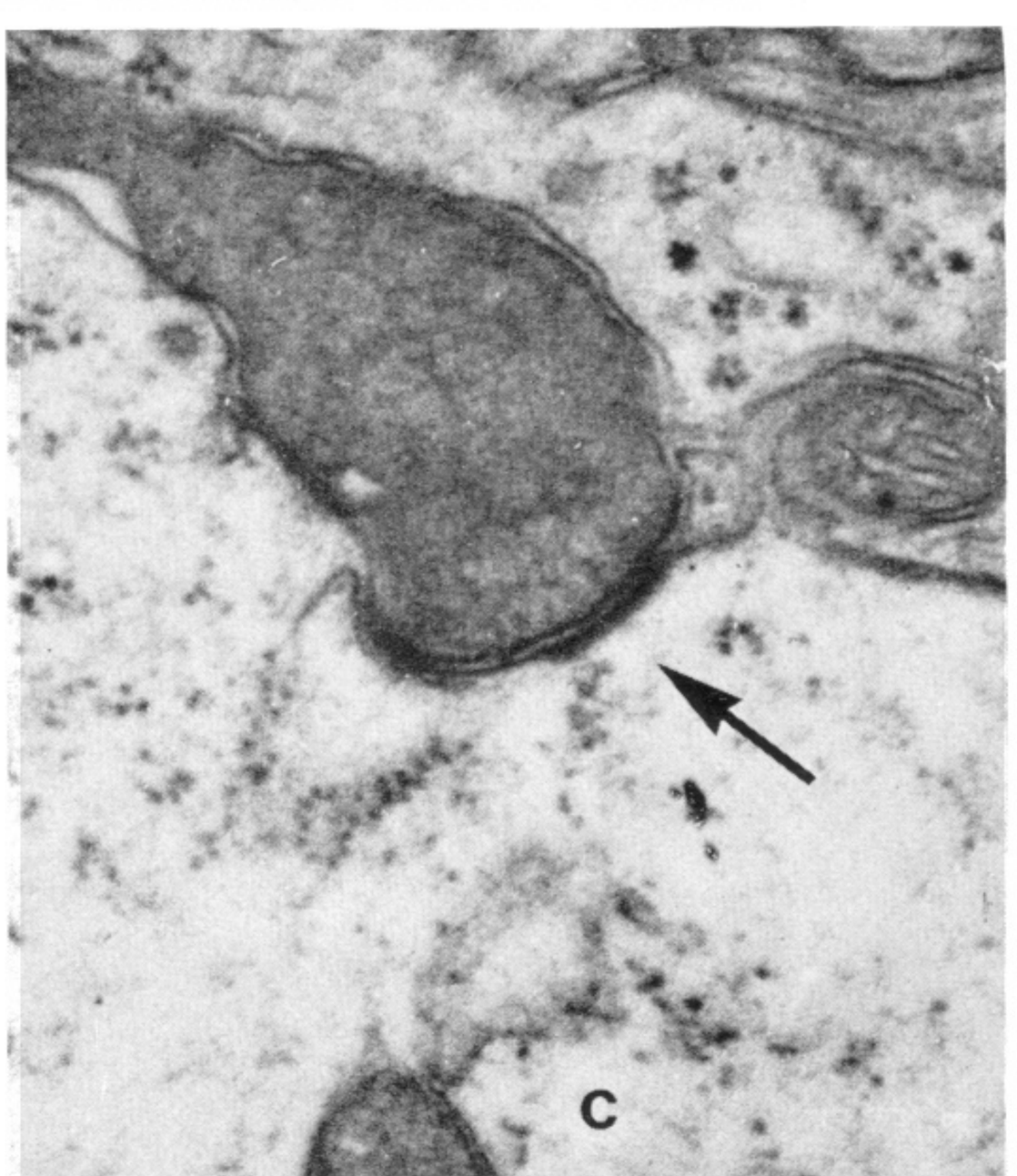
Webster, K. E. 1965 The cortico-striatal projection in the cat. *J. Anat.* **99**, 329–337.

Westrum, L. E. 1966 Electron microscopy of degeneration in the prepyriform cortex. *J. Anat.* **100**, 683–685.

Wilson, V. J. & Yoshida, M. 1969 Monosynaptic inhibition of neck motoneurons by the medial vestibular nucleus. *Expl Brain Res.* **9**, 365–380.





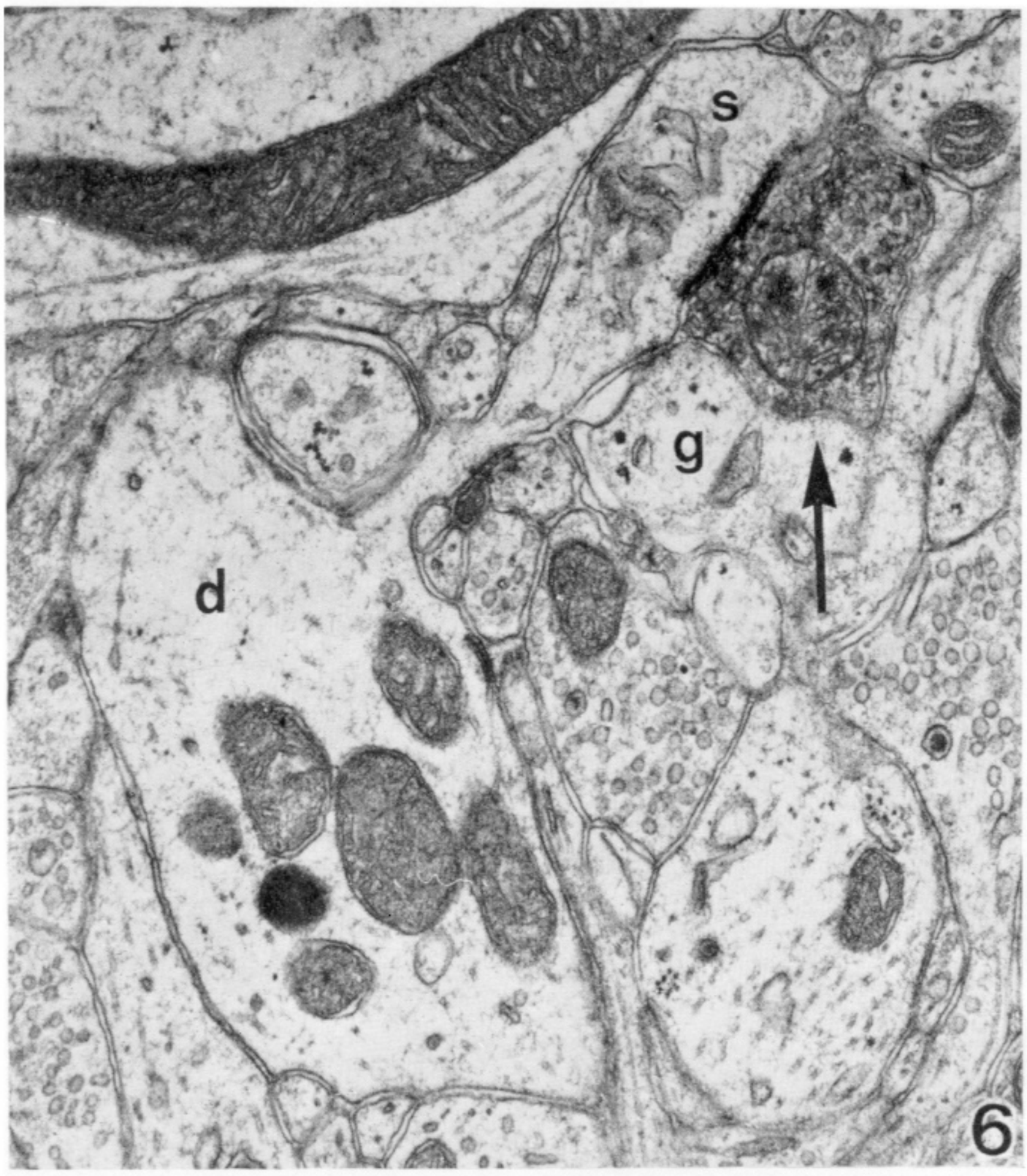


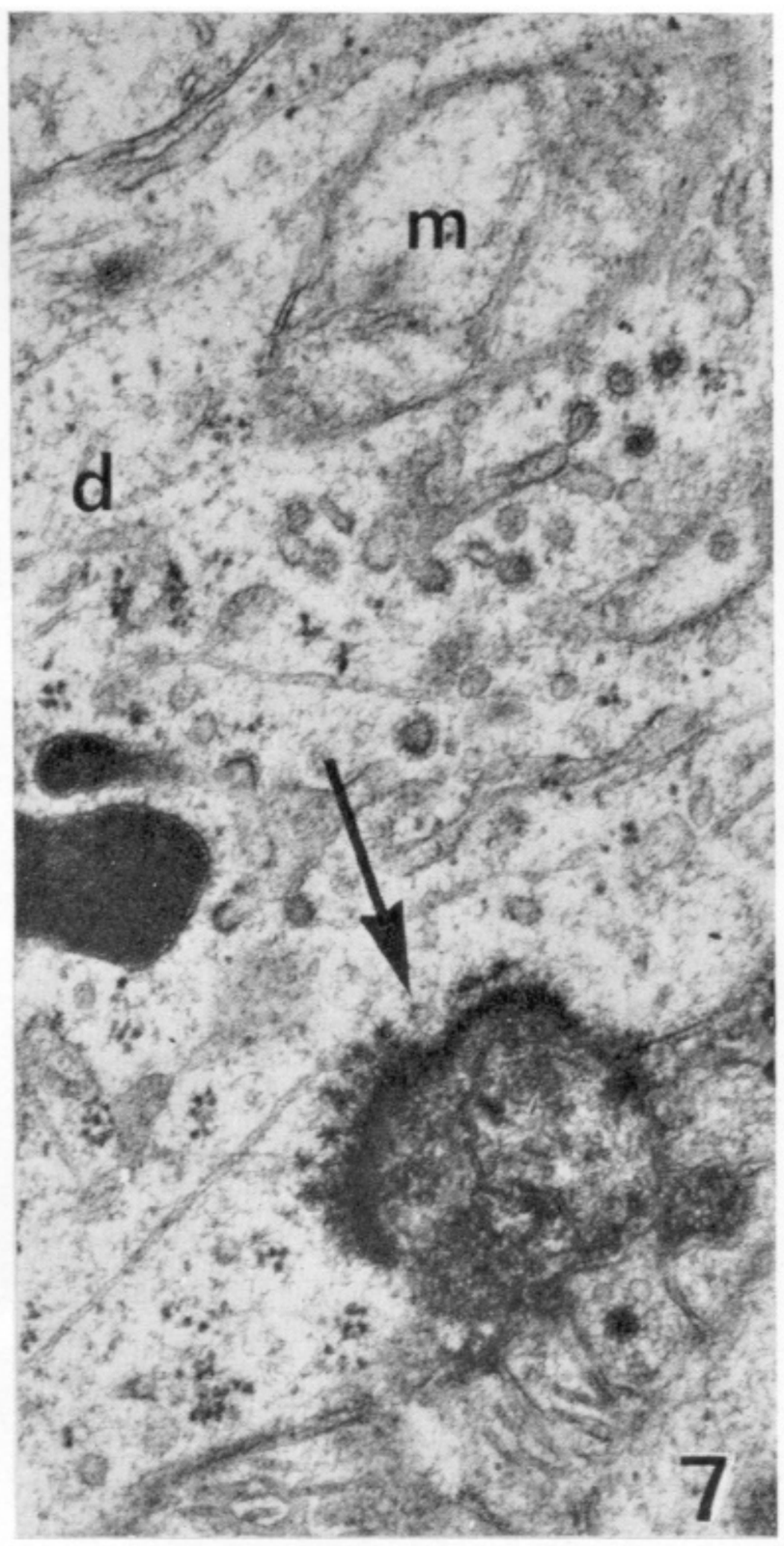
FIGURES 3 to 5. Some of the types of profiles contacted by degenerating terminals (arrows) after a lesion in the cerebral cortex.

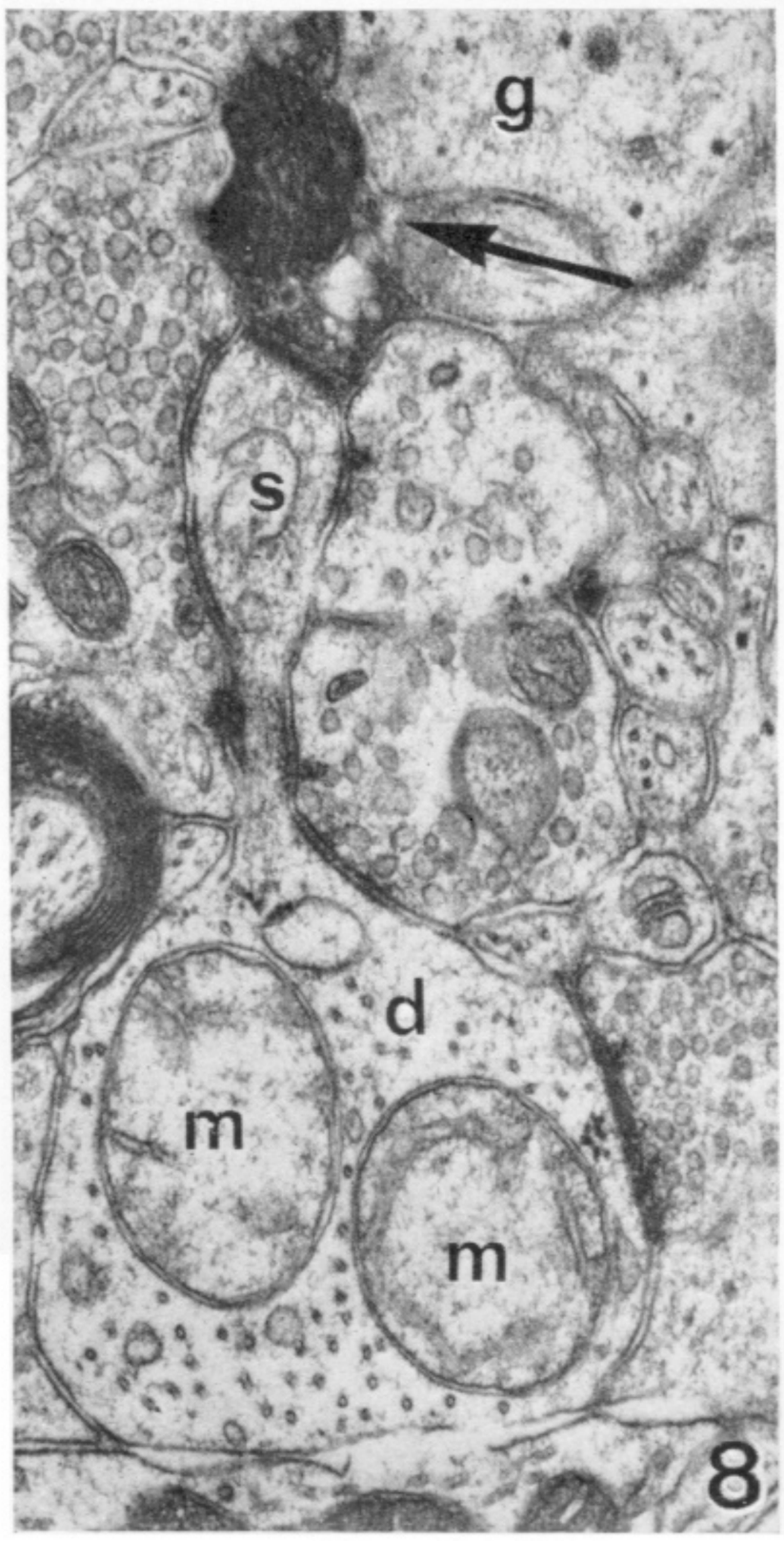
FIGURE 3. Varicose dendrite (vd). × 25000.

