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AN ELECTRON MICROSCOPIC STUDY OF THE LAMINAR PATTERN AND MODE OF TERMINATION OF AFFERENT FIBRE PATHWAYS IN THE SOMATIC SENSORY CORTEX OF THE CAT

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In a series of experiments, the extrinsic afferent pathways to the somatic sensory areas have been selectively interrupted and the distribution and mode of termination of degenerating synaptic endings studied at intervals of 2 to 6 days. Degenerating commissural fibres terminate on spines attached to dendrites of medium and small size in all cortical layers, but the endings are concentrated in the deeper parts of layers I and III and in layer IV. Cortical association fibres passing from SII to SI end on spines of small and medium-sized dendrites mainly in the intermediate layers (III, IV and V) of the cortex, but a small number are invariably seen in the molecular layer. Some of the latter are probably derived from thin myelinated axons which spread radially from a lesion and run just beneath the pia mater. Degenerating thalamo-cortical axons terminate on spines and to a lesser extent on shafts of dendrites of small diameter, mainly in layer IV but with overlap into adjacent parts of layers III and V and with an additional small but consistent number ending in the molecular layer. Thus, the molecular layer and layer IV receive the terminations of all extrinsic afferents, while the relations of these to the other laminae and their mode of termination is, in each case, slightly different. One interpretation of the results is that all three sets of extrinsic afferents terminate in the middle portion of the apical dendritic tree of pyramidal neurons, and that thalamo-cortical fibres have additional terminals on stellate neurons. The functional implications of this arrangement are discussed.

Introduction

Gray & Hamlyn (1962) showed conclusively that characteristic degenerative changes become visible under the electron microscope following experimental interruption of fibre pathways in the central nervous system, and since that time, the electron microscope has been used to study axonal degeneration in many parts of the central nervous system. These range from the cerebral cortex (Colonnier 1964; Westrum 1966) to the spinal cord (Ralston 1968; Heimer & Wall

1968), but until recently most of these investigations have been confined either to demonstrating degenerating axon terminals in some new site, or to establishing the criteria and time course of the degeneration. This work is important and an essential basis for future studies, and some significant findings have emerged: for example, in certain sites such as the cortex (Westrum 1966; Jones & Powell 1970*a*), the degenerative process may be cyclical and prolonged, whereas in others such as the substantia gelatinosa (Heimer & Wall 1968) it may be abrupt and rapidly completed.

Now that the nature of, and criteria for terminal degeneration have been established and it is accepted that two types of degeneration—shrinkage and darkening (e.g. Colonnier & Gray 1962) or filamentous (e.g. Gray & Hamlyn 1962)—occur it is possible to use the electron microscope in experimental material to obtain the information which it alone can provide. One approach, for example, is to establish the site and mode of termination of selected fibre systems; in unequivocally demonstrating individual axon terminals, the electron microscope can show the exact site of termination of a given fibre pathway. This is especially important in laminated structures such as the cerebral cortex where in light microscope preparations, the presence of degenerating fibres of passage can lead to errors of interpretation. Furthermore, in permitting the synaptic contact zone to be visualized, the electron microscope can provide significant information regarding the relationships which exist between axons derived from a given source and the neurons with which they make synaptic contact. This is not only important for distinguishing possible excitatory and inhibitory synapses (see Walberg 1968; Uchizono 1968) but may also be significant in another sense. From the work of Rall and his collaborators (Rall 1959; Rall, Burke, Smith, Nelson & Frank 1967) it has become obvious that the position of a synaptic contact made by an axon terminal upon the surface of the postsynaptic neuron has important functional implications. Recent studies on the distribution and mode of termination of selected afferent pathways (see, for example, Alksne, Blackstad, Walberg & White 1966) have shown the value to be derived from such an approach, for each offers possibilities for the correlation of structure and function.

The cerebral cortex is one of the more complex parts of the brain, both structurally and functionally, and its ultimate analysis will undoubtedly depend upon repeated investigations with more and more refined electron microscopic and other techniques. The present study, however, attempts to provide information concerning one of the more obvious aspects of its organization: the laminar pattern and mode of termination of the extrinsic afferent pathways to one of its functional subdivisions.

Material and methods

Lesions were placed in the brains of 13 adult cats. In six, the cortex covering the anterior half of the hemisphere and including the first (SI) and second (SII) somatic sensory areas was removed on one side; in three, SII alone was removed unilaterally; in another three, large electrolytic lesions were made stereotaxically to destroy the ventral nucleus of the thalamus on one side; in the remaining animal, the hindlimb subdivision of SI was isolated from the rest of the cortex by a series of knife cuts around and beneath it, but made in such a way as to preserve as far as possible the continuity of the overlying pia mater and, therefore, the vascular supply of the isolated region. The animals were killed 2, 4 or 6 days after operation by perfusion with the buffered glutaraldehyde-formaldehyde mixture described in the preceding paper (Jones &

Powell 1970*a*). In taking blocks from SI, no attempt was made to distinguish between the architectonic fields, areas 3, 1 and 2, because the extrinsic connexions of these are identical and also because it would not be possible in such small blocks to be certain of the identification of these areas.

The cortical layers in which degenerating axon terminals were observed were identified on the basis of qualitative criteria, by micrometer measurements made with the electron microscope (Alksne *et al.* 1966) and by comparison of these with a thick section cut from the long face of each block.

Results

The normal fine structure of the first somatic sensory area has been described in detail in other publications (Jones & Powell 1970*b*, *c*, *d*). For the purposes of the present study it is sufficient to note that the six laminae of the cortex have characteristic features which enable them to be readily identified under the electron microscope. It should be pointed out that while each lamina has distinctive features, the boundaries between adjacent laminae are by no means clear-cut, one tending to merge insensibly with the other. A degenerating terminal could, therefore, be assigned to the middle of a particular lamina with some degree of confidence on qualitative grounds alone, but in the case of those situated at the junction of two laminae the assignment has had to be to a certain extent arbitrary. However, by carefully correlating qualitative impressions with micrometer measurements made during observation of the thin sections, and these in turn with the more distinct laminar pattern seen in the thick section of each block, the error should have been reduced as far as possible.

Within every layer of the normal cortex, axon terminals are observed on dendritic spines and shafts and on neuronal perikarya, with those on spines predominating, especially in layers I to V. These spines may be identified even when not attached to a dendrite in a single section, by the absence of the usual dendritic organelles such as neurotubules, ribosomes and (usually) mitochondria, and the common presence of the characteristic 'spine apparatus' (Gray 1959).

The characteristic features, including the time course of degeneration in the somatic sensory cortex, have been described in detail in the preceding paper (Jones & Powell 1970*a*).

For the purposes of mapping the laminar pattern of the degeneration, only those degenerating terminals which make indisputable synaptic contact, by means of distinct synaptic thickenings, with a postsynaptic profile have been counted. Many other, undoubtedly degenerating terminal or preterminal fragments were observed in each experiment, but because it was not possible to be certain that many of these did not represent the unmyelinated terminal segments of degenerating axons, unequivocal terminals only, have been included. It is felt that the sample of the latter is sufficiently large to prevent undue bias.

Commissural afferents

In the six animals in which the first and second somatic sensory areas were unilaterally ablated, careful examination of several hundred groups of thin sections from the opposite first and second areas indicates that commissural fibres terminate in all layers of the cortex. To give an indication of the absolute numbers of degenerating endings found in thin sections of the size used, a number of protocol counts will be presented. For example, the distribution of unequivocal degenerating terminals in SI is plotted accurately from approximately every fourth section of two series of 31 and 28 thin sections, respectively from the superficial and deep halves

of a block of cortex, in figure 1*A*. Nineteen degenerating terminals which made definite synaptic contacts were observed in this short series, being encountered at all levels of the cortex. From these observations alone there is little indication that the terminals are distributed unequally among the six cortical laminae. When, however, the total number (177) of degenerating terminals observed in this quantitative study of repeated series from the same block, are collated and plotted on the outline of a thick section from the block (figure 1*B*), a definite laminar pattern emerges. Degenerating terminals are present throughout the full thickness of the cortex

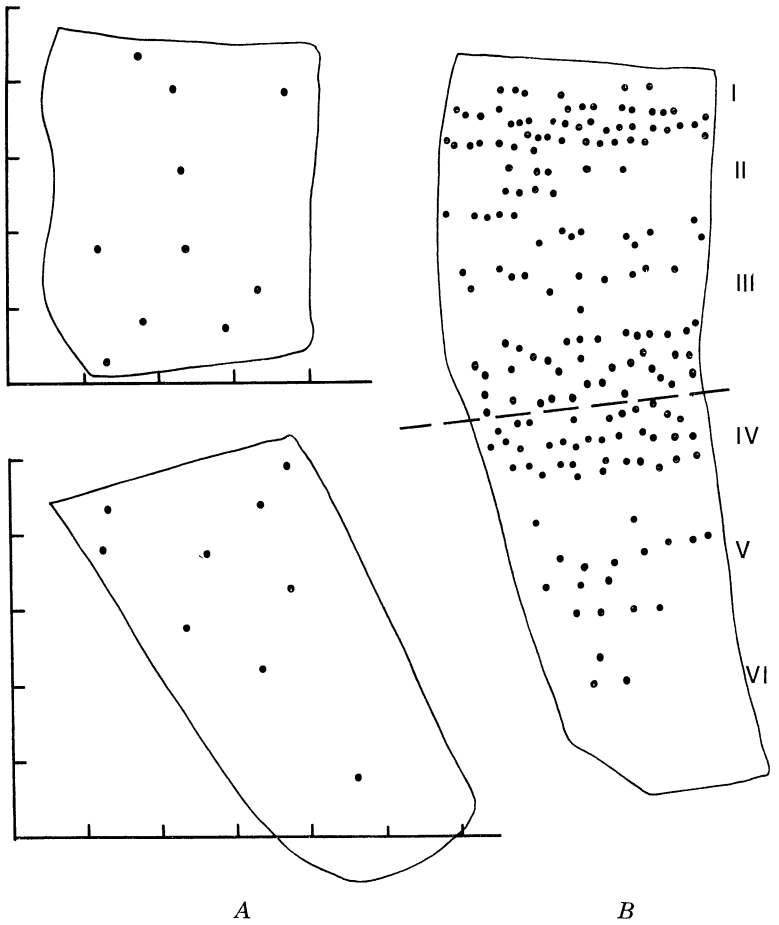

FIGURE 1. *A*, showing the distribution of degenerating terminals in two series of thin sections from the superficial (above) and deep (below) halves of a block of cortex taken from SI of a brain in which the contralateral SI and SII had been destroyed four days previously. The bars on the graphs are at approximately 170 μm intervals. *B*, the distribution of 177 degenerating commissural terminals seen in a single block of cortex, reconstructed on the outlines of a 'thick' section from the same block. The broken line indicates the line of junction separating the two series of thin sections used. Note that in both *A* and *B*, the *positions* of individual terminals are plotted accurately but the dots are not drawn to scale.

but concentrations are found in two regions: (i) at about 150 μm below the pia mater; (ii) in a zone extending from a level of about 500 μm to one of about 1250 μm deep to the pia mater. By correlating these measurements with others made in the thick section, and taking qualitative features into account, these concentrations would appear to be situated in the deeper aspect of layer I on the one hand, and in layer IV and the deeper aspect of layer III on the other (figure 6, plate 41).

FIGURE 6. Two degenerating axon terminals (arrows) ending in relation to dendritic spines (S) in the deeper aspect of layer III following a lesion of the contralateral somatic sensory cortex. Layer III can be recognised by the presence of large apical dendrites (D) and relatively few myelinated axons (M). The superficial aspect of the brain is towards the left. × 10000. *Inset*: an enlarged view of the upper of the two degenerating axon terminals showing the asymmetrical synaptic thickening (T) and the spine apparatus (SA) in the postsynaptic profile. × 70000; lead citrate stain.