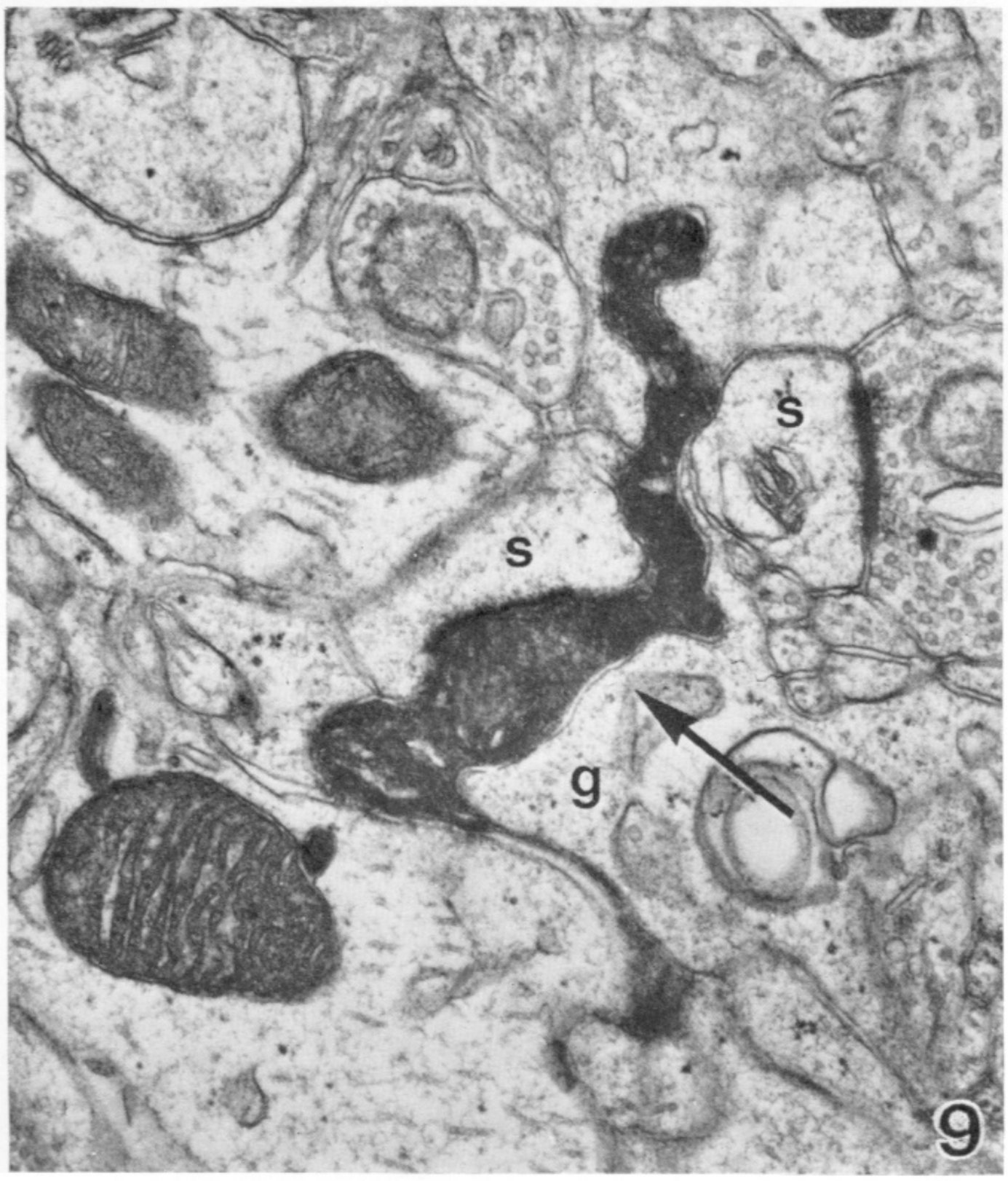
FIGURE 4. Dendrite of a medium spiny cell (d). × 80000.

FIGURE 5. Cell soma (c). × 50000. n, nucleus.









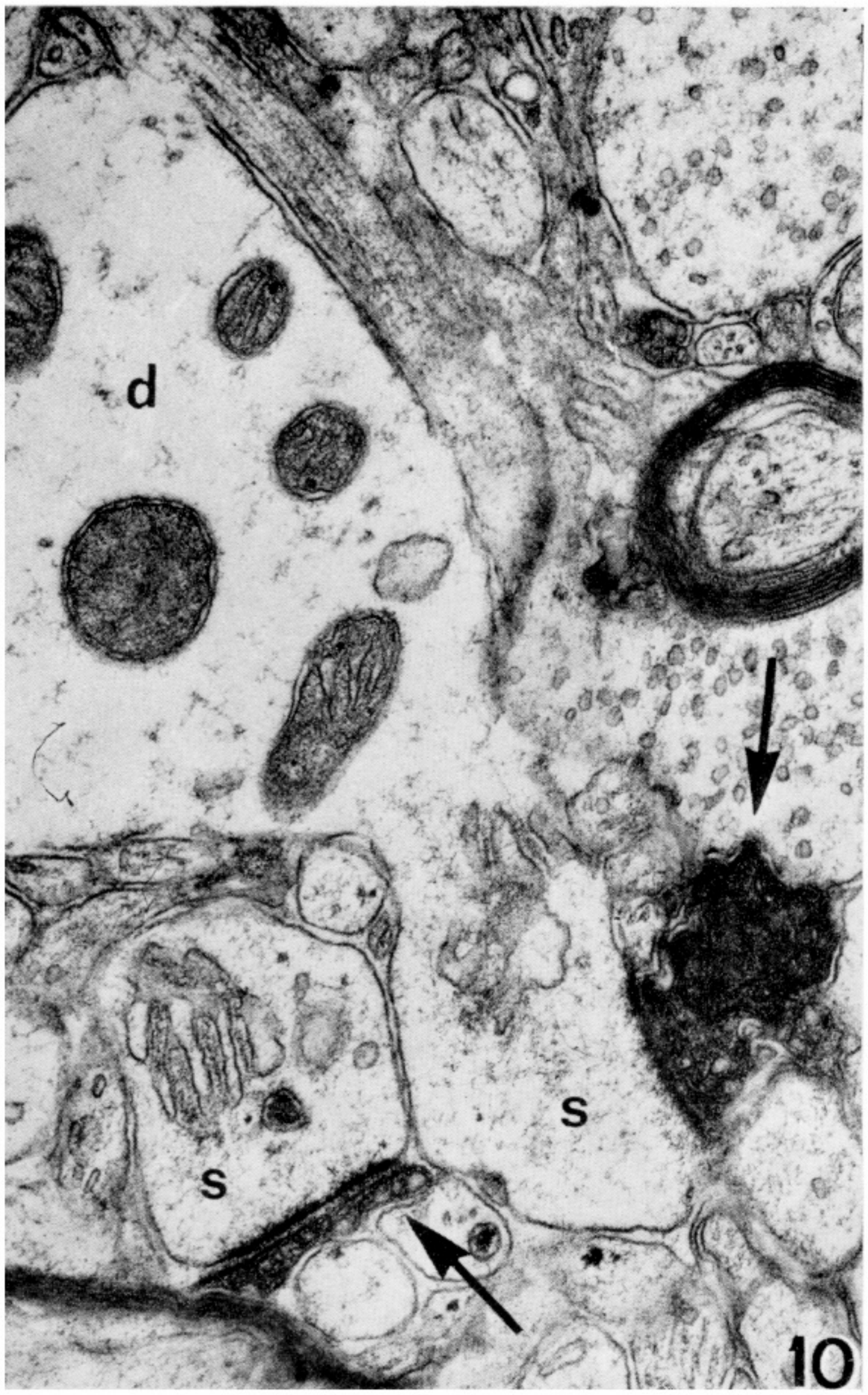
FIGURES 6 to 9. Varieties of profile contacted by degenerating terminals (arrows) after a lesion in the thalamus.

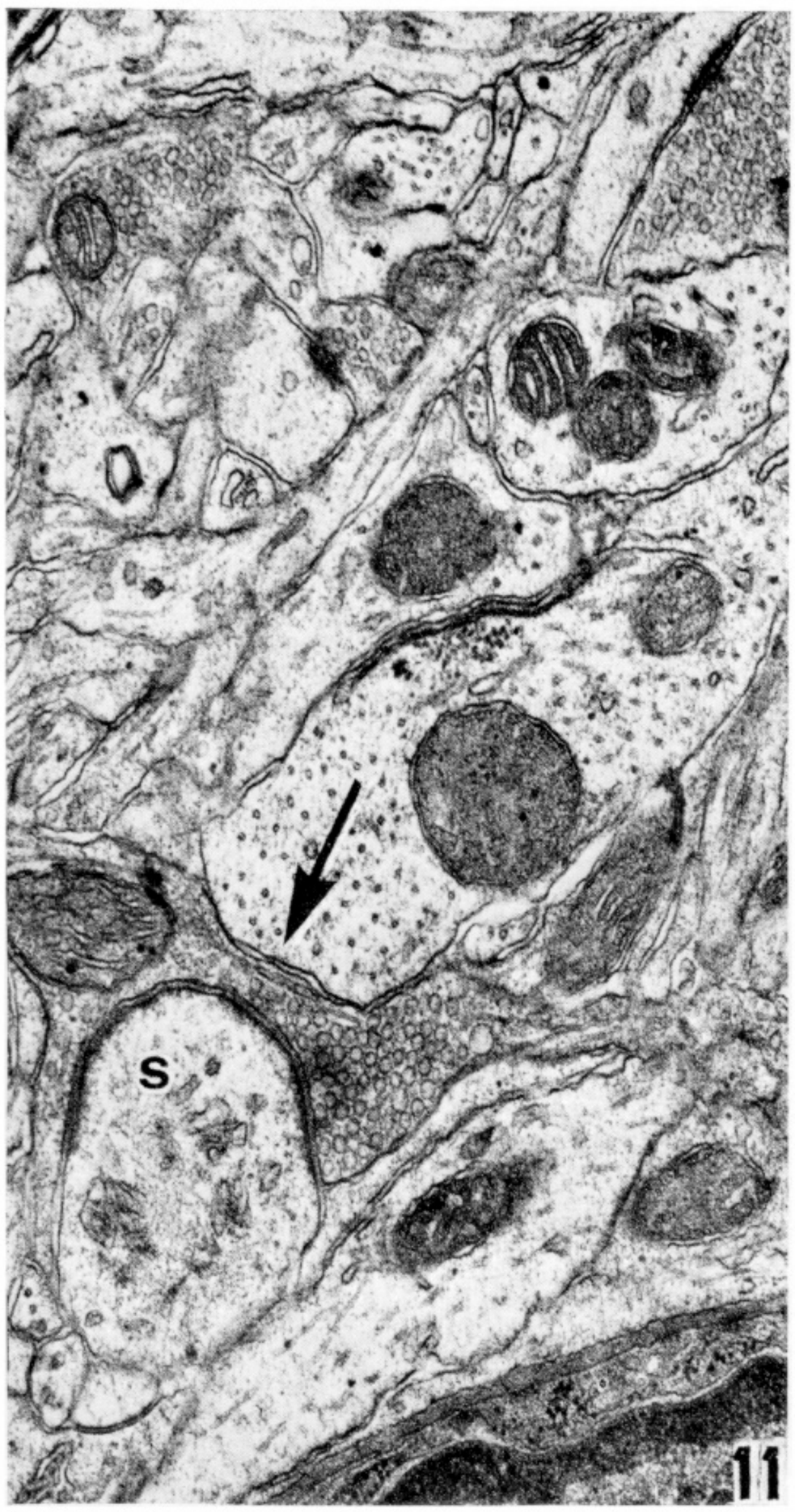
FIGURE 6. Spine (s) from the dendrite (d) of a medium spiny cell. × 30000. g, glia.

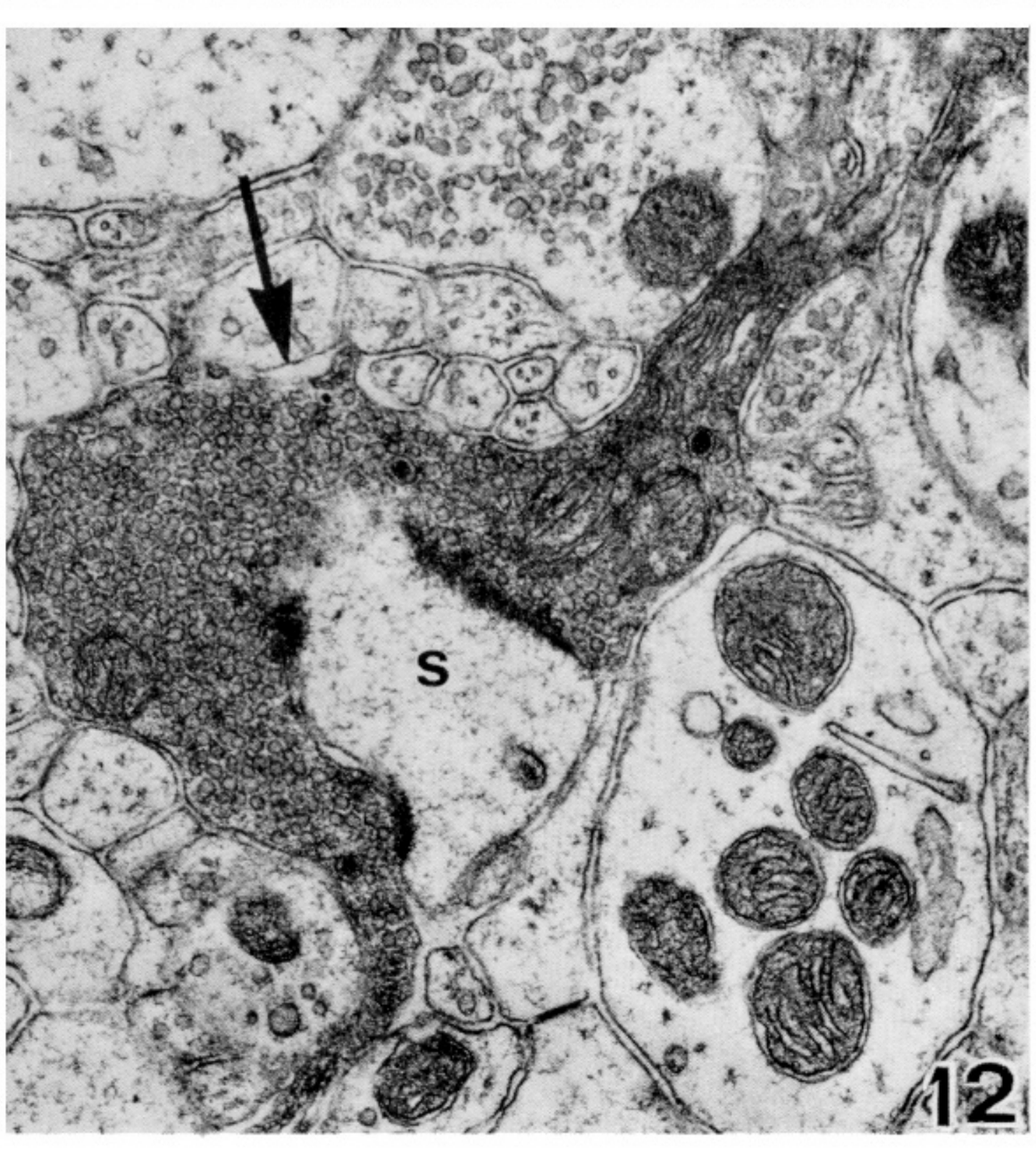
FIGURE 7. Main stem dendrite (d) of a giant cell containing pale mitochondria (m). × 40000.

FIGURE 8. Spine (s) arising from the peripheral dendrite (d) of a giant cell. Note the pale mitochondria (m). × 40,000. g, glia.

FIGURE 9. Degenerating terminal 'en passant' in contact with a spine (s). × 30000. g, glia.







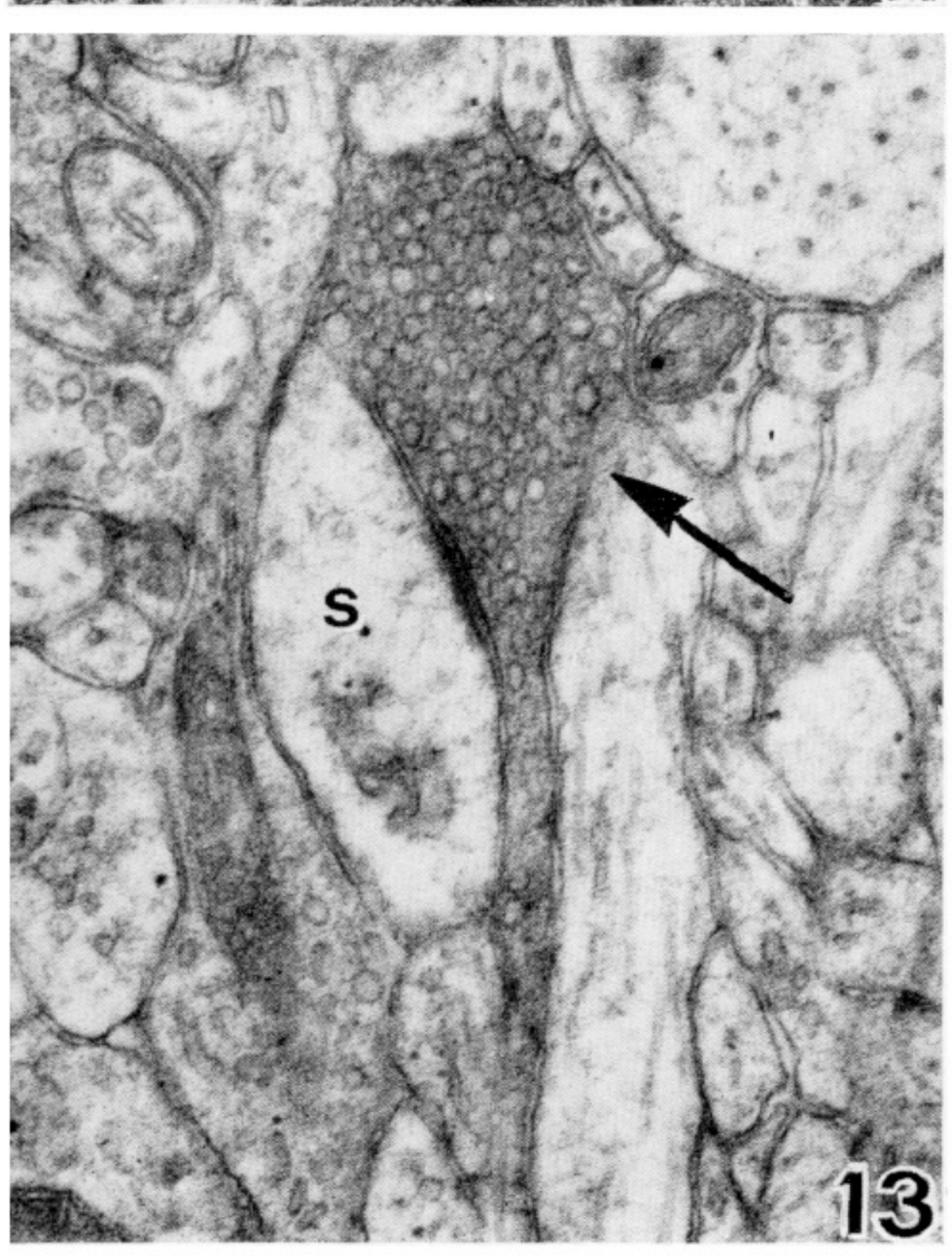
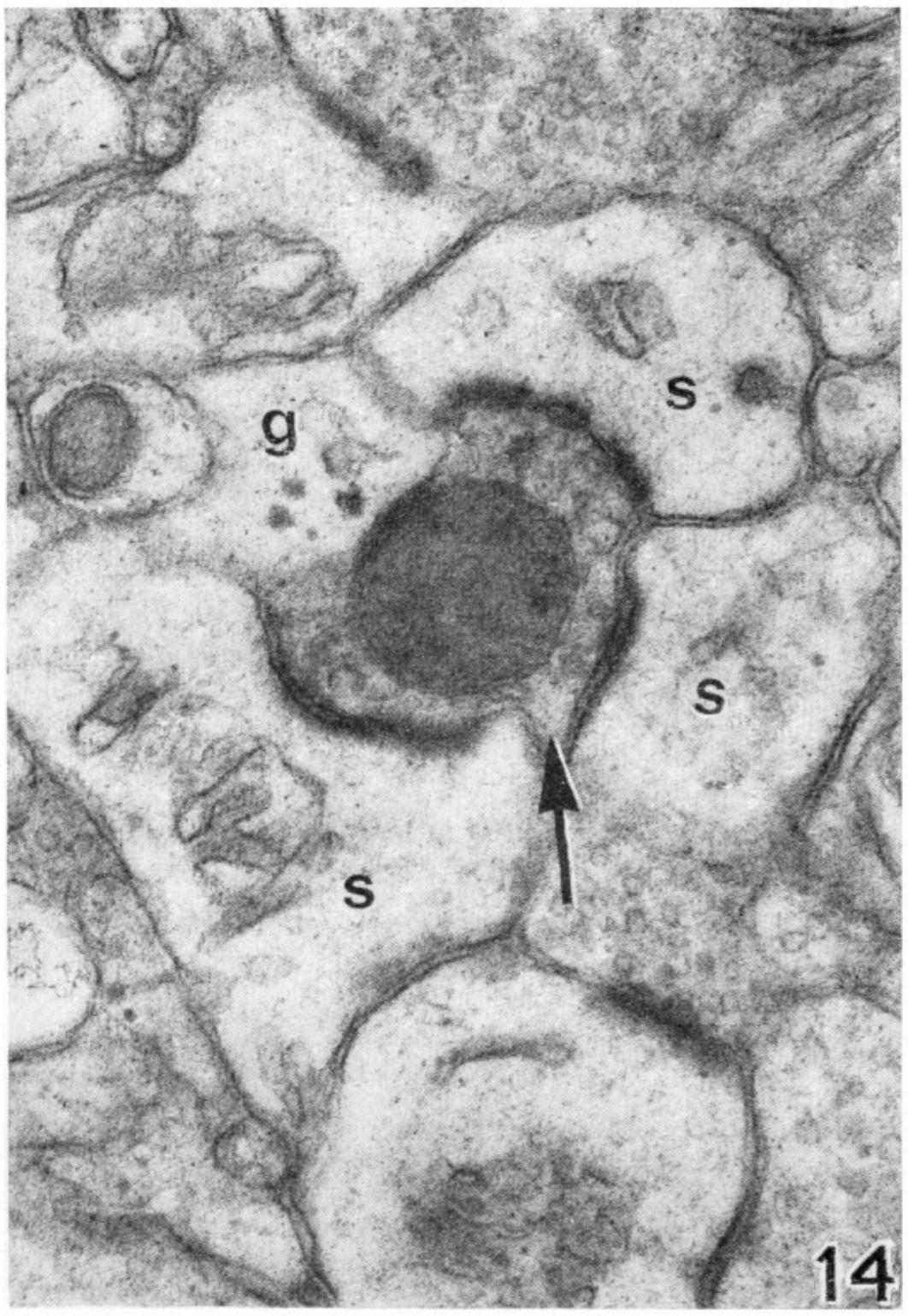


FIGURE 10. Two degenerating terminals (arrows) in contact with spines (s) after a lesion in the contralateral cerebral cortex. × 40000.

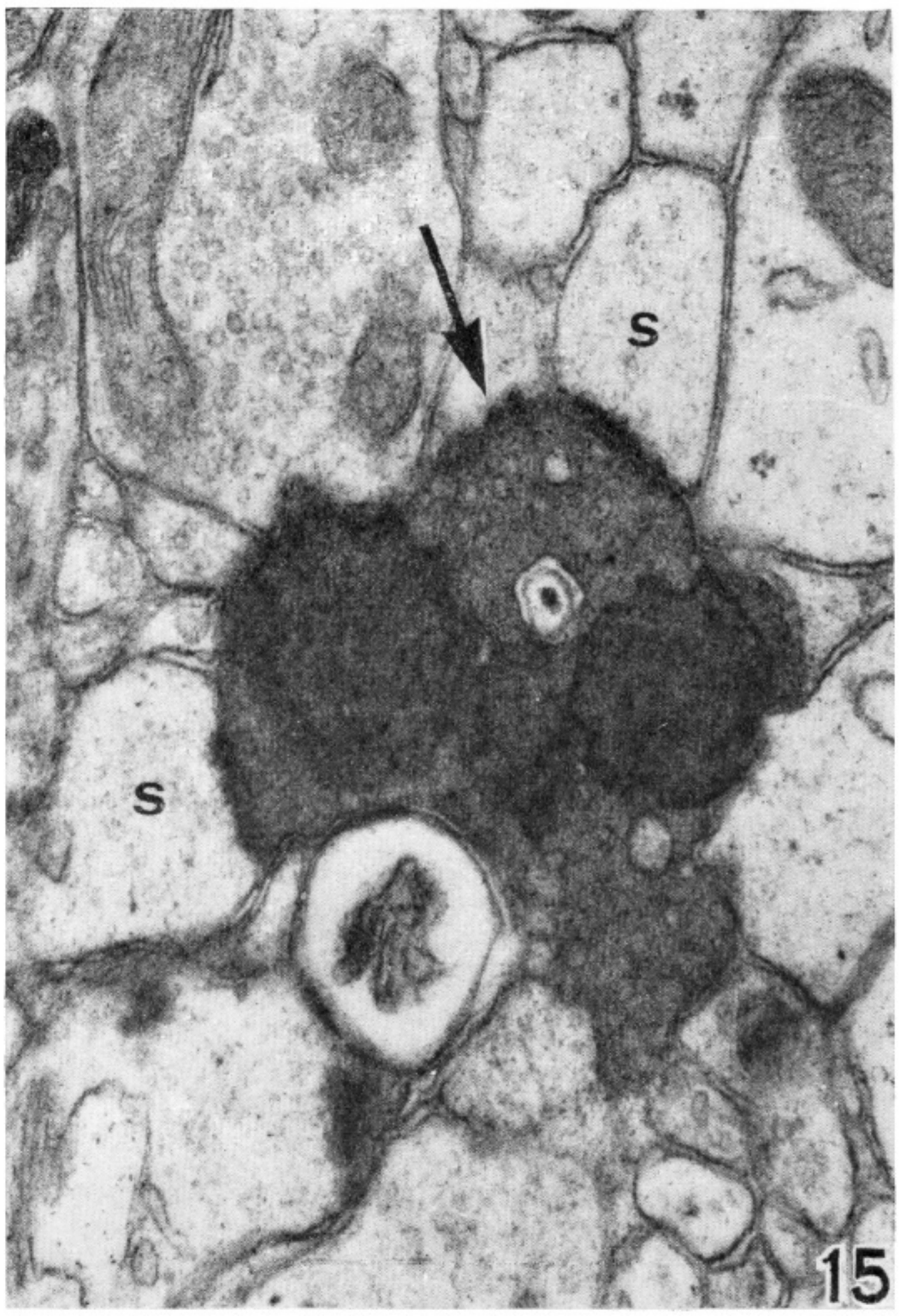
FIGURE 11. Terminal *en passant* (arrow) showing early degenerative changes after a lesion in the midbrain. × 25000.