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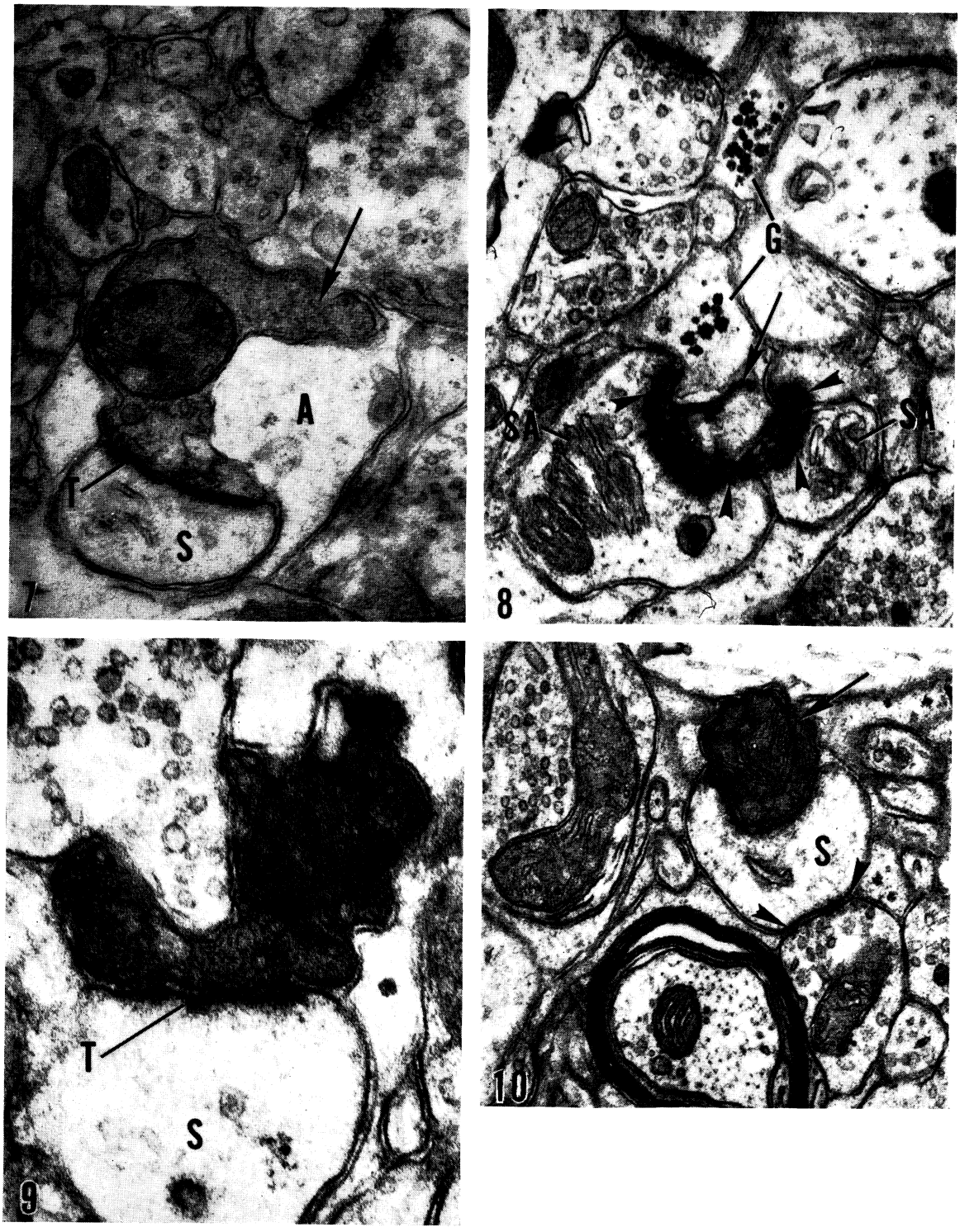


FIGURE 7. A degenerating commissural axon terminal (arrow) ending on a dendritic spine (S) by means of an asymmetrical thickening (T) in layer I of the cortex of SI. A, astroglial process. × 44000; lead citrate stain.

FIGURE 8. A degenerating commissural axon terminal (the arrow points to its attenuated 'tail') making synaptic contact (arrow heads) with three profiles in layer III. Two of the postsynaptic profiles may be recognized as dendritic spines by the presence of spine apparatus (SA). A, astroglial processes containing glycogen granules. × 44000; lead citrate and uranyl acetate stain.

FIGURE 9. Degenerating commissural axon terminal in SI ending by means of an asymmetrical thickening (T) on a dendritic spine (S). Layer IV. × 84000; lead citrate and uranyl acetate.

FIGURE 10. A degenerating commissural axon terminal (arrow) ending on a spine (S) which also receives another normal axon terminal (arrow heads). × 40000; lead citrate.

As additional confirmation of these distinct concentrations of the terminals of commissural afferents, one block taken from SI of the same brain was sectioned parallel to the pial surface, systematically throughout its full thickness. It was felt that these tangential sections, in containing at each level a greater proportion of an individual lamina than the perpendicular ones from the previous blocks, would give an indication as to whether the two concentrations were apparent or real. After each successive series of thin sections, a thick section for light microscopy was cut at right angles to them so that the cortical layer being examined electron microscopically could be more readily identified. The sections from this block confirmed that, while degenerating terminals appear in all layers—extending from just beneath the pia mater to the white matter—they are definitely concentrated in the deeper aspects of layers I and III and in layer IV.

The distribution of degenerating axon terminals in SII is identical to that in SI and following a lesion of SI and SII of the opposite side, the numbers seen in each area are approximately equal. After a lesion of SII alone, however, the number of degenerating terminals in the opposite SII is considerably less, though they appear in all layers. It should be emphasized that this quantitative study of the commissural, as of the other afferents, formed only a minor part of the complete investigation, and that the 177 degenerating terminals forming the sample described above are but a fraction of the few thousand such endings studied qualitatively (figure 4).

Within all six layers of the cortex of both SI and SII, commissural axons terminate in the same manner. In every case in which a synaptic contact zone was visible, the postsynaptic profile could be positively identified as a dendritic spine (figures 6 to 14, plates 41 to 43). In single thin sections, a degenerating commissural terminal rarely made synaptic contact with more than one dendritic spine, but a small number of examples in which two spines were involved were encountered (figure 8, plate 42). An examination of serial sections suggested that this latter situation was relatively uncommon. No spine received more than one degenerating terminal and few spines received a degenerating and a normal terminal. In two instances only, both in the same section, degenerating terminals were seen to make synaptic contact with both a dendritic spine and an adjacent dendritic shaft (figure 14, plate 43). It was not possible to determine whether these spines were attached to that shaft, but their close proximity suggested that they were. It was also rare in single sections to see a dendritic spine both receiving a degenerating axon terminal and attached to its parent dendrite. Even repeated examination of serial sections was unsatisfactory in this respect because the pedicles of many spines are often very long and very attenuated. However, in all those cases in which spines receiving a degenerating terminal were observed attached to a dendrite, this dendrite was of medium diameter (2 to 3 μm) (figures 11, 12, plate 43). In all cases in which the synaptic contact zone between the degenerating terminal and its postsynaptic profile was clearly visible, it was of the asymmetrical type (Gray 1959; Colonnier 1968), with a considerable accumulation of electron-dense material in the cytoplasm deep to the postsynaptic membrane (figures 6 to 14, plates 41 to 43). The asymmetry was most obvious in material double stained with lead citrate and uranyl acetate. In single sections, the contact could be either single or multiple (usually double). Degenerating commissural terminals appear singly, at intervals throughout the neuropil, and not in clusters, suggesting that callosal fibres or their terminal branches end as single terminals or as terminals distributed at spaced intervals.

In the brains with a lesion of the opposite SI and SII, small, thinly myelinated degenerating

axons (figures 15, 16, plate 44) are seen in all six cortical laminae. Because of the distortion of the degenerating axon and varying degrees of obliquity of section of the fibre, it is difficult to give an exact measurement of their diameter but in all layers, from I to VI, it appears to fall into a constant range of 1 to 1·5 μm (including the myelin sheath). In favourable sections cut perpendicular to the pial surface, a single degenerating commissural fibre may be seen ascending vertically through several layers of the cortex (figures 15, 16, plate 44). The vertical intracortical course of these callosal axons is confirmed from the blocks sectioned tangentially for, here, in all cortical layers, the small degenerating fibres are almost invariably cut in cross-section. While it was obvious that commissural fibres are of relatively constant diameter and that at least some remain myelinated throughout all cortical layers, it was not possible to ascertain the nature or extent of their terminal ramifications. In some cases, degenerating terminals were observed which possessed a thin 'tail' of dense material (figure 8, plate 42); this probably represents the unmyelinated preterminal axon segment but the total length of the latter, and conversely, the point at which the commissural fibre loses its myelin sheath, were obscure.

In the early stages of this investigation, blocks were examined from all topographic subdivisions of the first somatic sensory area following destruction of the somatic sensory cortex of the opposite side. The results were initially disconcerting in that blocks from certain subdivisions contained degenerating axons and their terminals while others displayed neither. The problem was resolved by a concurrent investigation using experimental light microscopic techniques (Jones & Powell 1968), which demonstrated that the parts of SI and SII in which the distal segments of the limbs are represented neither send nor receive commissural fibres. A careful re-evaluation of the regions from which the negative blocks had been taken showed that all were from the distal limb regions, so that the present results may be taken as confirmation of the light microscopic findings on the organization of the callosal projection. Hence, all the observations described in this account of commisural fibres were made in the head, trunk and proximal limb regions of SI and SII.

Thalamo-cortical afferents

Examination of thin sections from the first somatic sensory area of animals in which the ventro-posterior nucleus of the thalamus had been destroyed by stereotaxic lesions, shows that thalamo-cortical axons terminate at very restricted depths in the cortex. In a double series of sections numbering 27 and 30, and respectively from the superficial and deep halves of a block of cortex (figure 2*A*), 22 degenerating terminals made definite synaptic contact with other profiles. Twenty-one of these were in a region situated between 700 and 1500 μm deep to the pial surface. By comparing these measurements with a thick section from the block and taking qualitative impressions into account, this region would correspond to layer IV and the adjacent parts of layers III and V. The single remaining degenerating terminal was situated in the deeper aspect of the molecular layer.

In multiple series from the same block, 110 degenerating terminals which made definite synaptic contacts were encountered. When their positions are plotted on a standard thick section from the same block (figure 2*B*), the bilaminar pattern seen in the single series persists. Seven degenerating terminals are present in the molecular layer and of the remainder, the vast majority are in layer IV and in adjacent parts of layers III and V. Only a very small number extend a little more towards the surface—into more superficial parts of layer III. This pattern of termination of thalamo-cortical fibres was also observed in further blocks from the same brain and in the other two brains with lesions in the ventral thalamic nucleus (figure 4).

The majority of degenerating thalamo-cortical terminals make synaptic contact with dendritic spines, either with one spine only, or with two adjacent ones (figures 17, 19, 21, 22–24, plates 45 to 47). The latter situation was more obvious in serial sections than in single ones; no spine, however, received more than one terminal. When the spines which received a degenerating thalamo-cortical terminal could be traced in continuity with a dendritic shaft the latter was of relatively small diameter (1 to 1.5 μm) (figure 22, plate 47), and usually thinner than those

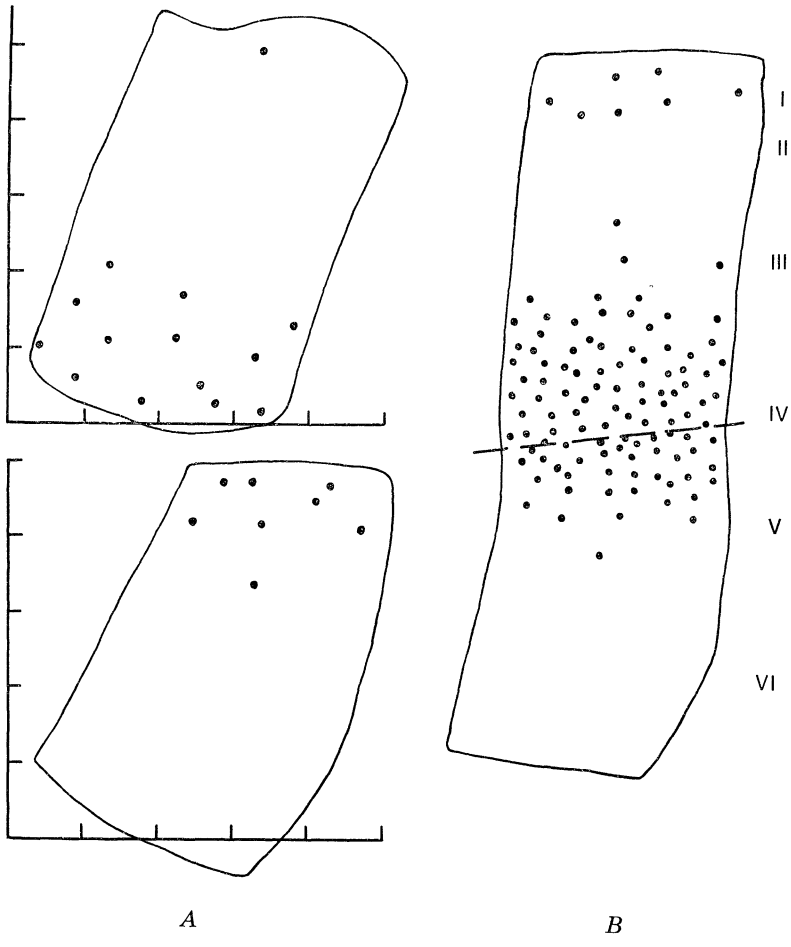


FIGURE 2. *A*, showing the distribution of 22 degenerating thalamo-cortical axon terminals observed in two short series of sections from a single block of SI. *B*, the distribution of 110 degenerating thalamo-cortical terminals seen in repeated series from the same block, reconstructed on the outlines of a thick section of the same block.

dendrites which received commissural terminals. A number of degenerating thalamo-cortical terminals (approximately 25 % of the total encountered) made synaptic contact directly with the shafts of small dendrites of similar diameter to those described above (figures 18, 20, plate 46). No degenerating endings, however, made synaptic contact with both a spine and a dendritic shaft. Small clusters of degenerating terminals are far more common in the cortex of brains with thalamic lesions than in those with lesions of the opposite cortex or of the ipsilateral SII. In cases in which serial sections were examined, two or three degenerating terminals were often seen to be joined by a short thin segment of degenerating axoplasm (figure 24, plate 47).