FIGURE 12. Degenerating terminal *en passant* (arrow) in contact with a spine (s) after a lesion in the contralateral cerebral cortex. × 25000.

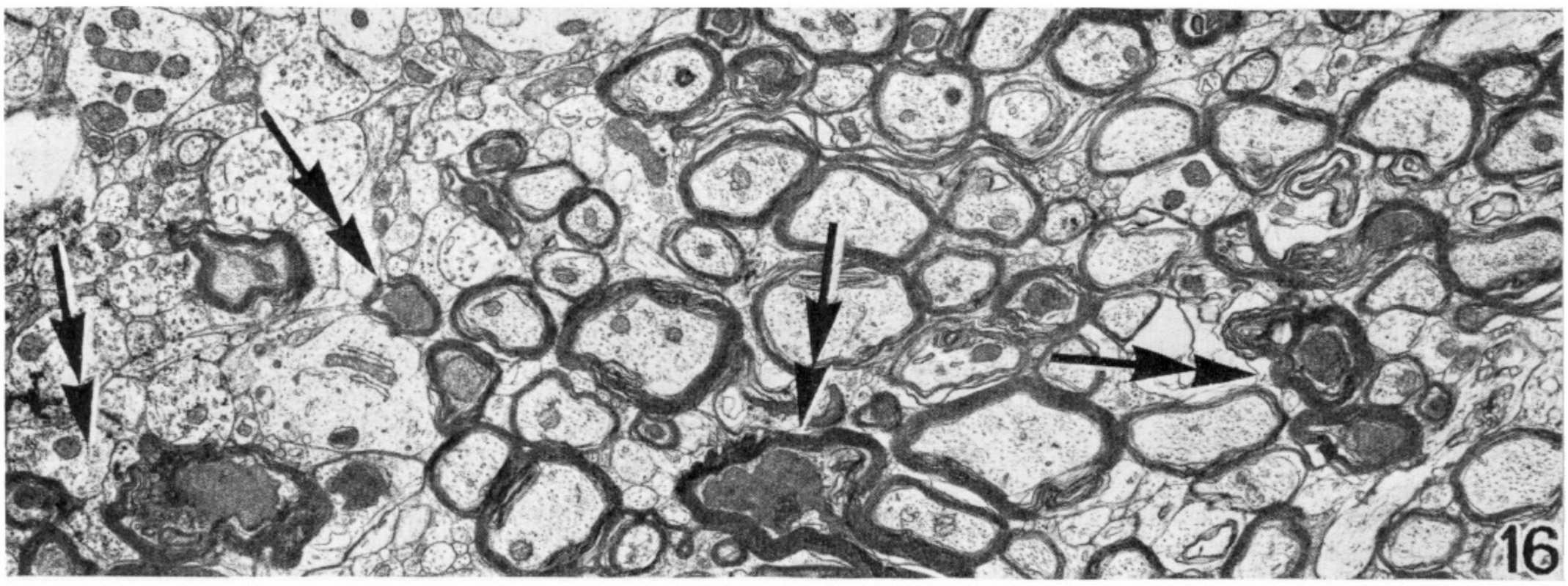
FIGURE 13. Degenerating terminal (arrow) in contact with a spine (s) after a lesion in the midbrain. × 30000.



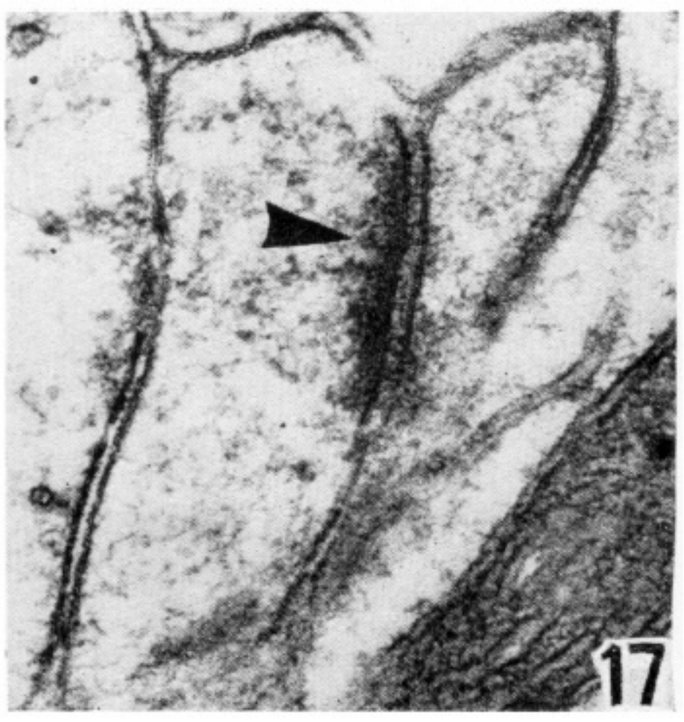
14



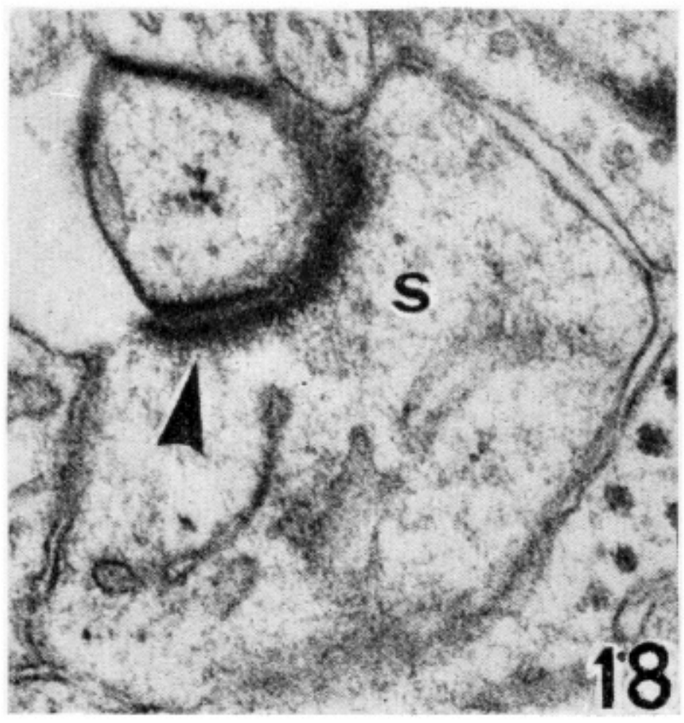
15



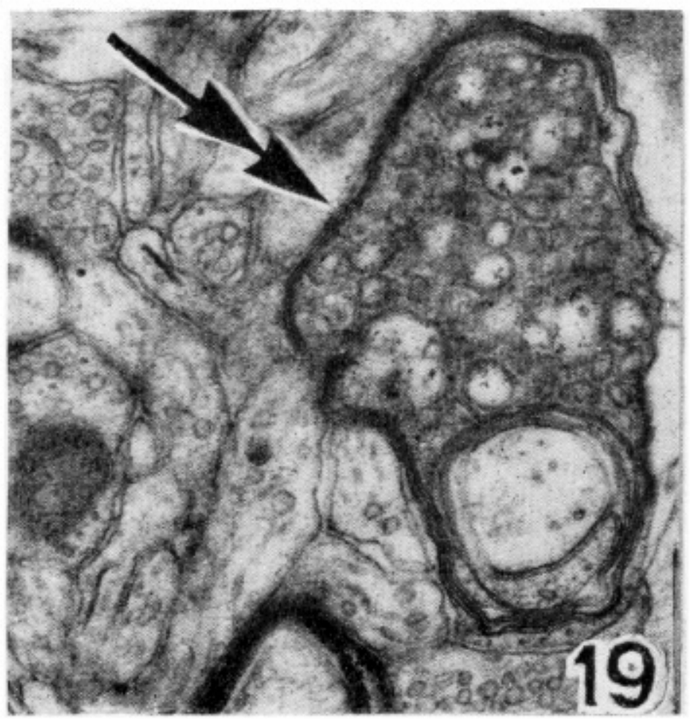
16



17



18



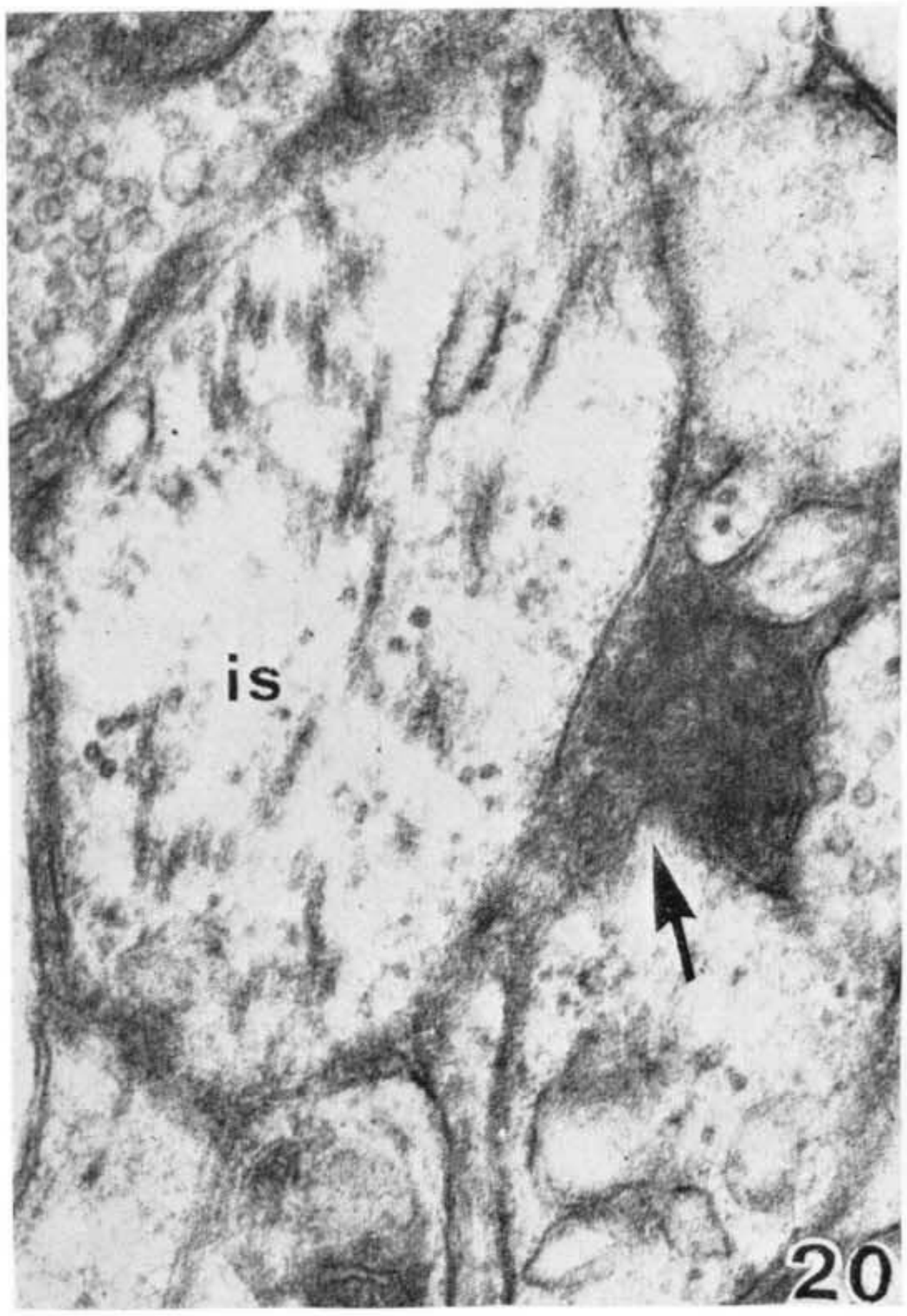
19

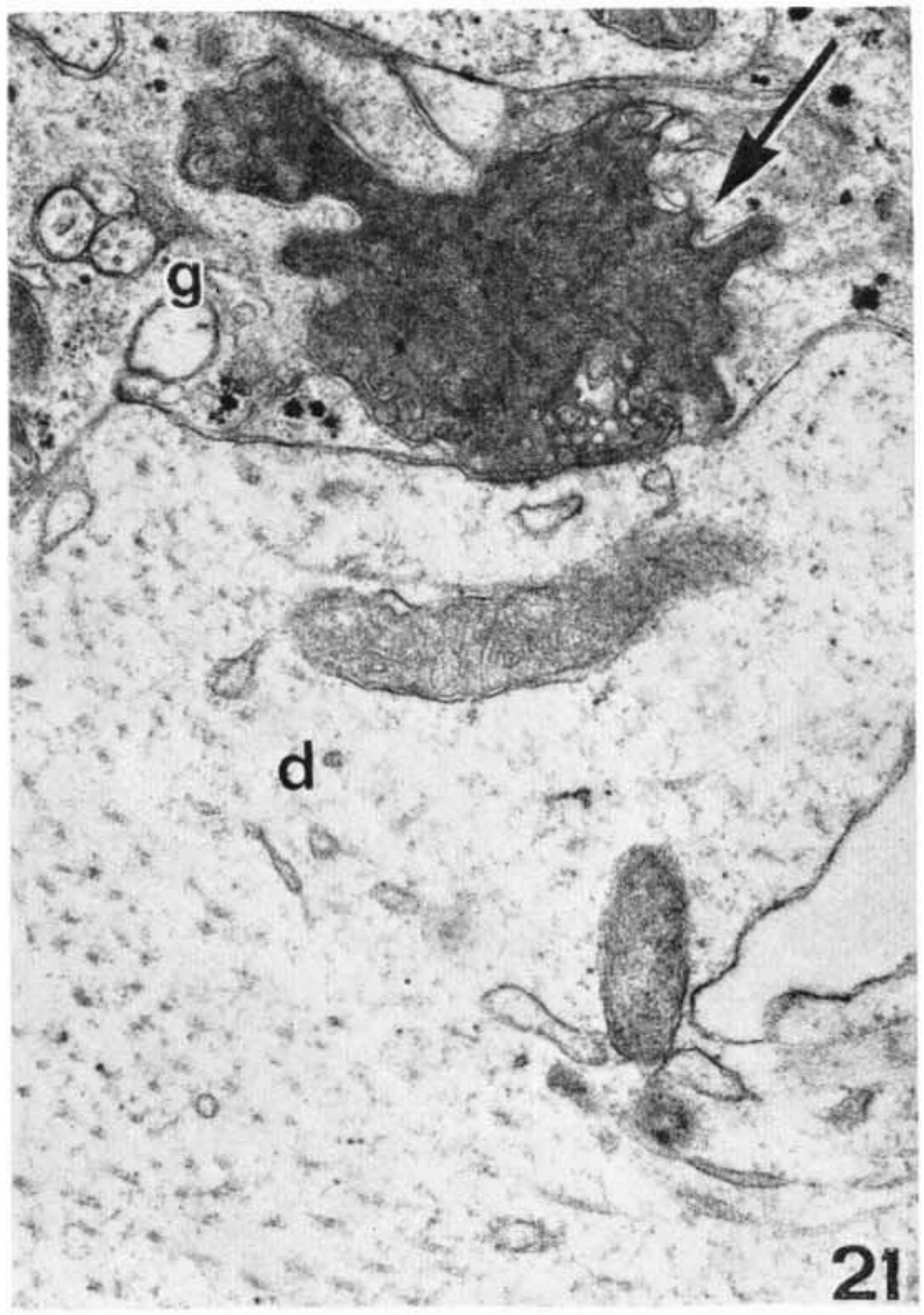
FIGURES 14, 15. Large degenerating terminals (arrows), after a combined lesion of the cerebral cortex and thalamus, each forming synaptic contacts with more than one spine (s). g, glia. 14, × 45000; 15, × 40000.

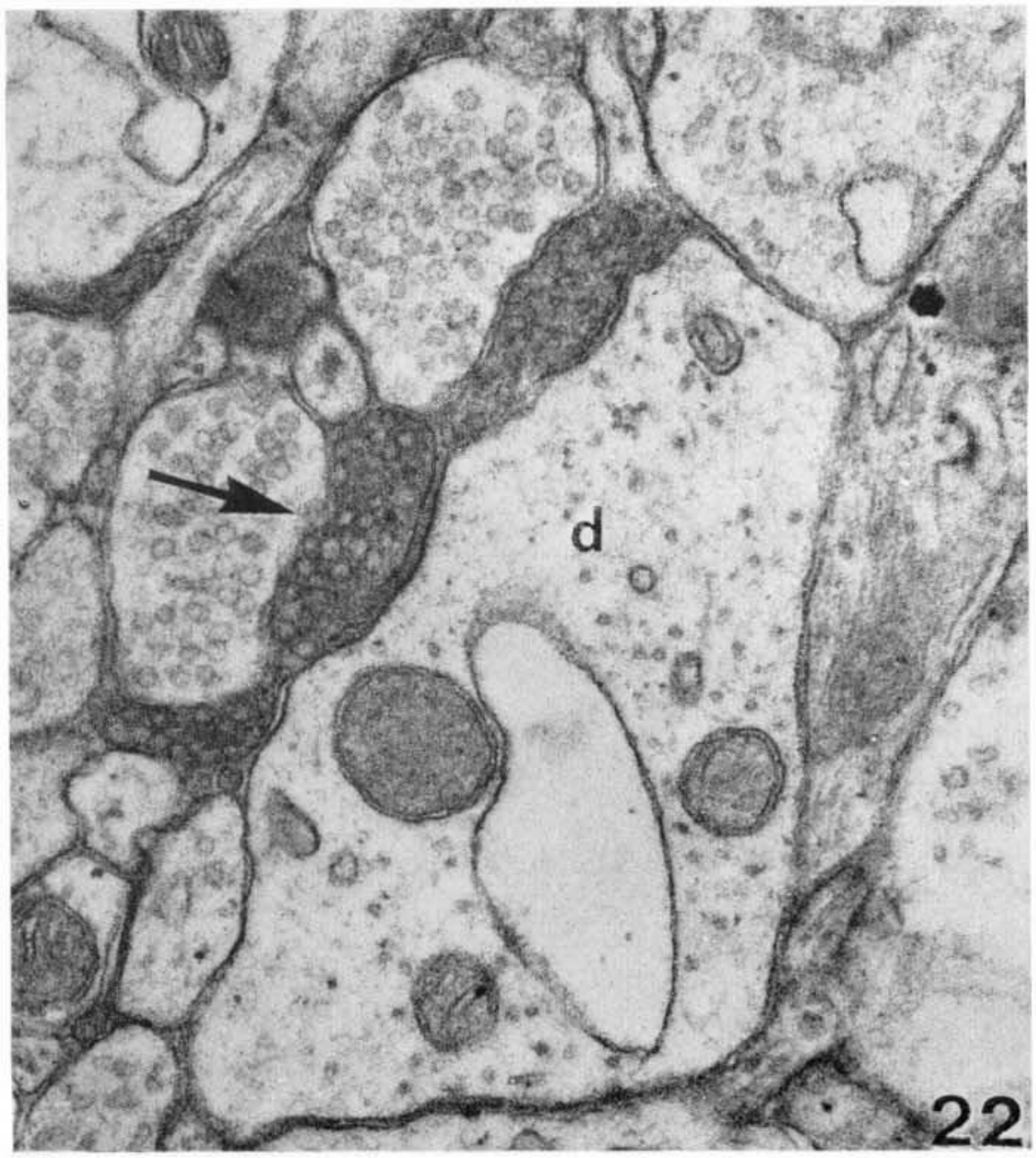
FIGURE 16. Part of a bundle of myelinated fibres some of which are degenerating (double arrows) after a lesion in the thalamus. × 7000.

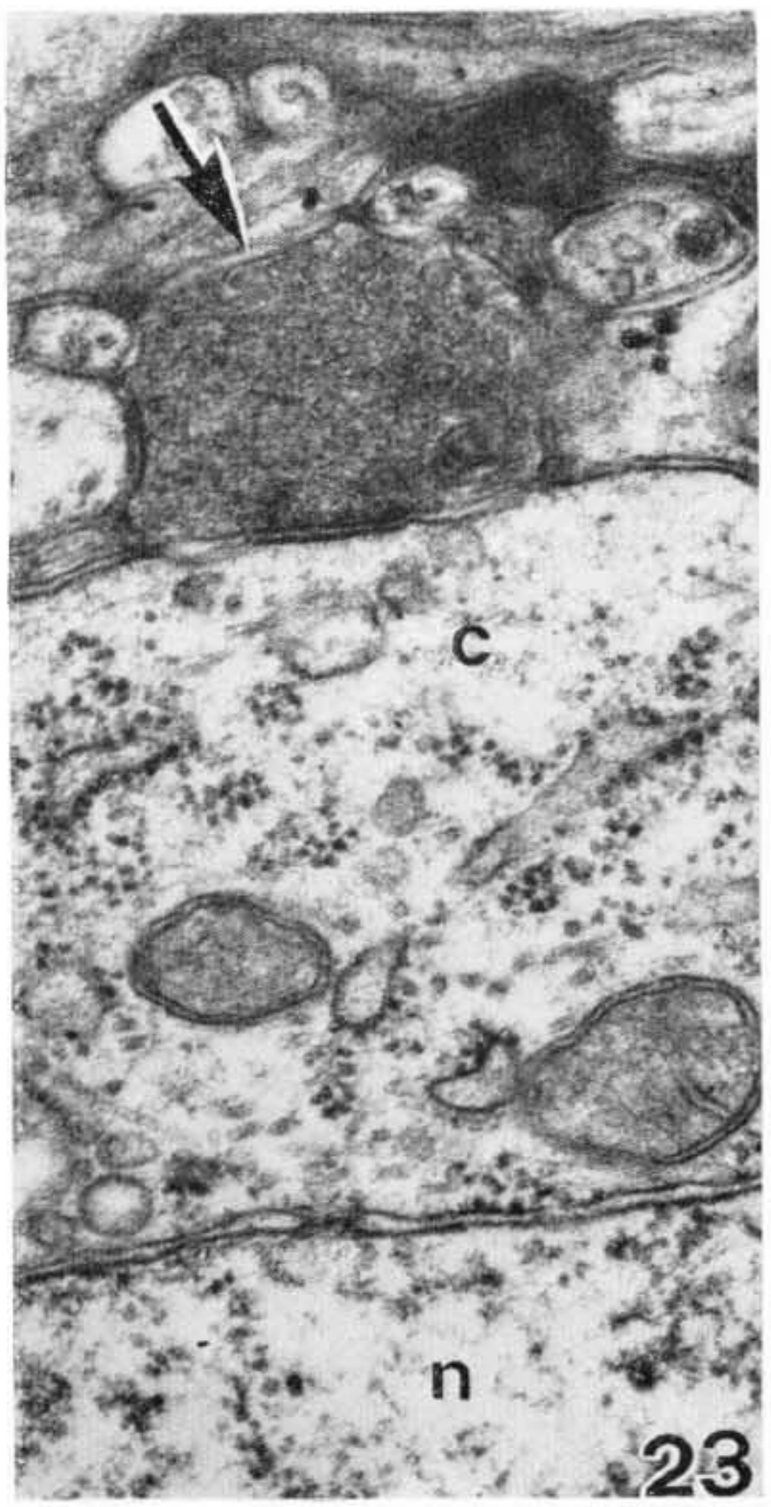
FIGURES 17, 18. Exposed postsynaptic membrane thickenings (arrow heads) in the caudate nucleus 112 days after a combined lesion in the cerebral cortex and thalamus. × 80000. s, spine.

FIGURE 19. Degenerating myelinated nerve fibre (double arrow) after a lesion in the midbrain. × 30000.









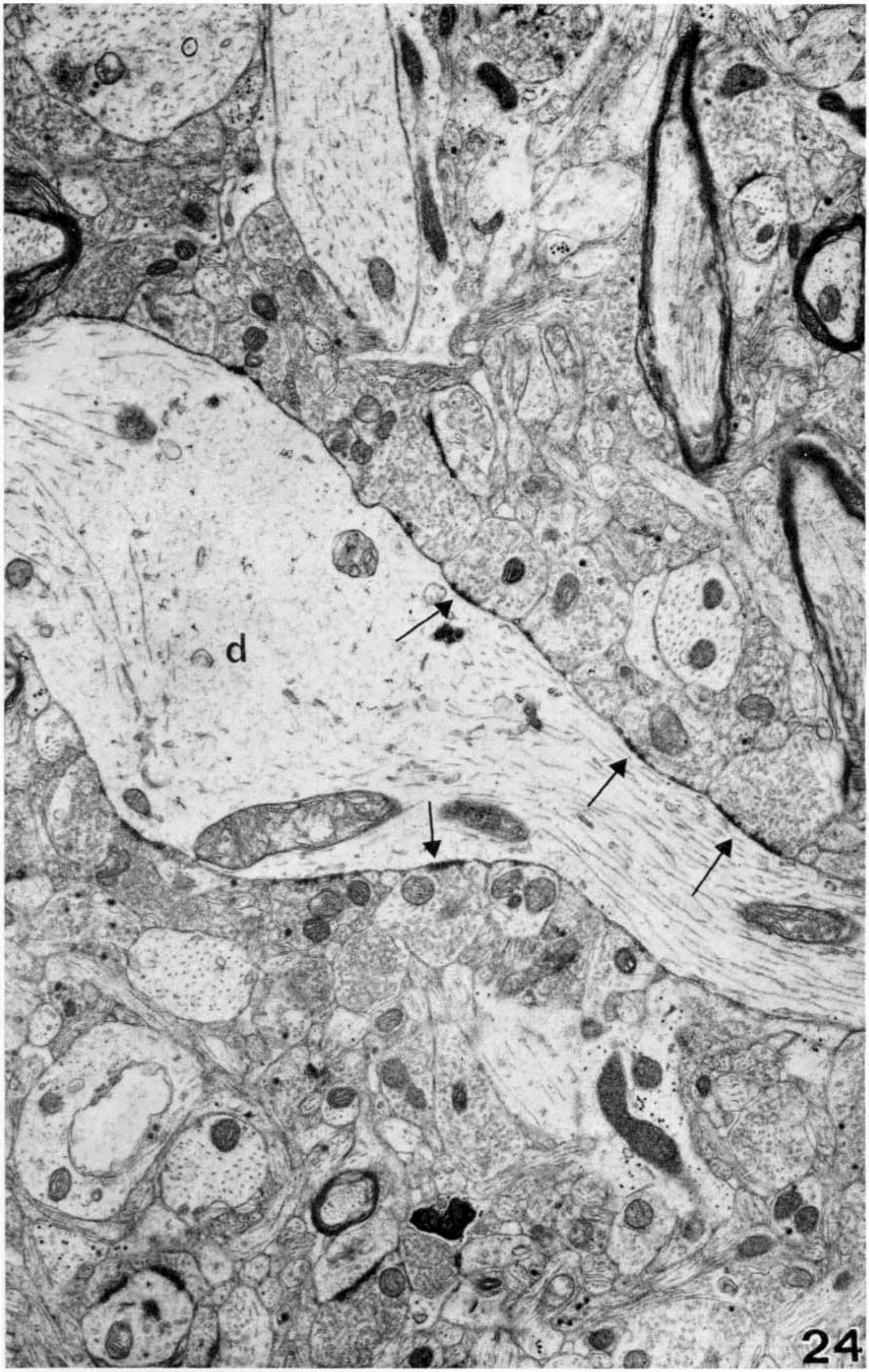
FIGURES 20 to 23. Varieties of processes of caudate neurons contacted by degenerating terminals (arrows) with symmetrical membrane thickenings after a lesion in the caudate nucleus.