As in the case of commissural terminals, the synaptic contact was of the asymmetrical type, with an accumulation of dense material deep to the postsynaptic membrane. Both single and multiple points of synaptic contact were observed (figures 17 to 24, plates 45 to 47).

Degenerating thalamo-cortical fibres are myelinated and fall into one of two general ranges of diameter depending upon their depth in the cortex. In the deepest layers (V and VI) they are quite thick (3 to 4 μm) and in a single section relatively few, whereas the majority of those in layer IV and the small number seen in the more superficial layers are thin (*ca.* 1 μm). The

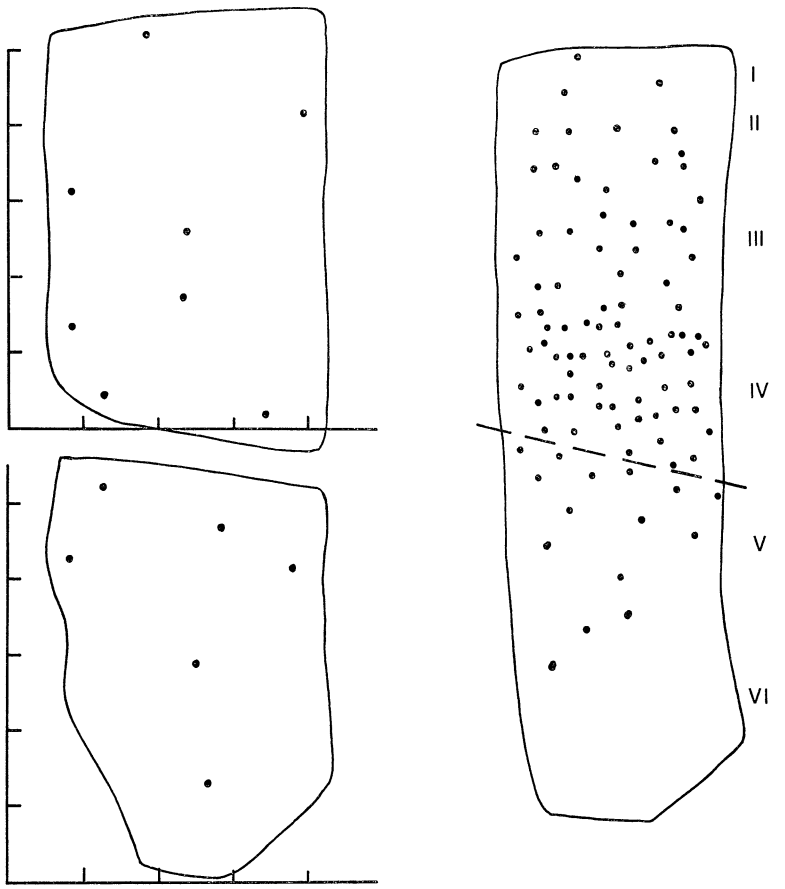


FIGURE 3. *A*, the distribution of 14 degenerating axon terminals observed in two series of thin sections from S I following removal of the ipsilateral S II. *B*, the distribution of 92 degenerating cortico-cortical axon terminals seen in repeated series from the same block.

impression is also gained that the total number of degenerating fibres is greater in layer IV than in the deeper layers. This suggests that thalamo-cortical fibres divide into thinner branches before terminating. Degenerating fragments which can be interpreted as the unmyelinated terminal segments of thalamo-cortical axons are frequently encountered (figure 18, plate 46), being far more common than in brains with lesions of the opposite cortex. As in the case of commissural fibres, it is impossible to be certain of the length of the unmyelinated terminal segment, but the frequency with which these segments are seen suggests that they are longer than those of commissural fibres.

Cortico-cortical afferents

The terminal distribution of association fibres passing from SII to SI was investigated by examining blocks from SI following lesions which destroyed most of the ipsilateral SII. These lesions, which were largely confined to the cortex, could be expected to destroy fibres passing from SII to SI via the white matter but to spare intracortical association fibres arising and terminating in SI. Degenerating terminals are relatively sparsely distributed in SI: in two series, one from the superficial and one from the deep half of a block, and numbering 34 and 29 sections respectively, only 14 unequivocal degenerating terminals were observed (figure 3).

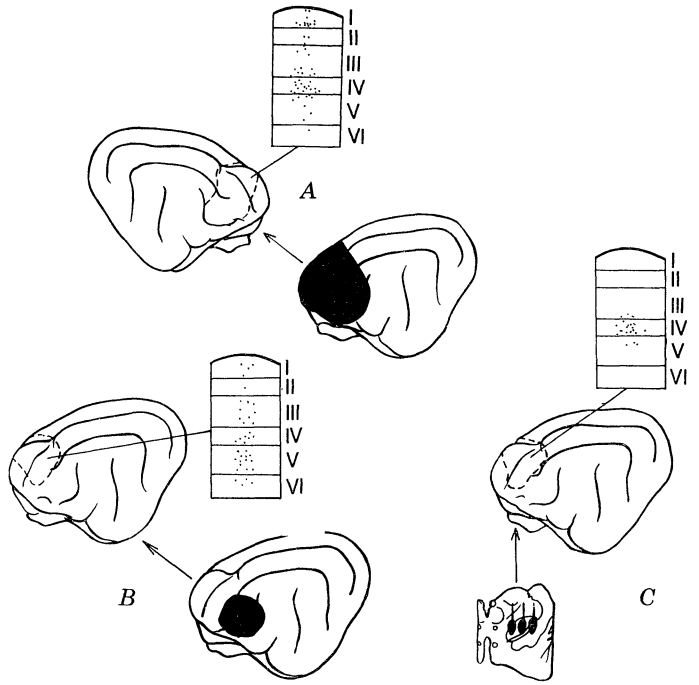


FIGURE 4. The distribution of degenerating axon terminals in repeated series of thin sections from single blocks of SI, in experiments in which commissural (*A*), cortico-cortical (*B*) and thalamo-cortical (*C*) afferents were interrupted. The lesion is in each case shown in black. Note that because adjacent laminae of the cortex tend to merge with one another, the lines indicating the boundaries between them are somewhat arbitrary.

These were, however, distributed to all cortical layers. In repeated series from this block 92 degenerating terminals showing definite synaptic contacts were encountered. These were scattered throughout all six laminae of the cortex but were especially concentrated in the intermediate layers—III to V (figure 3). A similar laminar pattern was observed in series from other blocks and in the other two brains with similar lesions (figure 4).

Most cortico-cortical terminals make synaptic contact with one, or occasionally two dendritic spines (figures 26 and 27, 29 to 31, plates 48 to 50), which are sometimes seen to be attached to dendrites of small (*ca.* 1 μm) to medium (*ca.* 3 μm) diameter (figure 27, plate 48). A number, however, seem to end directly on dendritic shafts. In these, the dendrite was of small to medium diameter; unfortunately, in all the examples collected, the profile was somewhat irregular and it is possible that the endings were in fact upon a very short spine and with a broad base—a

'sessile' spine (figure 26, plate 48). Synaptic contact zones on both spines and dendrites were of the asymmetrical type (figures 26 and 27, 29 to 31, plates 48 to 50). Degenerating cortico-cortical terminals usually appear singly and not in groups; in three instances (figure 29, plate 48), they were seen to be *en passant* terminals of unmyelinated axon segments.

Degenerating cortico-cortical fibres are myelinated and in the deep layers of the cortex of SI vary from 3 to 4 μm in total diameter. Superficial to layer V some degenerating fibres of this size are still present but the majority are thinner (1 to 1.5 μm), though still myelinated. This suggests that some degree of branching occurs in the deeper layers. The thin degenerating fibres are found as far superficially as layer I but, again, no comment can be made concerning the nature of their preterminal ramifications.

Intrinsic association fibres

The distribution of intrinsic association fibres (i.e. fibres arising and terminating in the same cortical area) has not been studied in detail. This would be a long and difficult task entailing extensive and systematic use of very small lesions. However, a certain number of observations made in the brain in which a segment of the cortex was isolated from neighbouring regions, are sufficiently significant to justify their inclusion. In this brain a part of the hindlimb region of SI at the medial end of the posterior sigmoid gyrus, was separated from the rest of the cortex by knife cuts made in such a manner as to preserve as far as possible the continuity of the overlying pia mater and, therefore, the blood supply to the isolated cortex. Such a lesion could be expected to divide all the extrinsic afferents to the hindlimb area, and also to destroy a considerable number of the intrinsic association fibres passing between different parts of the hindlimb representation.

Four days after operation, oedema in and around the isolated region of cortex was scarcely noticeable and thin sections of blocks taken from the middle of the affected area showed surprisingly good fixation, indicating that the vascular supply had not been greatly compromised. In such thin sections, degeneration was intense: 51 degenerating terminals, all showing distinct synaptic contact zones, were observed in a single thin section which encompassed only layers I to IV of the cortex. In the deeper layers of the cortex, degeneration was equally heavy, 33 degenerating terminals being seen in a thin section from the deep half of the same block. This total of 84 unequivocal degenerating terminals is approximately thirty times greater than the total number seen in any comparable pair of sections after interruption of any one of the extrinsic afferents and approximately nine times the total seen in three pairs of sections after separate interruption of the three sets of extrinsic afferents. The vast majority of degenerating terminals in this brain make synaptic contact by means of asymmetrical thickenings with dendritic spines, but unlike in the other experiments, a considerable number end directly on the shafts of dendrites of medium and large diameter (figure 31, plate 50). It is significant that many of these terminals are associated with symmetrical membrane thickenings. Degenerating terminals still form a minority of the total axon terminals present (see figure 28, plate 48), very large numbers of normal ones persisting in all layers.

Degenerating myelinated axons of every diameter are present in all layers. In all blocks from this region, bundles of very thin (*ca.* 0.5 μm) degenerating myelinated fibres were encountered in layer I, lying immediately deep to the subpial glia (figure 30, plate 49). In sections cut perpendicular to the pial surface, they are seen in both transverse and longitudinal section and gave the impression of radiating out in all directions from the knife cuts. In other brains, thin

degenerating fibres of this type were only observed in blocks taken from parts of SI lying close to a lesion in SII. They were not encountered in blocks from more distant parts of SI, nor in brains with lesions in the thalamus or somatic sensory cortex of the opposite side.

Discussion

The more significant features of this investigation are that the three main sets of extrinsic afferents to the first somatic sensory cortex show differences in the laminar distribution of their terminals, and that the majority of the fibres in all three systems terminate in asymmetrical synaptic contacts on dendritic spines. Such a study seemed to be the logical starting-point for a detailed structural analysis of the neo-cortex, but the results must represent no more than a mere fragment of the total body of anatomical information which will be required before our understanding of the cortex is anywhere near complete. It may serve as a basis, however, for the formidable task of unravelling the intrinsic organization of even a single cortical area and does indicate that, to a certain extent at least, the latter should be amenable to analysis.

Highly characteristic laminar patterns of termination are shown by each of the three afferent systems. The most distinctive is that of the thalamo-cortical fibres. Following lesions in the thalamus, there is a very dense concentration of degenerating terminals in layer IV and in adjacent parts of layers III and V, and a second, far smaller but consistent, group in the deeper aspect of layer I. No degenerating terminals occur in other layers, with the possible exception of more superficial parts of layer III where a very occasional degenerating terminal was seen in some blocks. Such a distribution of thalamo-cortical terminals is virtually identical to that shown by Lorente de Nó (1949) in Golgi preparations, but whether the bilaminar pattern is indicative of two distinct sets of thalamic afferents akin to the 'specific' and 'non-specific' fibres of that author cannot be determined. In contrast to the very clear-cut bilaminar distribution of thalamo-cortical endings, the terminal distribution of commissural and cortico-cortical fibres is perhaps less marked, as they both end in all cortical layers. They do, however, display some differences in the relative concentration of degenerating terminals: commissural axons distribute endings chiefly to layer IV and the deeper aspects of layers III and I, whereas the terminals of cortico-cortical fibres are found chiefly in layers III to V.

The majority of fibres from all three sets of extrinsic afferents terminate in the same manner, that is, upon dendritic spines. Commissural fibres invariably end on spines and in only two cases was a commissural terminal seen to contact the adjacent dendritic shaft as well. Cortico-cortical fibres from SII also end mainly on spines; a small number of cases were seen in which such terminals apparently made contact with a dendritic shaft, although every sample was open to the alternative explanation that the contact could have been upon a very sessile spine. Degenerating axo-dendritic terminals were only encountered with any frequency in brains with lesions in the thalamus, although even here at least 75 % of the endings were of the axo-spinous type. The dendritic spine, therefore, is the main receiving surface for all extrinsic afferents. In the brain in which the hindlimb area of SI was isolated from the rest of the cortex, and in which a certain proportion of intrinsic association fibres must have been interrupted, many more degenerating endings were seen on dendritic shafts—some of them very large ones—in all cortical layers; none were seen to make synaptic contact with neuronal perikarya. In no case in which the extrinsic afferents alone were interrupted was a degenerating terminal seen on a large main stem dendrite close to its parent cell soma, nor upon the perikaryon itself. Although

perhaps unlikely, the theoretical possibility does exist, however, that the use of survival periods longer than six days might show such endings on large dendrites or upon perikarya, as other populations of fibres which degenerate at a slower rate could conceivably be present. The present evidence, as far as it goes, is that at least the terminals upon the proximal parts of large dendrites are derived from axons intrinsic of SI. It should be pointed out, however, that only one group of cortico-cortical afferents has been investigated—those passing from SII to SI. The mode of termination of similar fibres passing from the motor cortex to SI can be expected on *a priori* grounds to be similar but it should also be examined.

A further point of similarity between the three sets of extrinsic afferents is that, as far as can be seen in the experimental material, they make synaptic contacts of the asymmetrical type (Gray 1959; Colonnier 1968) with the postsynaptic profile. Recognition of the synaptic complex as an asymmetrial one is to some extent tentative, as it is based largely on the appearances of the postsynaptic membrane; any electron dense material deep to the presynaptic membrane would inevitably be obscured by the extreme density of the degenerating axoplasm. There is additional justification for interpreting these contacts as asymmetrical, however, because in normal material, virtually all endings on dendritic spines are of this type (Gray 1959). Such endings usually contain synaptic vesicles which are spheroidal in aldehyde-fixed material. If current speculation, that endings with spheroidal vesicles and asymmetrical thickenings are the basis of excitatory synapses, is correct (see Uchizono 1968; Colonnier 1968; Walberg 1968), then it would appear that all the extrinsic afferents to the primary sensory areas are excitatory. Following isolation of the hindlimb subdivision of SI, a certain proportion of the degenerating endings seen were found to terminate with symmetrical thickenings upon large stem dendrites. In normal aldehyde-fixed material many such endings in this position tend to possess synaptic vesicles which are flattened or irregular in shape (Colonnier 1968; Jones & Powell 1970*b*). These findings, together with the present knowledge that flattened vesicles and symmetrical synaptic thickenings are frequently associated with known inhibitory synapses (Bodian 1966; Price 1968; Uchizono 1968; Larramendi, Fickenscher & Lemkey-Johnston 1967) could lead to the speculation that all inhibition in a subdivision of the cortex is mediated by axons intrinsic to that subdivision. This is in keeping with certain observations of Mountcastle & Powell (1959): 'the fact that no first order afferent fibers are concerned with inhibition alone, and that inhibition has been observed at each successively higher level of the dorsal column-medial lemniscal system, suggests at once that some collateral mechanism is involved at each synaptic station. This is at least compatible with the observation that the latency of inhibition is slightly longer than that of excitation.'

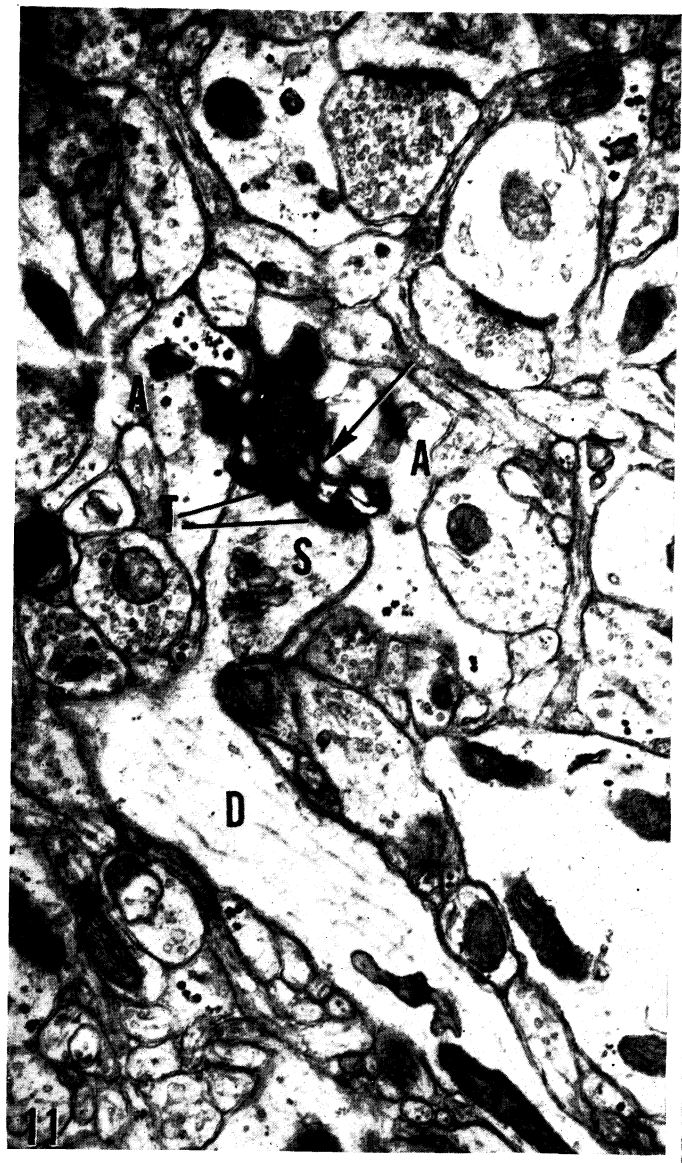
Description of plate 43

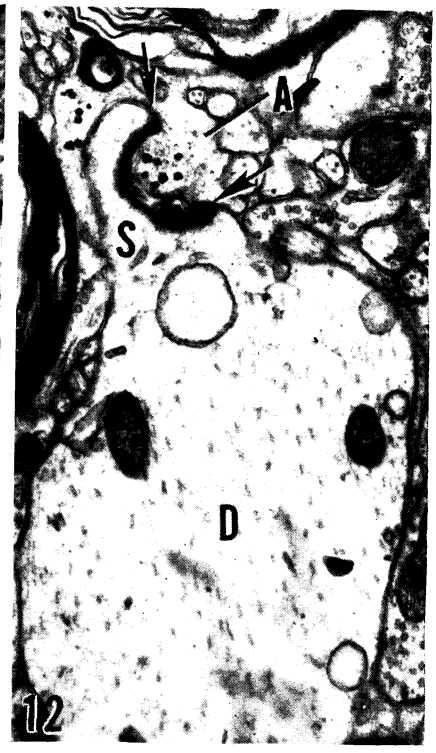
Figure 11. A degenerating commissural axon terminal (arrow) in layer III of SI. Note that it ends on a spine (S) attached by means of a short stalk to a dendrite (D) of small to medium diameter. Other abbreviations as in figure 10. × 25000; lead citrate and uranyl acetate.

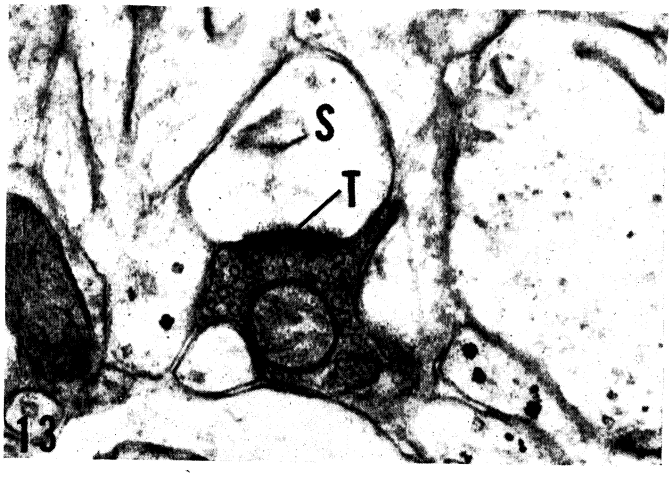
Figure 12. A commissural axon terminal at a very late stage of degeneration (arrows). It makes synaptic contact with a spine attached to a dendrite of medium diameter in layer V of the cortex of SI. × 29000; lead citrate and uranyl acetate.

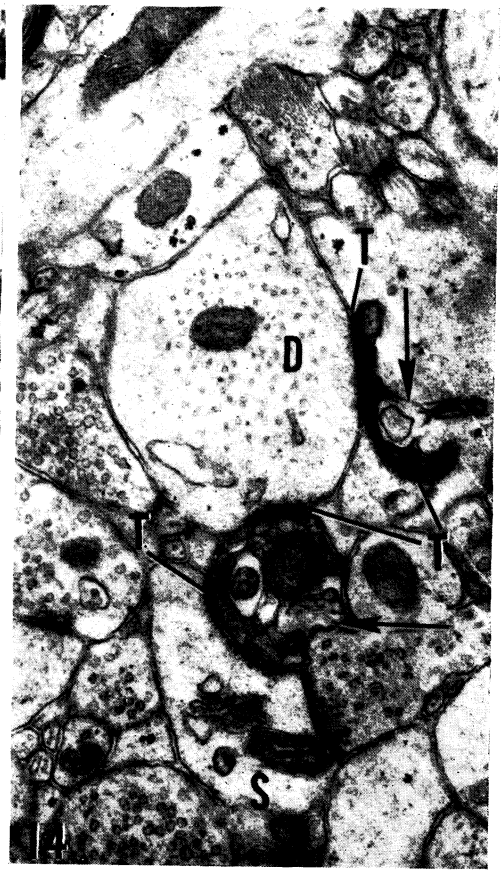
Figure 13. A degenerating axon terminal at a relatively early stage of degeneration ending on a dendritic spine in SII following a lesion confined to the contralateral SII. × 40000; lead citrate and uranyl acetate.

Figure 14. The single instance in which degenerating commissural axon terminals (arrows) were seen to make synaptic contact with both a dendritic spine and the shaft of an adjacent dendrite. The synaptic contact zones are indicated (T). × 35000; lead citrate and uranyl acetate.









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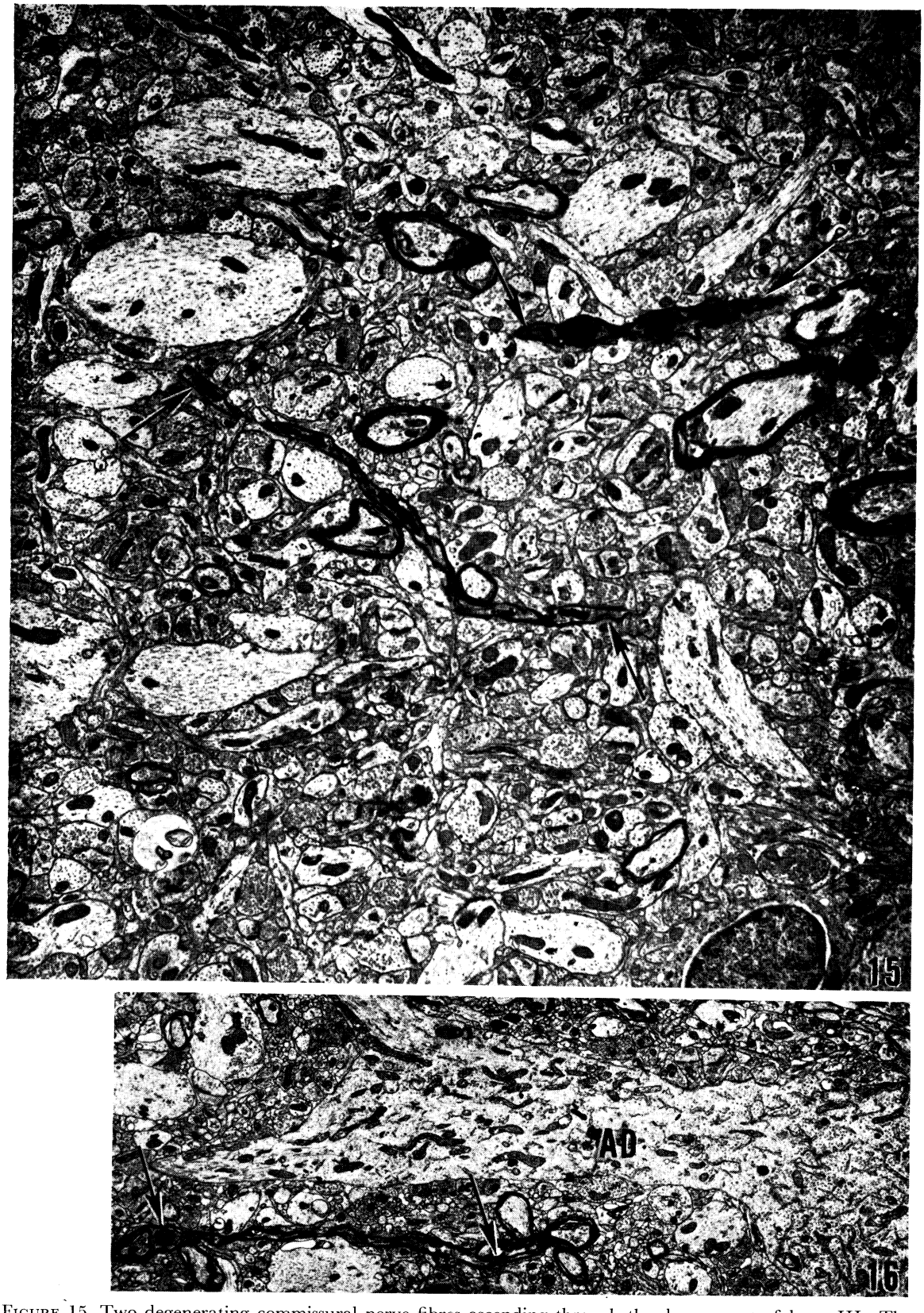


FIGURE 15. Two degenerating commissural nerve fibres ascending through the deep aspect of layer III. The fibres (arrowed) are thinly myelinated. The superficial aspect of the brain is to the left. × 8000; lead citrate and uranyl acetate.