FIGURE 20. The initial segment of an axon (is). Note the grouped neurotubules and undercoating of the axon membrane. × 80000.

FIGURE 21. Large dendrite (d). × 30000. g, glia.

FIGURE 22. Peripheral dendrite (d). × 48000

FIGURE 23. Cell soma (c). × 40000. n, nucleus.



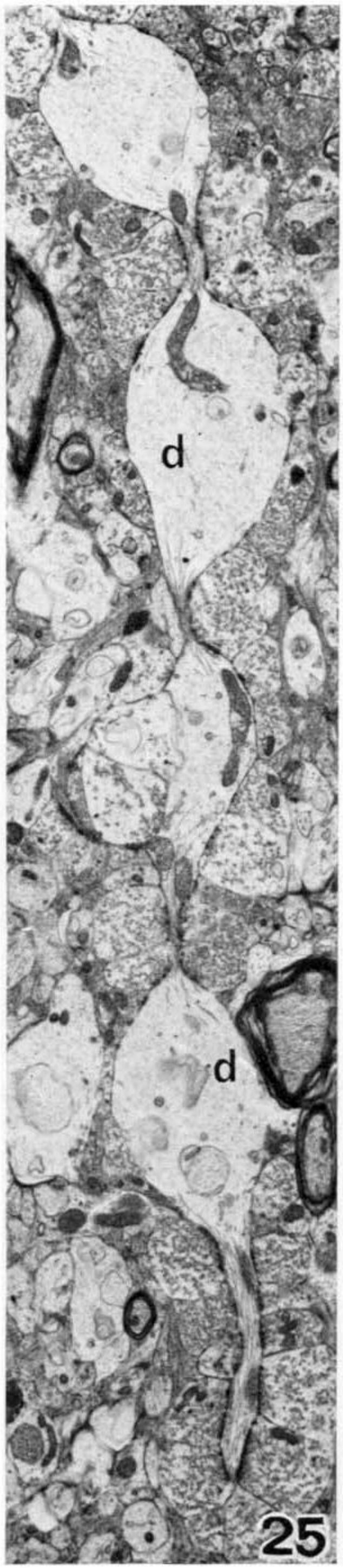
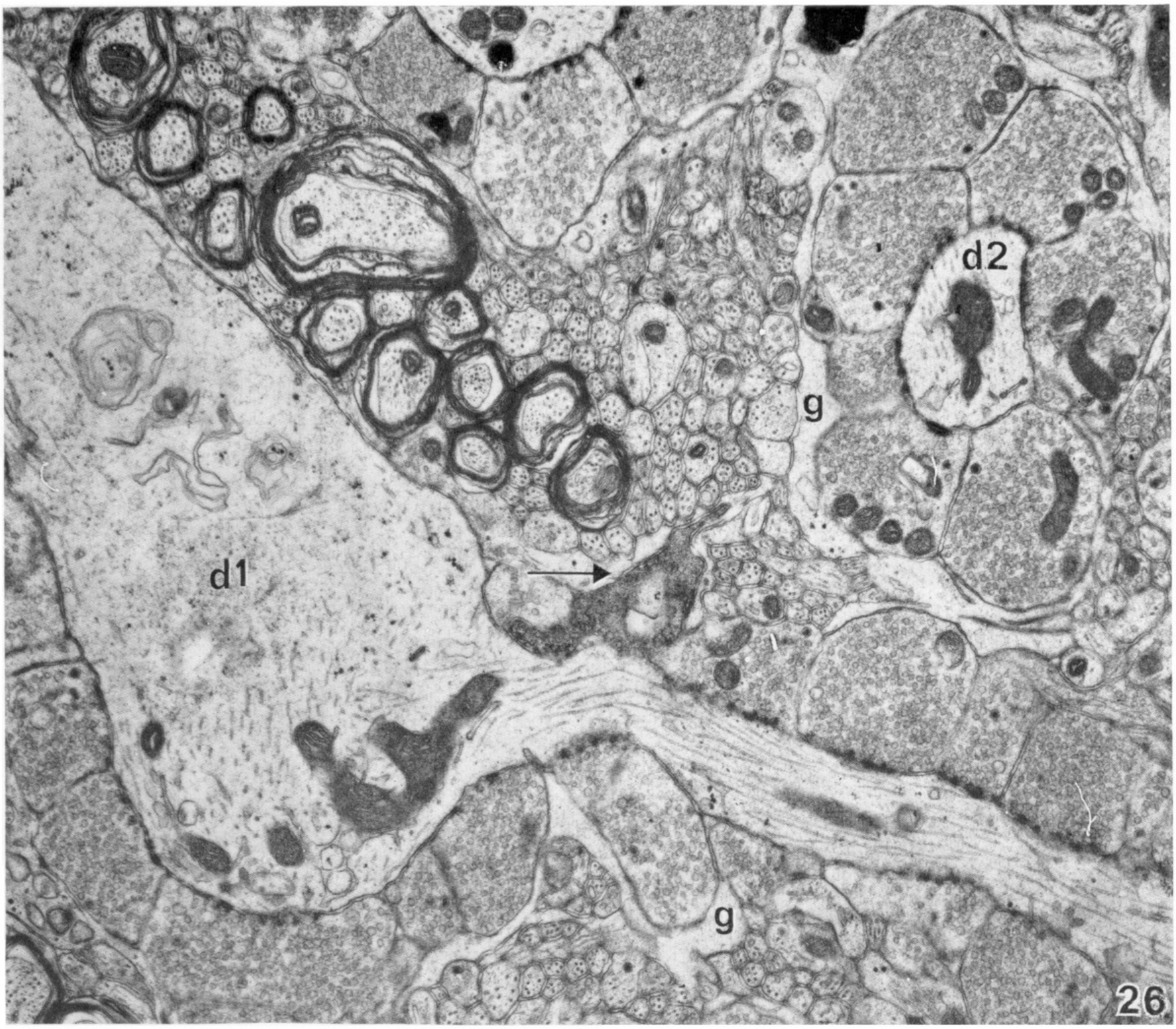
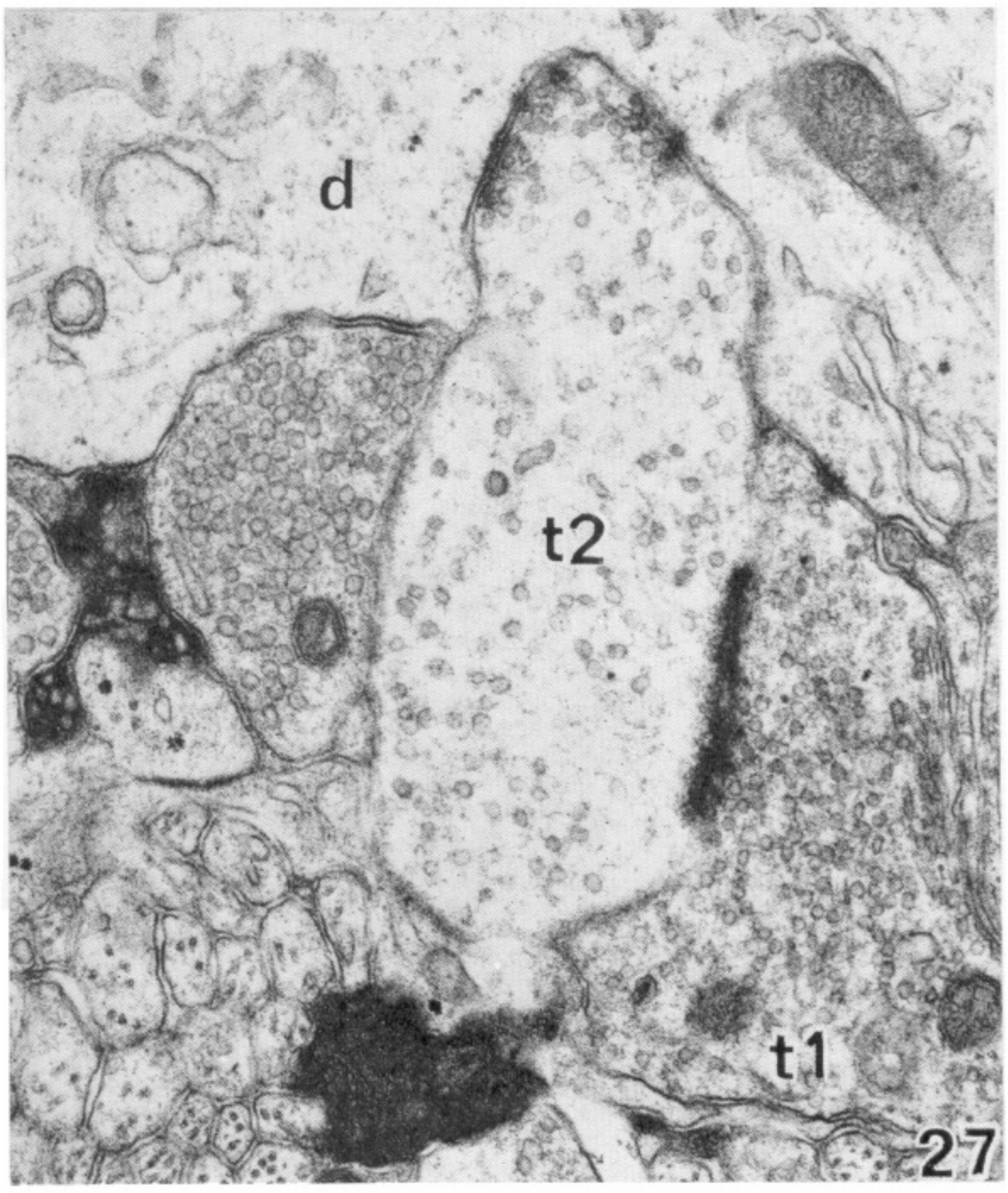


FIGURE 24. Dendrite (d) of the globus pallidus covered with axon terminals many of which are making synaptic contact (arrows) with it. × 9500.

FIGURE 25. Varicose dendrite (d) of the globus pallidus receiving many synapses. × 7000.