FIGURE 16. A further small degenerating commissural fibre (arrows) ascending through layer V in association with the apical dendrite (AD) of a large pyramidal neuron. Orientation as above. × 5000; lead citrate and uranyl acetate.

FIGURE 17. A degenerating thalamo-cortical axon terminal (double arrows) ending on a dendritic spine (S) in the junctional region between layers III and IV. This region is characterized by a dense 'feltwork' of thin unmyelinated axons (arrows). A, astroglial processes containing filaments (F) and glycogen granules. × 30000; lead citrate.

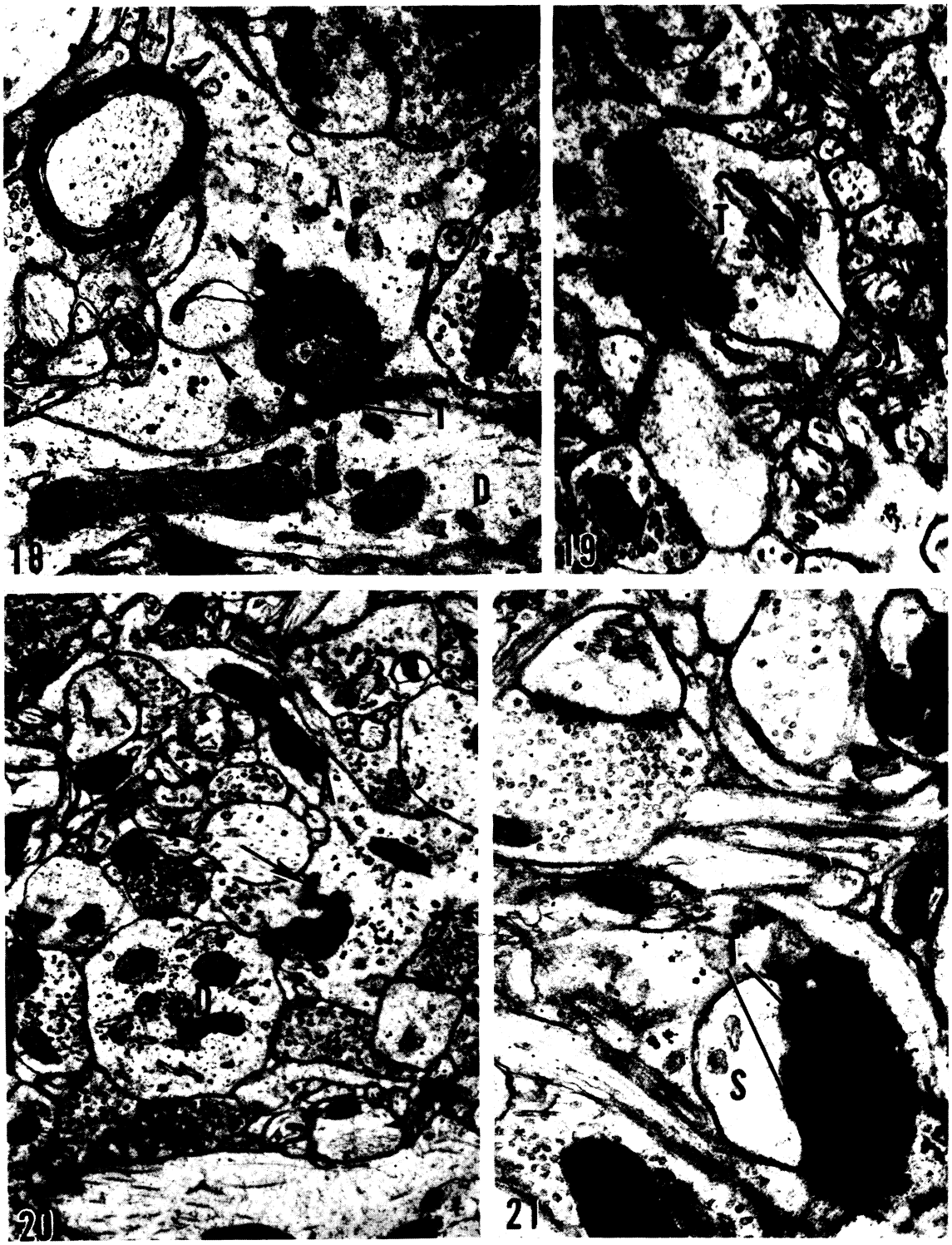
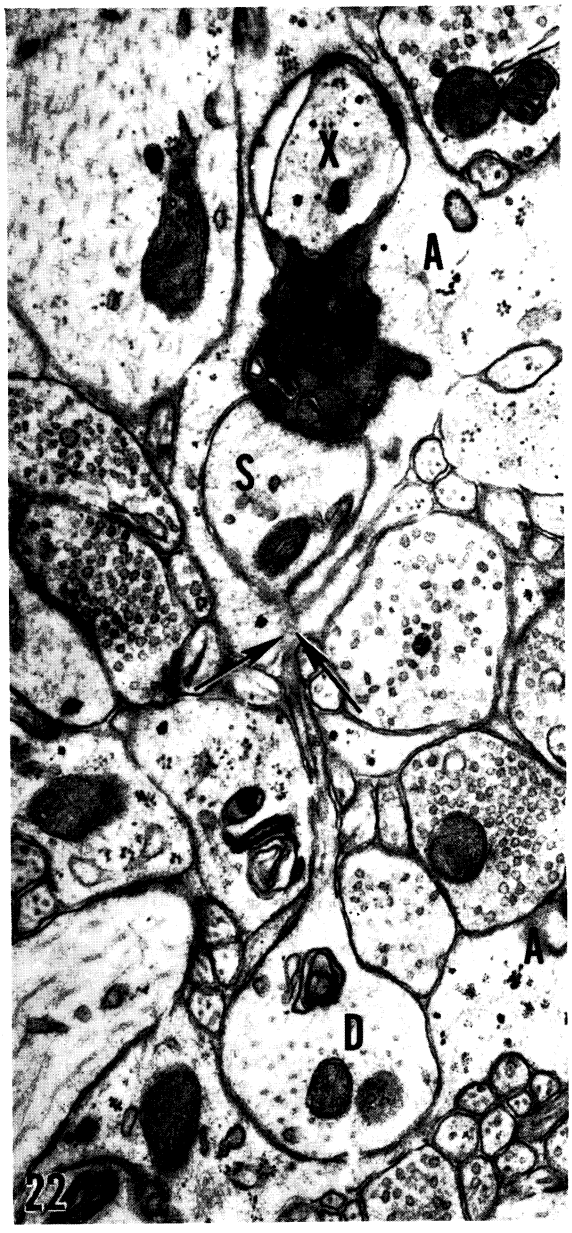


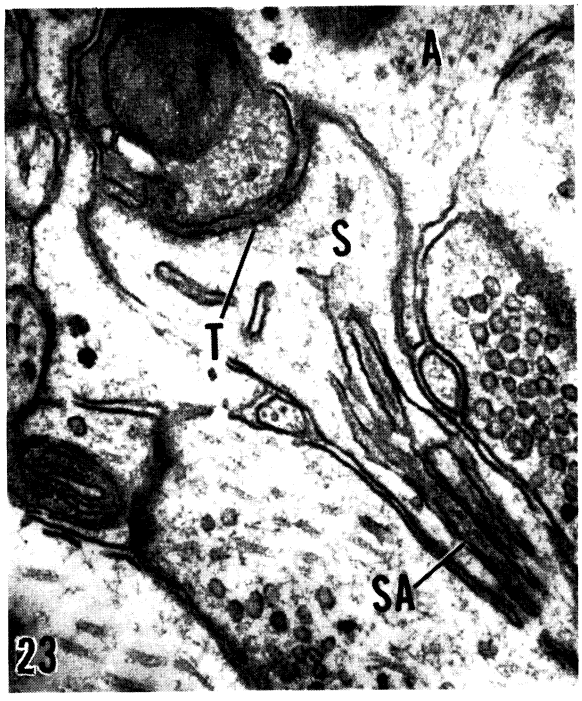
FIGURE 18. A degenerating terminal of a thalamo-cortical axon ending (T) on a small dendrite (D) in layer IV of SI. Note the manner in which the astroglial process (A) has enfolded itself (arrow heads) around the 'tail' of the terminal. × 33000; lead citrate.

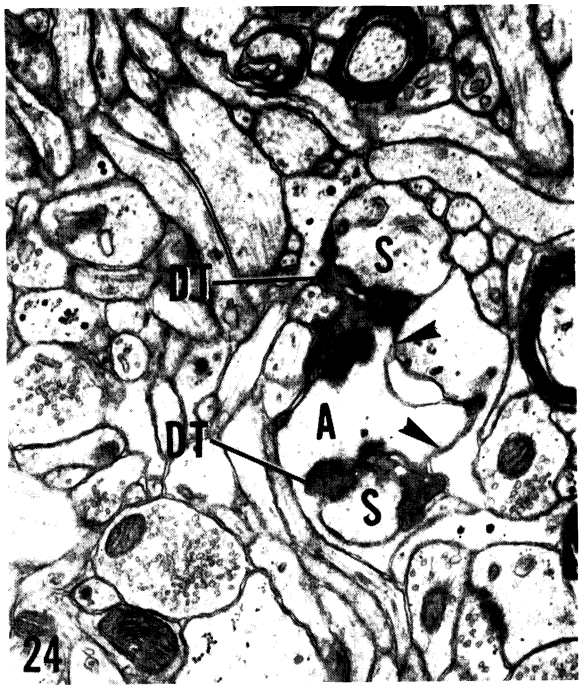
FIGURE 19. Degenerating thalamo-cortical axon terminal ending by means of a double synaptic contact (T) on a dendritic spine. The spine apparatus (SA) of the latter is particularly well shown. × 41000; lead citrate and uranyl acetate.

FIGURE 20. A degenerating thalamo-cortical axon terminal (arrow) making synaptic contact with a small dendrite (D) which also receives at least 4 other (normal) axon terminals. Note the reactive astroglial process (A) containing glycogen granules and folding around the degenerating terminal. × 20000; lead citrate.

FIGURE 21. A thalamo-cortical axon terminal at a very early stage of degeneration. There is a little shrinkage of the terminal but synaptic vesicles are still obvious. The terminal contacts a dendritic spine by means of a double synaptic thickening (T). × 29000; lead citrate and uranyl acetate.







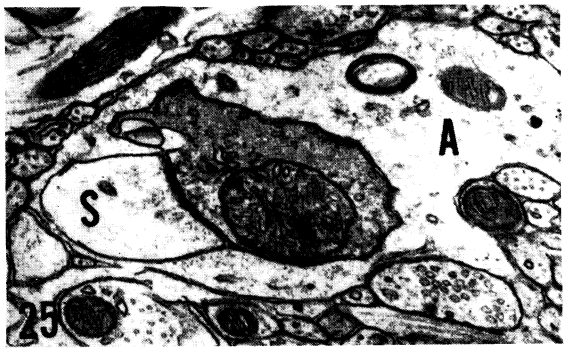
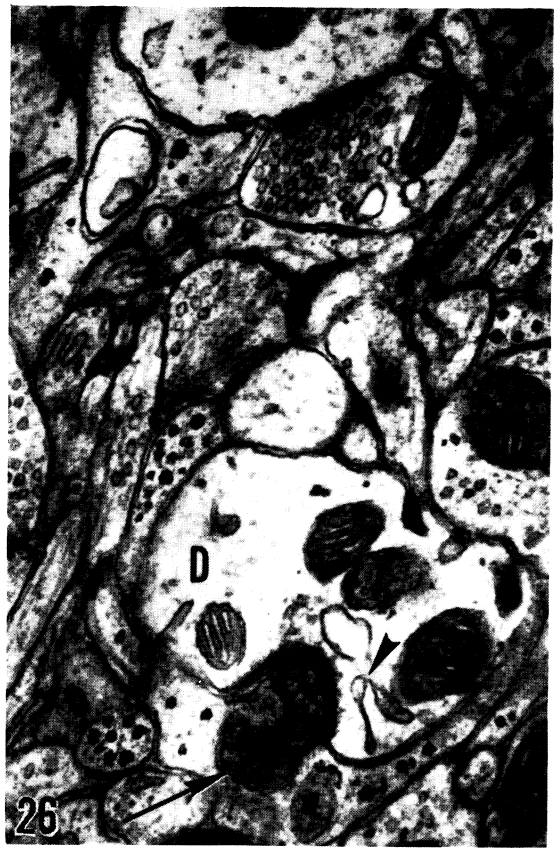


FIGURE 22. A degenerating thalamo-cortical axon terminal making synaptic contact with a dendritic spine which is in turn attached by a narrow pedicle to a small dendrite. Note how the astroglial process (A) has not only pierced the degenerating terminal (X) but has also wrapped itself around the attachment of the spine to its pedicle (arrows). × 30000; lead citrate.

FIGURE 23. A degenerating thalamo-cortical terminal ending on a dendritic spine which contains spine apparatus (SA) in its pedicle. × 66000; lead citrate.

FIGURE 24. Two degenerating thalamo-cortical terminals (arrows) which appear to be ending on adjacent dendritic spines (S) and which are joined by a narrow sliver of degenerating axoplasm (arrow heads) around which the astroglial process has wrapped itself. × 23000; lead citrate.

FIGURE 25. A degenerating thalamo-cortical terminal and the spine upon which it terminates both enwrapped by an astroglial process. Layer I of the cortex. × 29000; lead citrate.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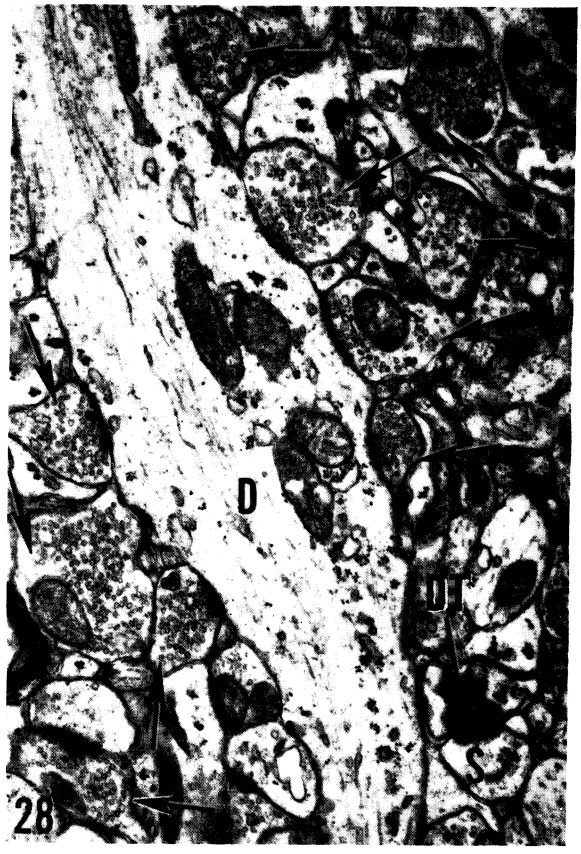
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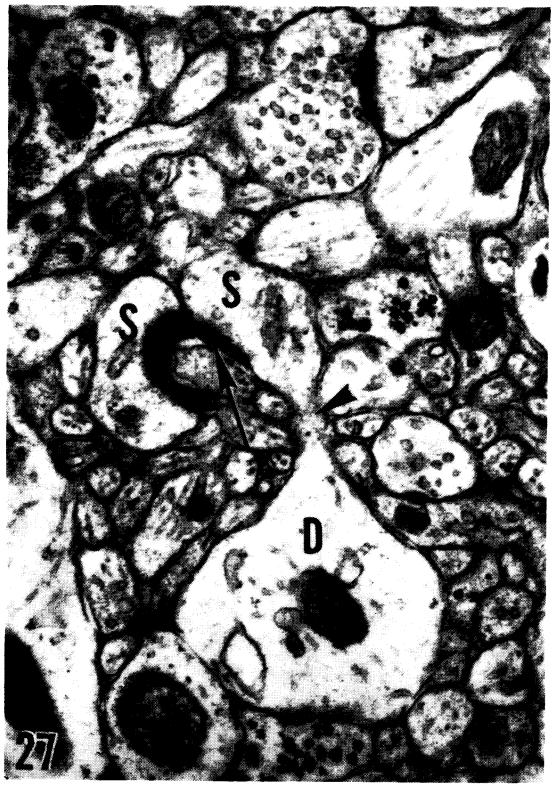
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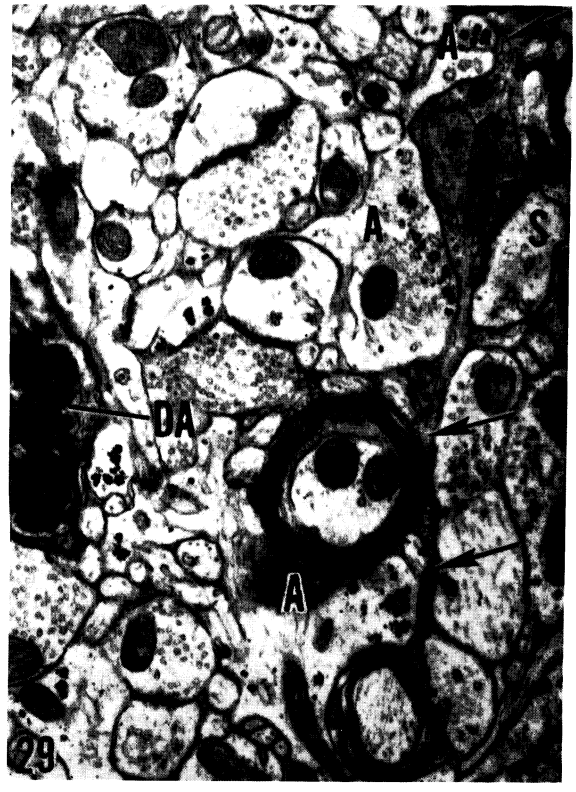
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Perhaps one of the most intriguing problems raised by the present results is whether the three sets of extrinsic afferents terminate on the same or on different cortical neurons. The fact that the majority of degenerating endings appear on dendritic spines suggests at once that the pyramidal cells are the main sites of termination of all three pathways; this type of cell has a heavy population of spines (Ramón y Cajal 1911; Globus & Scheibel 1967*a*; Valverde 1967), whereas stellate and fusiform cells have few or none (Globus & Scheibel 1967*a*). However, approximately 25 % of thalamo-cortical endings also end on small dendritic shafts and, moreover, in the same section these small shafts often receive many other (normal) endings as well (see figure 20, plate 46). There are some grounds for considering that the possession of small dendrites which receive many axon terminals along their length is a characteristic of stellate cells (Colonnier 1968) so the possibility exists that thalamo-cortical fibres could terminate on both pyramidal and stellate neurons. Of course, the alternative view, that they end on spines and shafts of the same pyramidal neuron, is by no means disproven and only the extensive use of serial sections could solve the problem. Studies of experimental Golgi-impregnated material, in which deafferentation or sensory deprivation are followed by failure of dendritic spines to impregnate (Globus & Scheibel 1967*b*, *c*; Valverde 1967, 1968), or by reduction in number and size of stellate cell dendrites (Coleman & Riesen 1968), would tend to support the conclusion that thalamo-cortical afferents terminate on both types of cell. If this is so, however, the present results indicate that, despite the large number of stellate cells in the primary sensory areas of the cortex, the *majority* of the thalamo-cortical afferents end not on these but on the pyramidal cells which are usually considered the efferent elements of the cortex (Lorente de Nó 1949). The function of the stellate cell should perhaps, therefore, be sought in terms of its being a modulator of cortical activity rather than as the prime receiving element. In having a short axon ramifying within the vicinity of its perikaryon, the stellate neuron is a good example of the Golgi type II cell which has been shown, for example, in the cerebellar cortex (Eccles, Ito & Szentágothai 1967) to have inhibitory functions. Therefore, the stellate cell of the cerebral cortex may be the morphological basis of the 'collateral inhibitory mechanism' of Mountcastle & Powell (1959). It is noteworthy that Mountcastle & Powell consistently observed that cells closely adjacent in the cortex were reciprocally related to (i.e. excited or inhibited by) appropriately located peripheral stimuli.

Description of plate 48

Figure 26. A degenerating axon terminal (arrow) in S I following damage to the ipsilateral S II. One interpretation is that it is ending upon the shaft of a dendrite (D), but the presence of a few irregular cisternae resembling spine apparatus (arrow head) and the associated invagination suggest that this could be a 'sessile' spine. × 42000; lead citrate and uranyl acetate.

Figure 27. A late degenerating cortico-cortical axon terminal (arrow) ending on two dendritic spines in layer III of the cortex. One of the spines is attached by a narrow stalk (arrow head) to a dendrite (D) of small diameter. × 33000; lead citrate and uranyl acetate.

Figure 28. An average field of view in sections from the brain in which the hindlimb subdivision of S I was isolated. Despite interruption of all extrinsic afferents and a considerable proportion of the intrinsic ones as well, a large number of axon terminals (arrows) remain unaffected. DT, degenerating terminal. × 18000; lead citrate and uranyl acetate.

Figure 29. A very thin unmyelinated axon (arrows) at a very early stage of degeneration making an *en passant* synaptic contact with a dendritic spine (S) in S I following a lesion in the ipsilateral S II. Note the glial reaction (A) in the vicinity of the degenerating axon. DA, degenerating myelinated fibre. × 21000; lead citrate.

In the case of commissural fibres, the situation is perhaps a little more clear, for they terminate almost exclusively on dendritic spines. It is to be assumed, therefore, that they end only on pyramidal neurons, and this is to some extent supported by the experimental Golgi studies on the visual cortex of the mouse and rabbit (Globus & Scheibel 1967*b*, *c*; Valverde & Estéban 1968). Cortico-cortical axons terminate mainly on spines, although a few may also end on shafts. As the former type of ending predominates, a high proportion, if not all, of their terminals must also be on pyramidal cells. All of the above interpretations rest upon the assumption that pyramidal neurons possess dendritic spines and that stellate and other short axon cells have few or none (Globus & Scheibel 1967*a*). The electron microscopic evidence for this is in general agreement (Colonnier 1968; Jones & Powell 1969*b*), though not necessarily conclusive, Ramón y Cajal (1911), for example, showing a few short axon cells in the molecular layer which have spiny dendrites.

Further detailed study is required before the exact topographic disposition of the three types of extrinsic afferent terminal upon the dendritic tree of the pyramidal neuron is estabished. The present results indicate that commissural fibres end on spines attached to mainly medium-sized dendrites, thalamo-cortical fibres on spines of small dendrites and cortico-cortical fibres on spines attached to dendrites of both sizes. This would imply that commissural axons end mainly on apical dendrites at some distance from the cell soma, whereas thalamo-cortical axons end mainly on side branches of the apical dendrite or on the basal dendrites, and cortico-cortical fibres end on both types. It is difficult to reconcile these findings with the experimental Golgi studies of Globus & Scheibel (1967*a*, *b*, *c*) and Valverde (1967, 1968). The results of these workers suggest that thalamo-cortical axons end on apical shafts and that commissural axons end on side branches of these. However, the discrepancy may be more apparent than real, because in the present investigation the sample of spines which in a single section both received a degenerating terminal and had an attachment to a dendritic shaft was quite small. It is conceivable that those receiving degenerating thalamo-cortical terminals were apical dendrites of small pyramids and that those receiving degenerating commissural terminals were side branches of very large pyramids.

It is noteworthy that axo-spinous terminals from all three sets of extrinsic afferents are concentrated in the deep part of layer I and in layers III to V, with relative or absolute sparing of the superficial part of layer I, and layers II and VI. One interpretation of this distribution is that they all end in relation to the middle portion of the apical dendritic tree of pyramidal cells in all layers. Thus, degenerating axospinous terminals in the deep aspect of layer I could be ending in relation to the middle segment of the apical dendritic tree of pyramidal cells having their somata in layer II and in the superficial part of layer III; those in layer III itself could end in the middle segment of the apical tree of pyramidal cells in the deeper aspect of layer III; those in layer IV on the middle segment of the apical tree of layer V pyramids; those in layer V on the middle portion of the apical tree of layer VI pyramids. The superficial part of layer I, containing only the terminal branches of the apical dendritic trees, and layer VI, containing mainly basal dendrites of pyramidal cells in layers V and VI and the proximal spine-free segments (Globus & Scheibel 1967*a*) of layer VI pyramids receive few if any terminals. This possible, albeit very tentative, interpretation of the topographic distribution of commisural, thalamo-cortical and cortico-cortical terminals upon the dendritic tree of pyramidal neurons is illustrated schematically in figure 5. It should be noted that this interpretation takes no account of 'inverted pyramidal cells' (Globus & Scheibel 1967*a*) and that there are probably additional terminals of