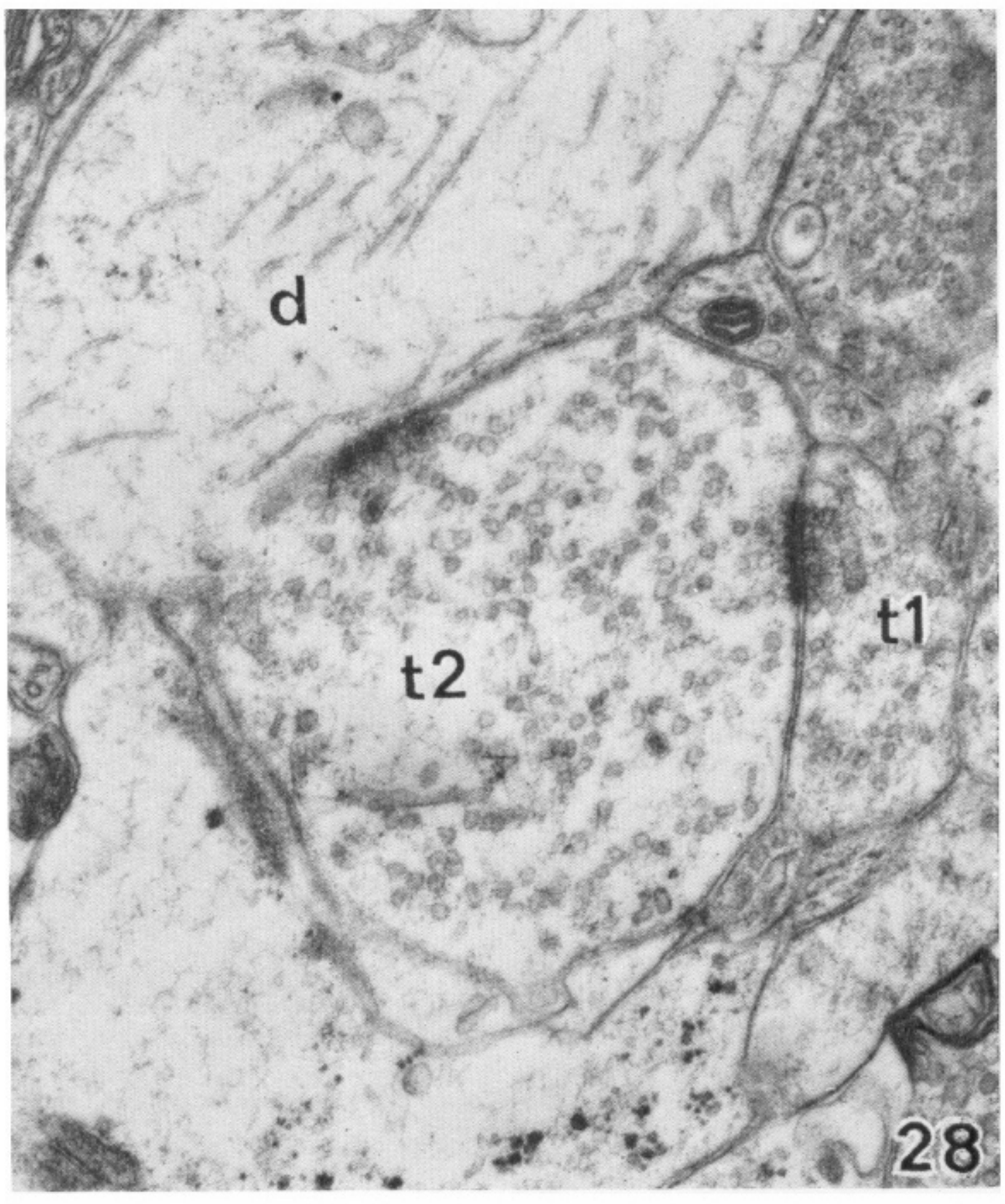
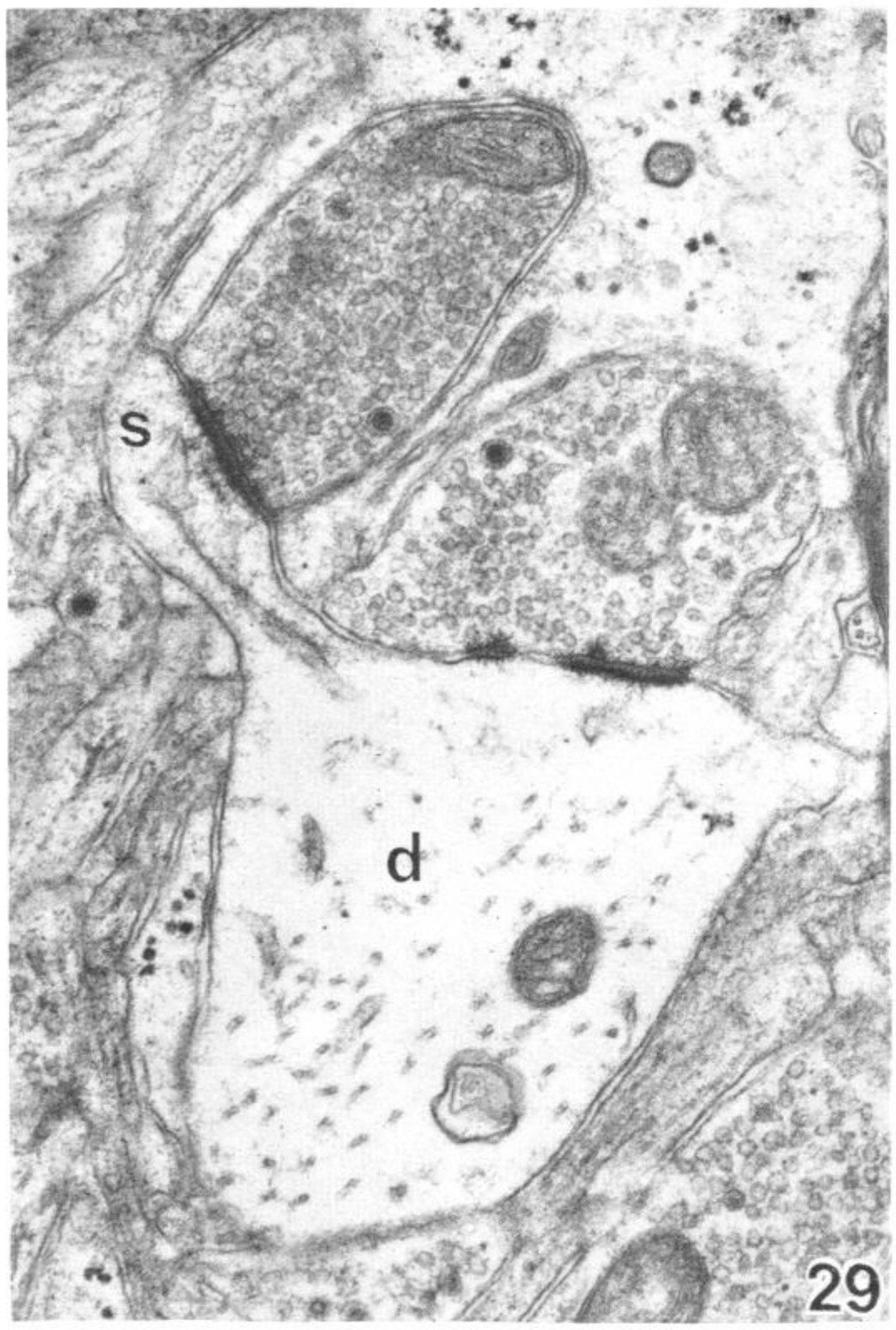
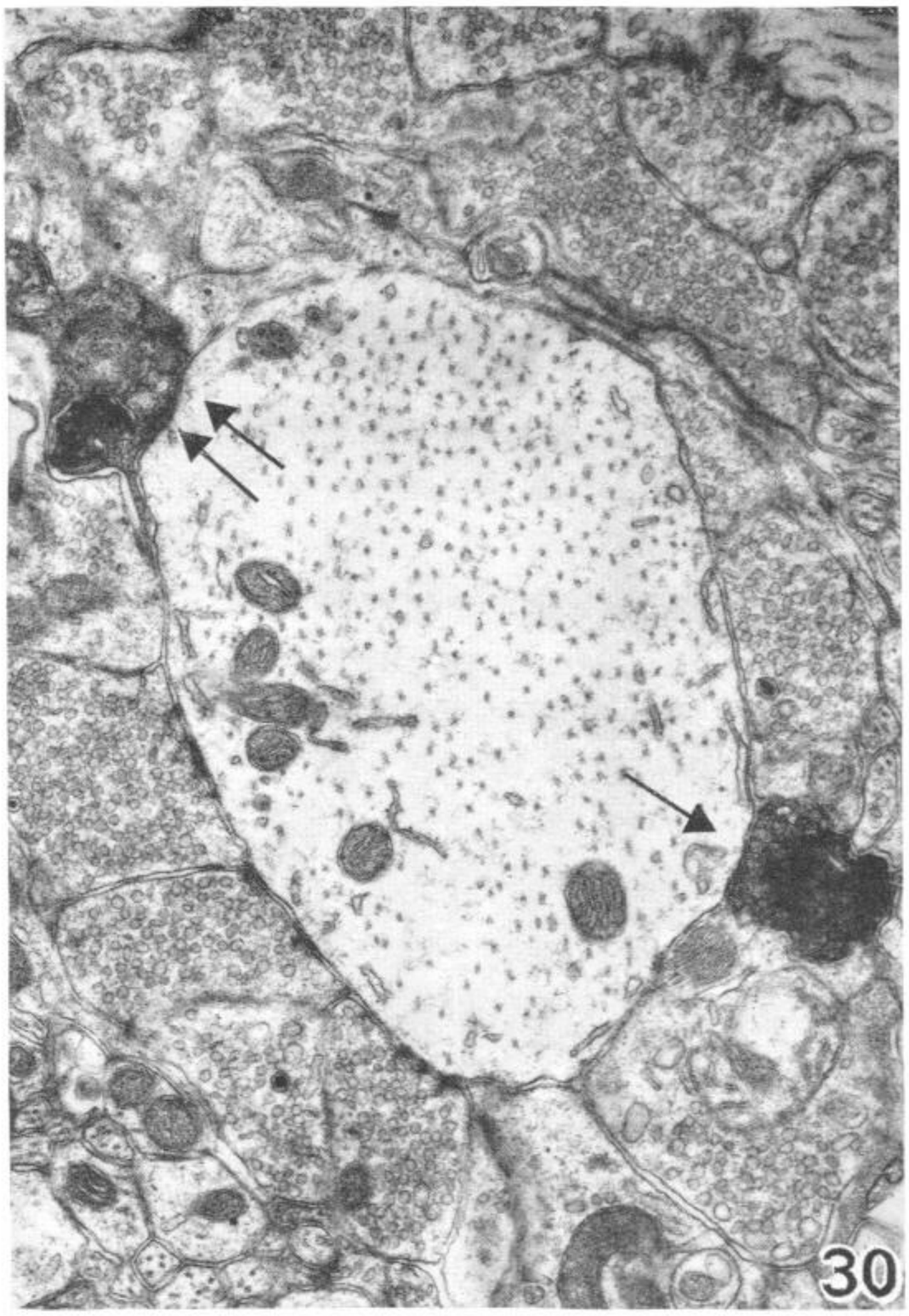


FIGURE 26. Two dendrites of the substantia nigra, one cut longitudinally (d 1) and the other transversely (d 2); both are in synaptic contact with numerous axon terminals, and the complex thus formed is ensheathed with glia (g). Arrow indicates a degenerating preterminal axon. × 21 500. Note the similarity in the structure and synaptic organization shown in this electron micrograph of the substantia nigra with that of the globus pallidus shown in figure 24.

FIGURES 27 and 28. For legends see facing page.