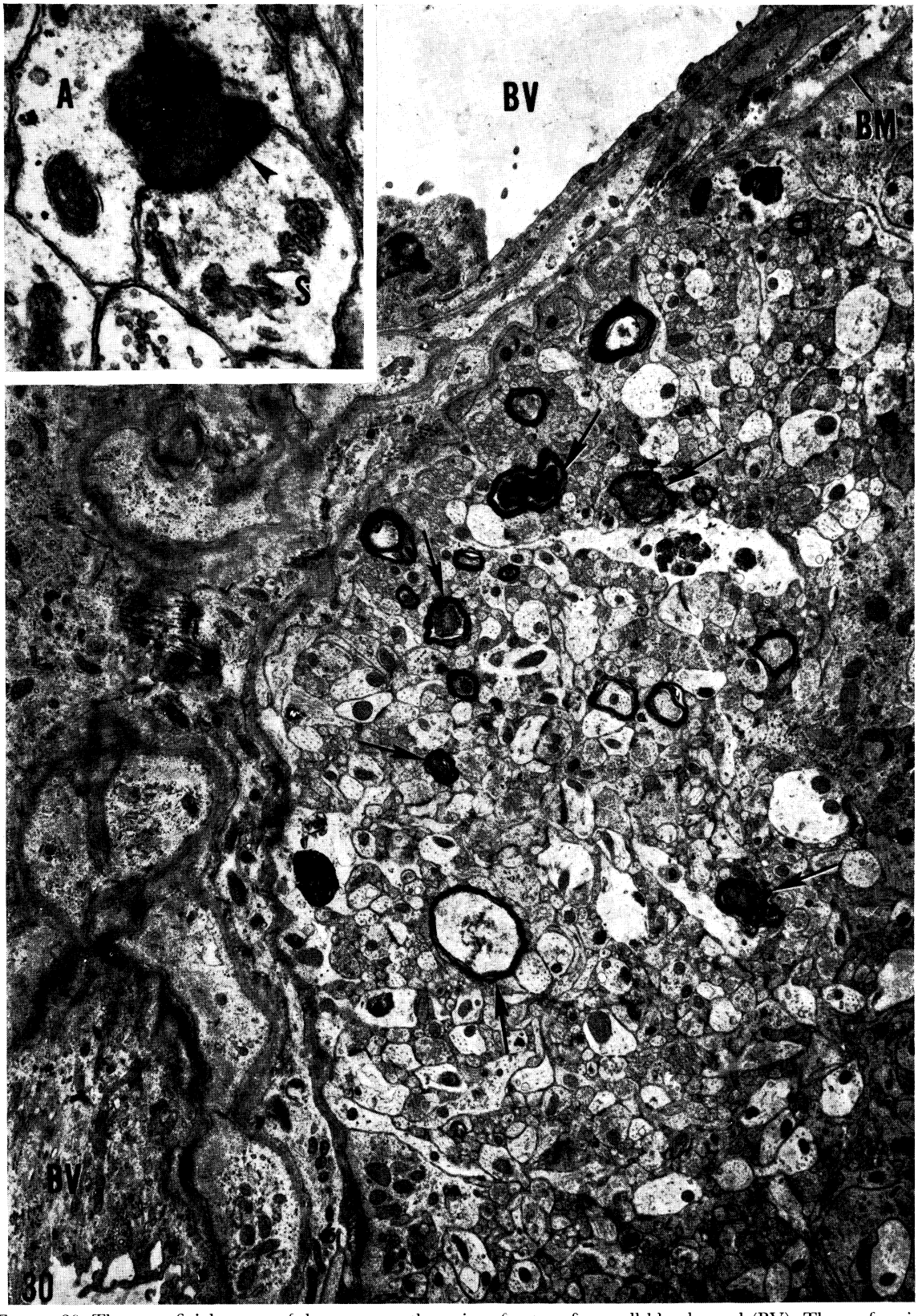

FIGURE 30. The superficial aspect of the cortex at the point of entry of a small blood vessel (BV). The surface is towards the top. The basement membrane (BM) which constitutes the most superficial layer of the brain substance is indicated. A small bundle of degenerating small myelinated axons (arrows) lie immediately deep to the surface. These arise from one of the knife cuts in the brain in which the hindlimb subdivision of SI was isolated and spread out in all directions in this position. × 9000; lead citrate. *Inset*: a degenerating axon terminal ending on a dendritic spine in layer I of SI following a lesion of the ipsilateral SII. The synaptic contact zone is indicated (arrow head). × 54000; lead citrate.

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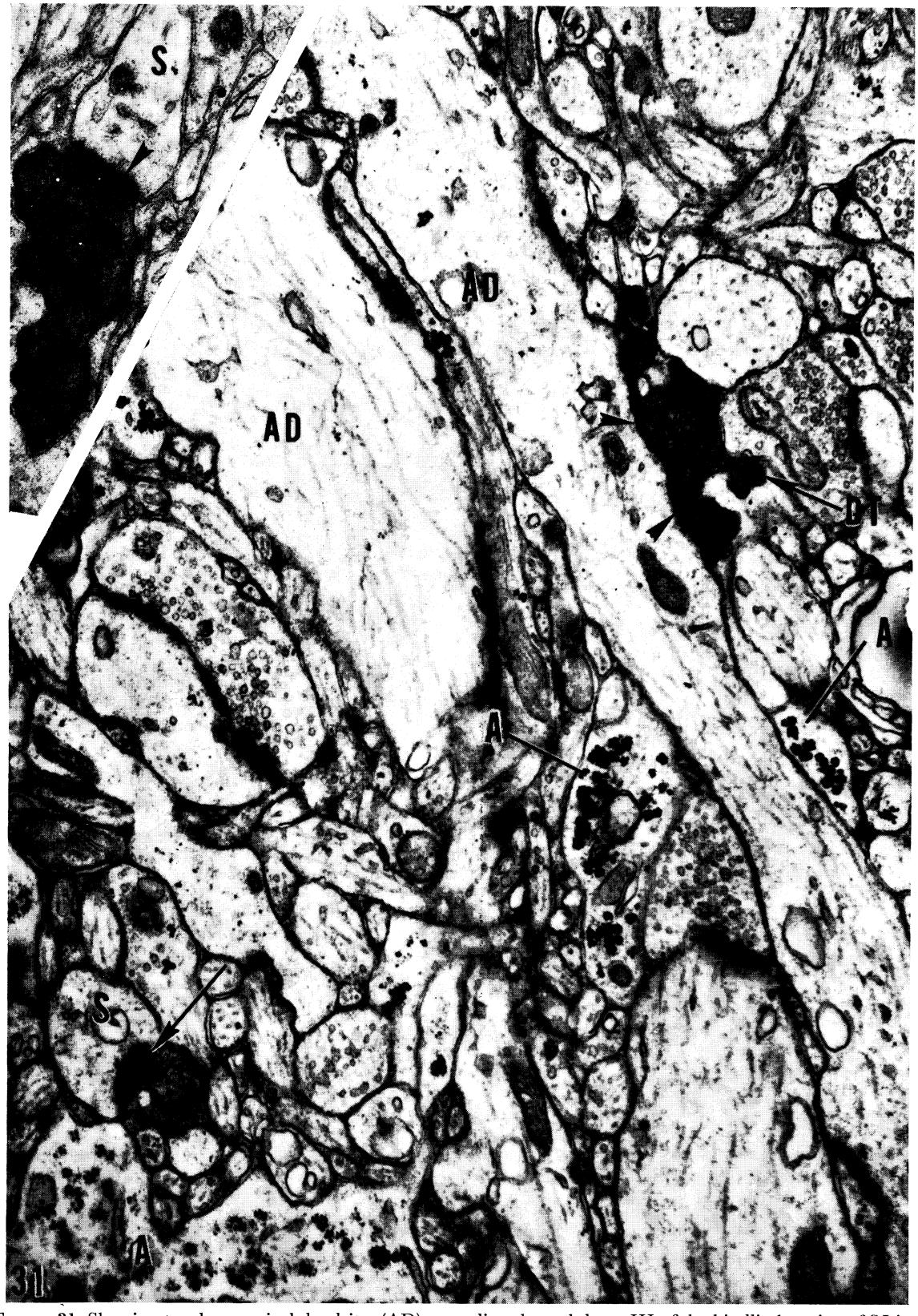

FIGURE 31. Showing two large apical dendrites (AD) ascending through layer III of the hindlimb region of SI in the brain in which this area was isolated from the rest of the cortex. One of the apical dendrites receives a degenerating axon terminal (DT) which apparently terminates in a symmetrical thickening (arrow heads). Another degenerating terminal is also present in the micrograph (arrow) ending on a dendritic spine. Note the very heavy accumulation of glycogen in the astroglial cytoplasm. × 31 000; lead citrate and uranyl acetate. *Inset*: a degenerating axon terminal making an asymmetrical synaptic contact with a dendritic spine in layer III of SI following a lesion in the ipsilateral SII. × 51 000; lead citrate and uranyl acetate.

thalamo-cortical axons upon stellate cells (right hand arrow). It is interesting that all the extrinsic afferent terminals are concentrated at the levels of the tangential bands of intracortical association fibres, including the two bands of Baillarger (figure 5). If, as now seems likely, these bands are composed of the axons of stellate cells and recurrent collaterals of pyramidal cells, then the parts of the pyramidal cells which receive the extrinsic afferent terminals are strategically situated to be influenced by intracortical mechanisms.

Apart from these somewhat speculative considerations, the exact significance of the differences in the laminar distribution of the three sets of extrinsic afferents will probably remain uncertain until it is conclusively determined whether they end on the same or on different cells, or on similar or different parts of the same cell. The observation that the majority of thalamo-cortical afferents terminate in or adjacent to layer IV may be considered in relation to the physiological observations in the visual cortex of Hubel & Wiesel (1962, 1965, 1968). These authors found that, particularly in the monkey and to a lesser extent in the cat, 'simple cells' (interpreted as receiving connexions directly from lateral geniculate neurons) were concentrated in layer IV. On the other hand, 'complex' and 'hypercomplex' cells (interpreted as receiving from many simple and complex cells respectively) were more common in layers II, III, V and VI. The interpretation of these authors would imply that afferents from the lateral geniculate nucleus terminate upon the simple cells which in turn have axons ending on complex cells. In one sense the present results could be taken to support this view but they also permit of another interpretation: it is possible, as pointed out above, that thalamic afferents terminate on two types of cell—on the dendrites of stellate cells of layer IV and on the apical dendritic tree of pyramidal cells in layers III to VI. Similarly, the few fibres to layer I could be terminating in relation to the shafts of the few stellate cells present at this level as well as on the apical dendritic tree of layer II pyramids. The interpretation that thalamo-cortical axons end on both stellate and pyramidal cells is perhaps more in keeping with the observations of Mountcastle (1957) and Powell and Mountcastle (1959) who found that units in columns extending through the full thickness of the somatic sensory cortex were excited simultaneously as the first response to a transient peripheral stimulus. Nor is it entirely contradictory to Hubel & Wiesel's interpretation, for the stellate cells could (and almost certainly do) (Lorente de Nó 1949) terminate on pyramids. This would then make the stellate cells the 'simple' cells and the pyramids the 'complex'. The final analysis however, must await conclusive identification of the neurons upon which the thalamic afferents terminate.

Perhaps the most significant feature of the distribution of commissural fibres is their straight course, their constant diameter at all levels, and their apparent lack of long terminal branches. These observations would suggest that a single such fibre ascends vertically through the cortex without branching widely and terminates only on dendritic spines in its immediate vicinity, though in all cortical layers. Impulses in individual commissural fibres must, therefore, exert an influence only upon a very narrow vertical column of cortex, but must affect neurons at all levels in the column. It is tempting to speculate whether such a column is the anatomical equivalent of the functional columns shown by Mountcastle (1957), Powell & Mountcastle (1959) and Hubel & Wiesel (1962, 1965, 1968) to be one of the basic elements of cortical organization. The axons of cortico-cortical fibres, unlike those of commissural fibres, appear to branch many times within the cortex so that, while they also terminate in all layers, the effect of impulses in such fibres would be distributed over a far greater volume of cortex. Thalamo-cortical axons appear to branch repeatedly, ramify widely and, unlike callosal and cortico-cortical