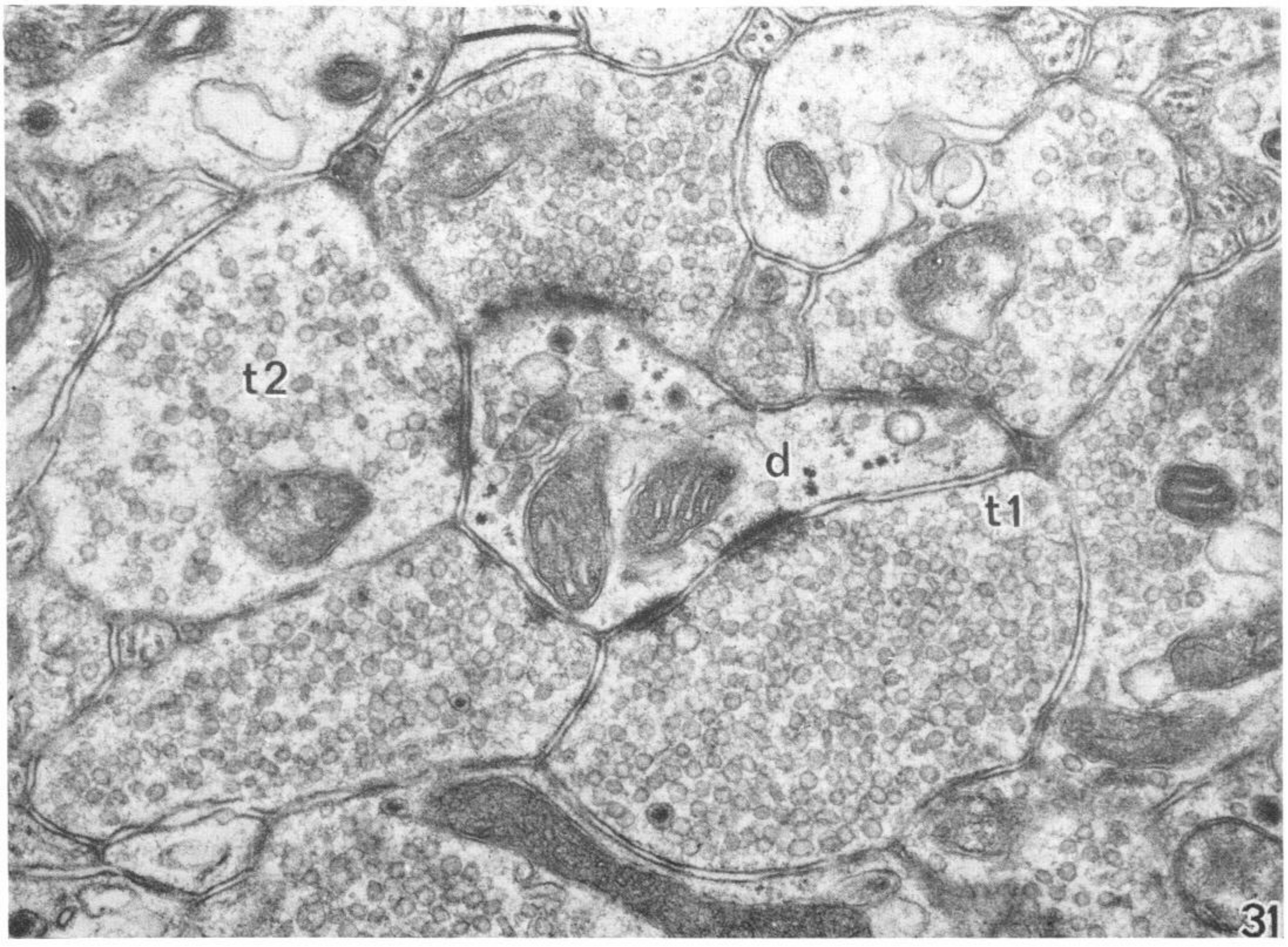
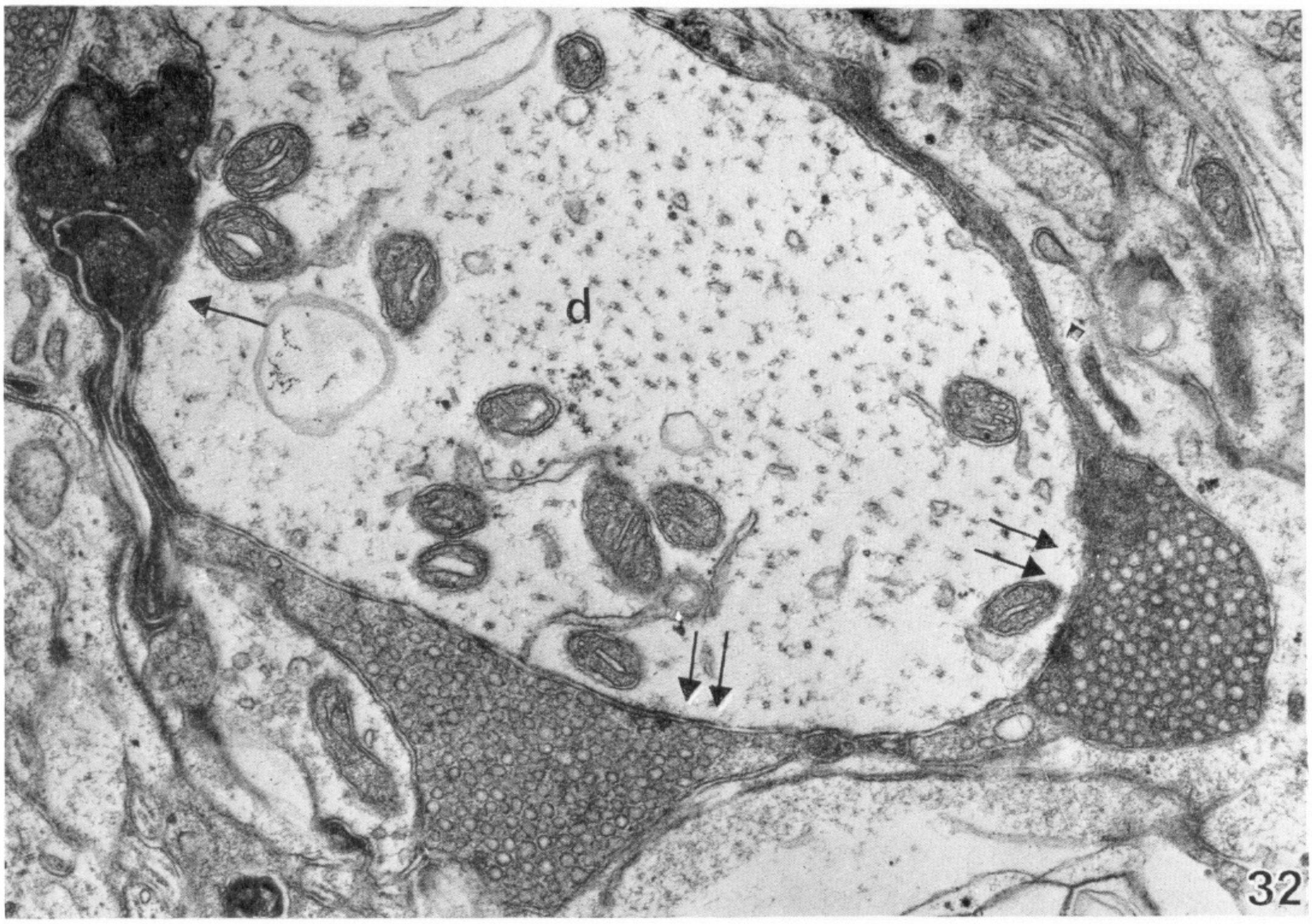
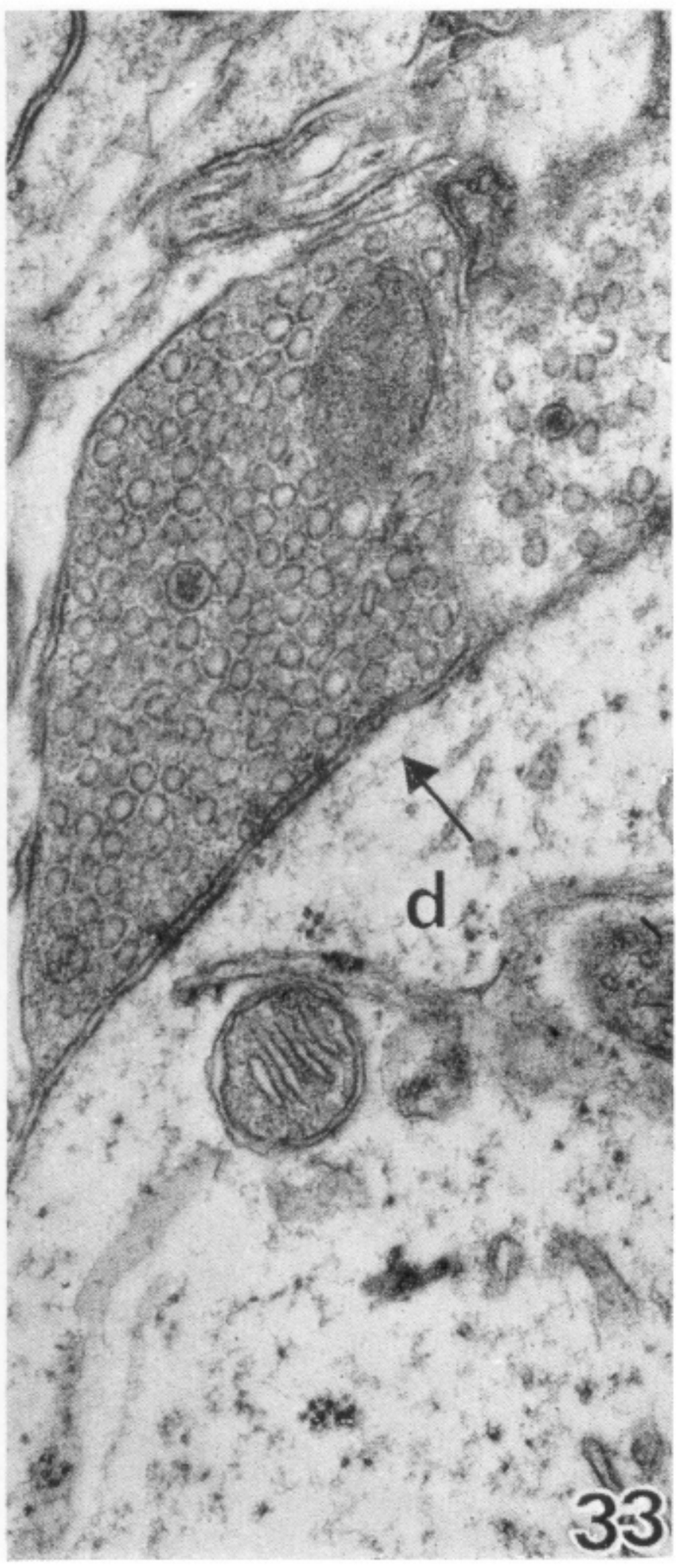


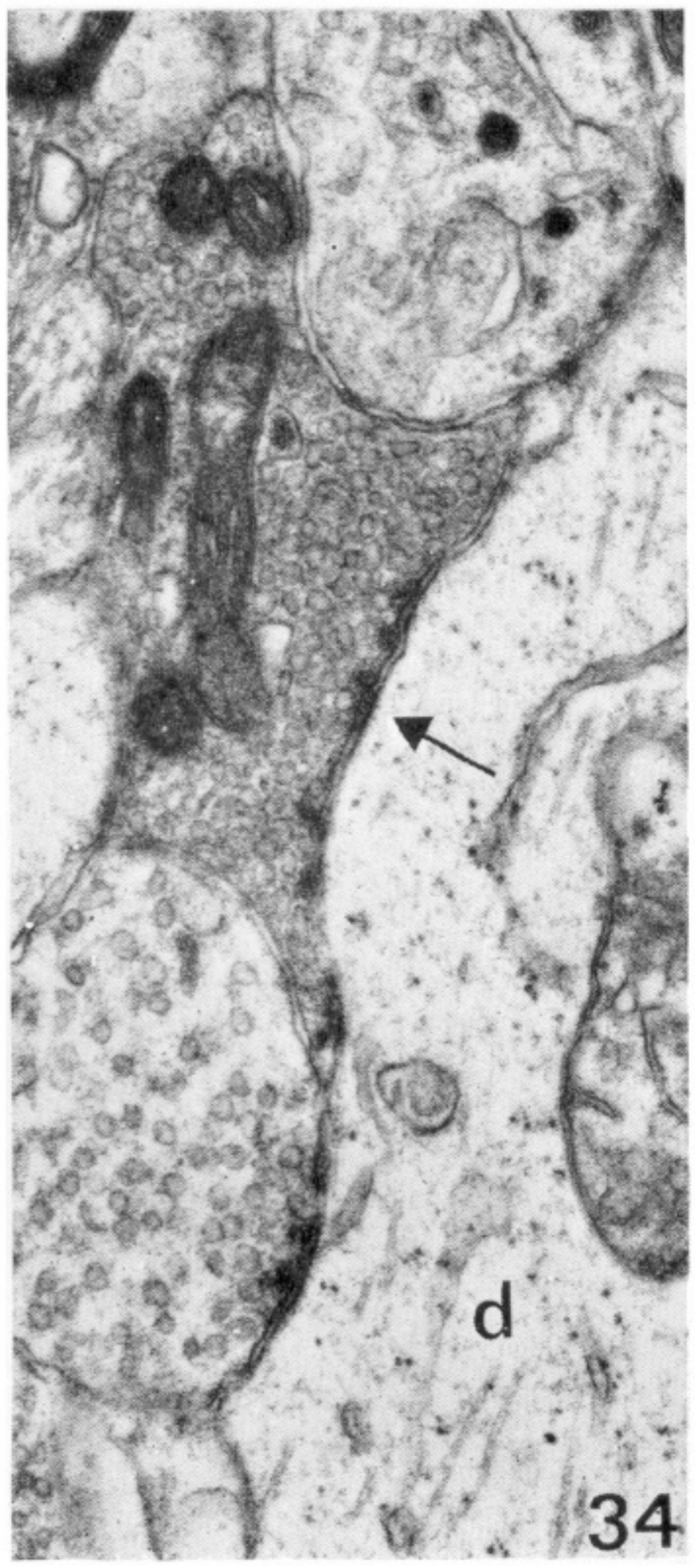
FIGURE 29. A dendritic spine (s) on a dendrite (d) of the globus pallidus. Axon terminals make asymmetrical synapses on to the spine and adjoining part of the dendrite. × 20000.

FIGURE 30. Degeneration of axon terminals (double arrows) and preterminal axons (arrow) in the substantia nigra 4 days after a lesion in the caudate nucleus. × 17000.

FIGURE 31. Dendrite of the substantia nigra (d) upon which an axon terminal (t1) makes an asymmetrical synapse and another (t2) makes a symmetrical synapse. × 43000.







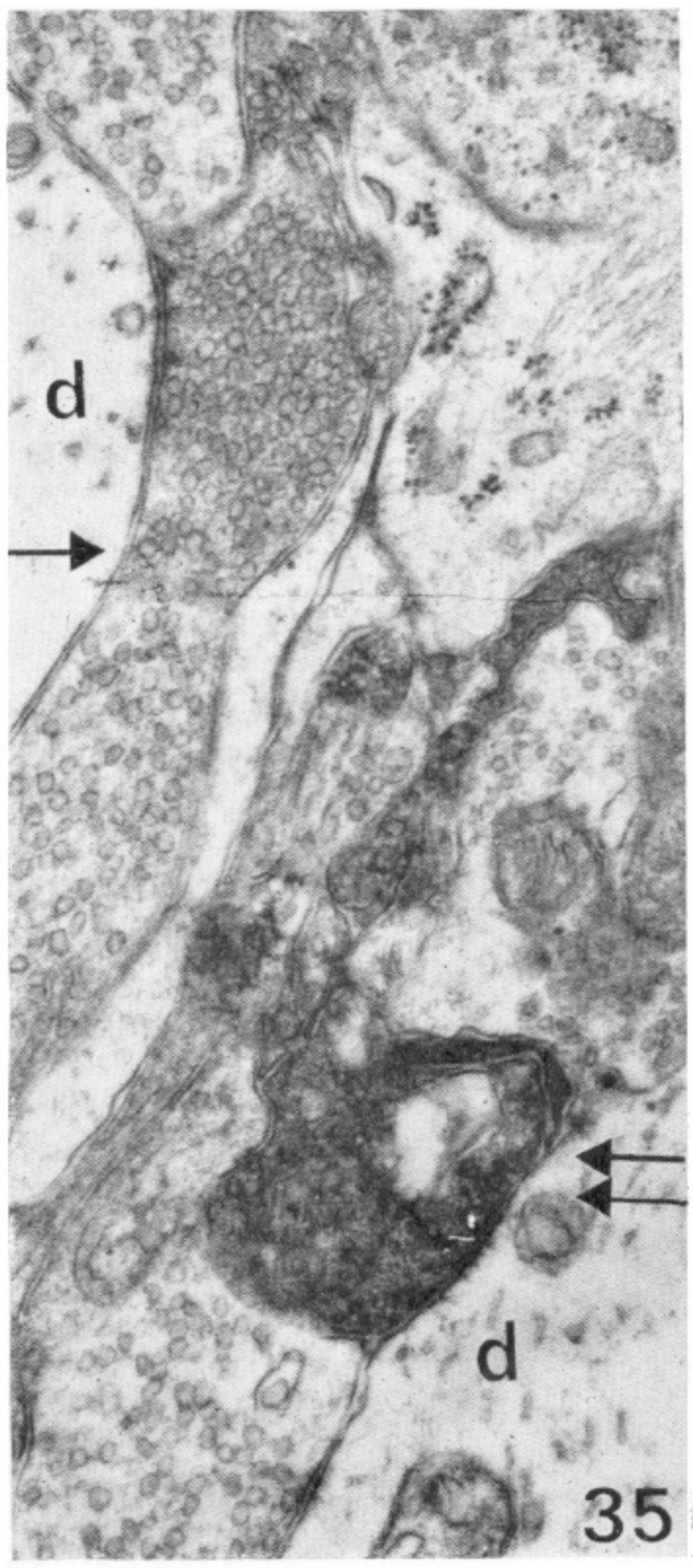


FIGURE 32. Axon terminals (double arrows) and preterminal axon (arrow) in the substantia nigra at different stages of degeneration 4 days after a lesion in the caudate nucleus. d, dendrite. × 29000.

FIGURE 33. Axon terminal (arrow) which is making a symmetrical axodendritic synapse in the substantia nigra in an early stage of degeneration 4 days after a lesion in the caudate nucleus. d, dendrite. × 37000.

FIGURE 34. Degenerating axon terminal (arrow) in symmetrical synaptic contact with a dendrite in the globus pallidus; 4 days after a lesion in the caudate nucleus. d, dendrite. × 30000.

FIGURE 35. Two axon terminals making axodendritic synapses in the globus pallidus and at different stages of degeneration 4 days after a lesion in the caudate nucleus. The one above (arrow) is at a very early stage of degeneration and is darker than the normal terminals on either side of it; the terminal below (double arrow) is at a later stage and is much darker and distorted. d, dendrite. × 21000.