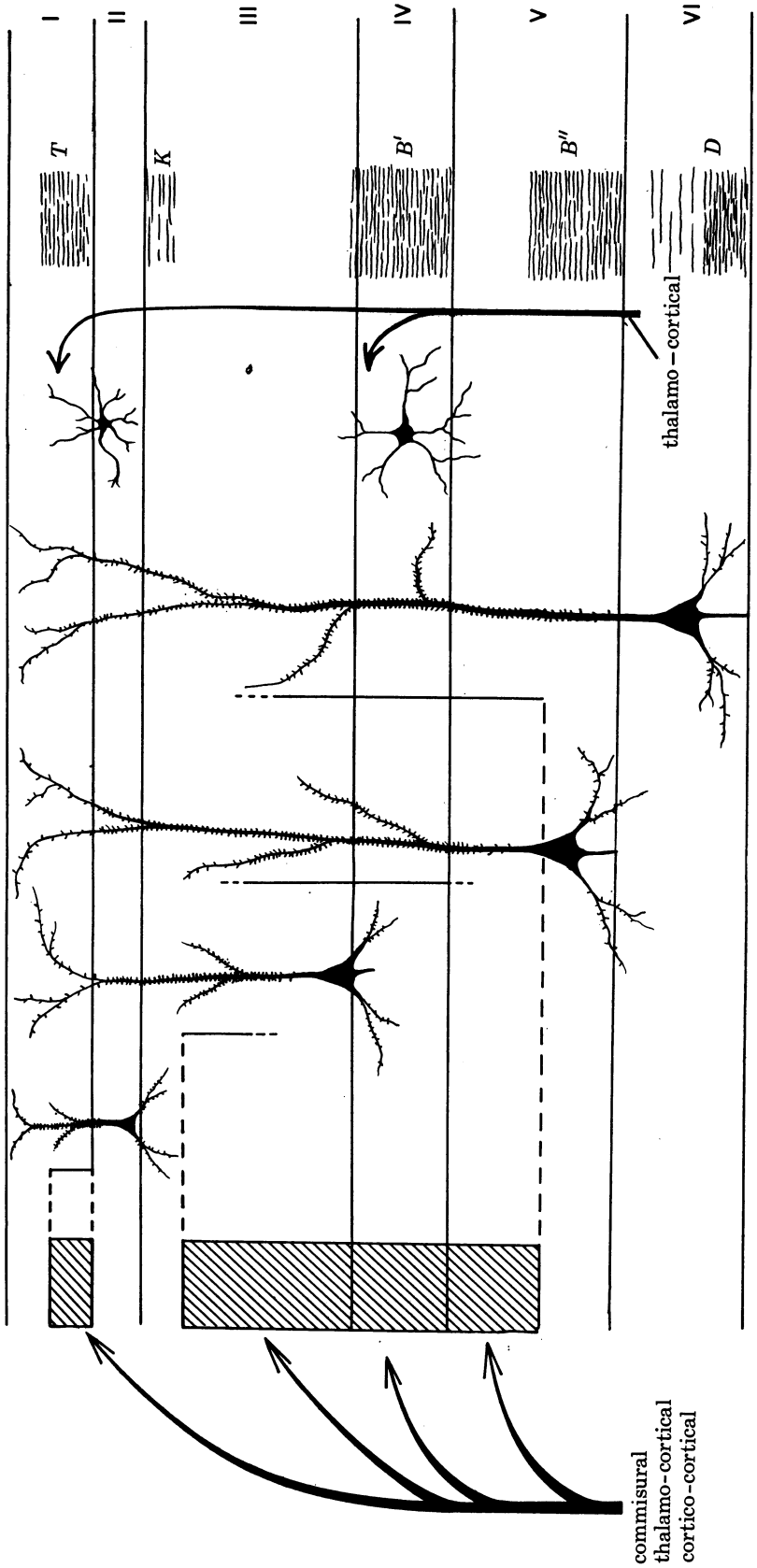

FIGURE 5. A schematic diagram to illustrate one possible interpretation of the results. While the laminar pattern of termination of each set of extrinsic afferents is different from that of the other two, in every case the heaviest concentrations of degenerating terminals fall within two zones (hatching), i.e. the deep part of layer I on the one hand, and layer IV and adjacent parts of layers III and V on the other. As the majority of axon terminals contact dendritic spines, it follows that the three sets of extrinsic afferents terminate mainly on pyramidal neurons, and the positions of the two regions of maximal concentration would suggest that they terminate on the middle segments of the apical dendritic tree of pyramidal cells in all layers (vertical lines). On the right are shown stellate cells of layers II and IV and it should be noted that some thalamo-cortical axon terminals may end on their dendrites. Also on the right the horizontally running bands of intracortical association fibres are indicated. *T*, tangential plexus of layer I; *K*, stria of Kaes; *B'*, *B''*: outer and inner bands of Baillarger; *D*, deep plexus of layer VI. ▨, Regions of greatest concentration of degenerating axo-spinous terminals.

fibres, end in clusters of terminals. These observations are in agreement with others made in normal Golgi-impregnated material (Ramón y Cajal 1911; Lorente de Nó 1949).

The number of degenerating axon terminals, even following total isolation of the hindlimb region of S I, is far less than would be expected by one approaching the question of degeneration in the cortex from a background of light microscopy and the Nauta technique. One reason for this is undoubtedly a conceptual difficulty: with the Nauta method, sections of about 25 μm thickness are commonly used, whereas the average thin section for electron microscopy—about 50 nm thick—represents a mere fraction of this. However, even in such thin sections, the number of normal axon terminals remaining even after undercutting the cortex is vast. This would support the impression that many of the terminals of stellate cells and recurrent collaterals of other cells terminate in the immediate vicinity of their cell of origin. It is also an indication of the complexity of the cortex and of the difficulties to be faced before it is finally analysed from the anatomical point of view. Material for the investigation of the intrinsic association connexions is at present too limited to enable many conclusions to be drawn about this aspect of cortical organization, but they are in accord with the observations of Szentágothai (1965) on 'chronically isolated slabs of cortex'. In such isolated areas of the cortex this author found a marked decrease in axo-spinous and axo-dendritic synapses, but no reduction in axo-somatic synapses and concluded that the latter must be of local origin. The present results, however, have shown that following lesions in the cortex, a small number of fine degenerating fibres radiate out in all directions immediately beneath the pia mater. The mode of ending of the fine fibres beneath the pia mater could not be ascertained in the present material and it is impossible to say whether they remain superficially placed or dip down into deeper layers.

In conclusion, the validity of the experimental electron microscopic technique may be considered. The question must necessarily arise as to whether some of the degenerating terminals could have degenerated as the results of factors other than the operative lesion. Ageing of neurons, and relative anoxia during the anaesthetic, could conceivably account for some of the degeneration. In such small tissue samples as are used for electron microscopy, the presence of a few spontaneously degenerating terminals could well present a false impression of the total distribution. Against this, however, is the fact that not one degenerating terminal was seen in an extensive search of the distal fore- and hindlimb regions of S I following a lesion of the opposite cortex. This observation further shows that it is essential to establish in detail with light microscopic methods the basic organization of a nervous pathway before approaching it from the electron microscopic point of view.

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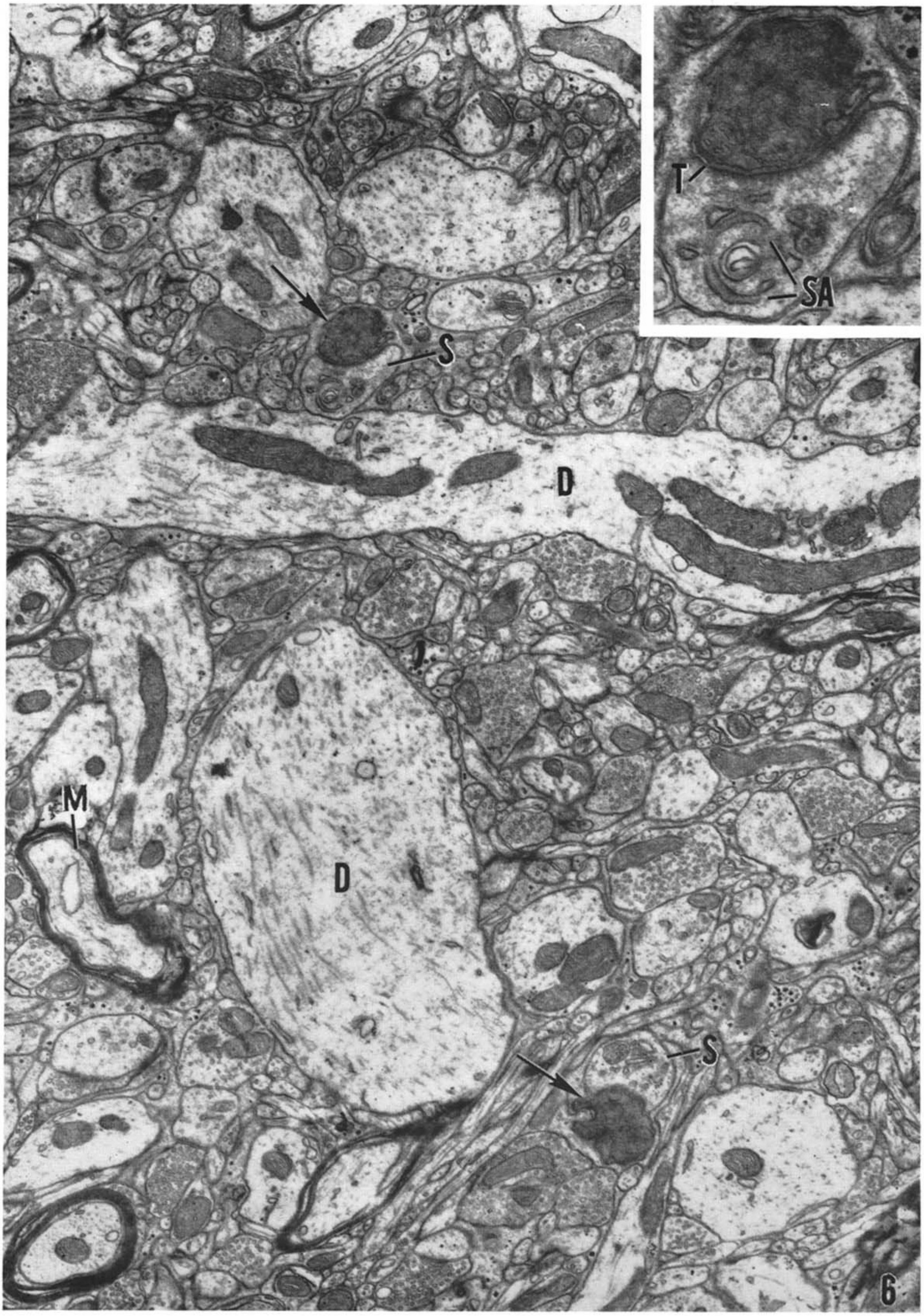
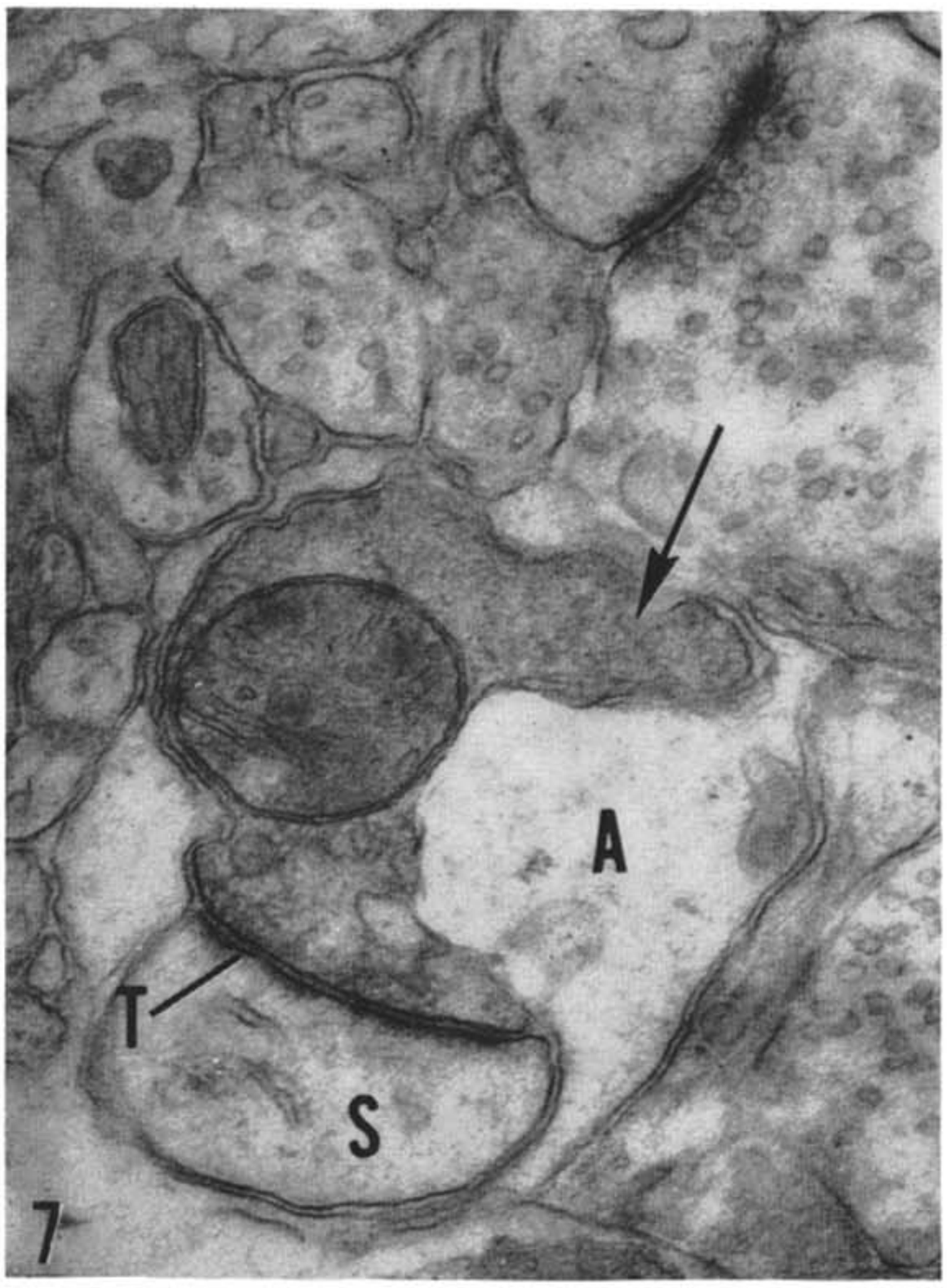
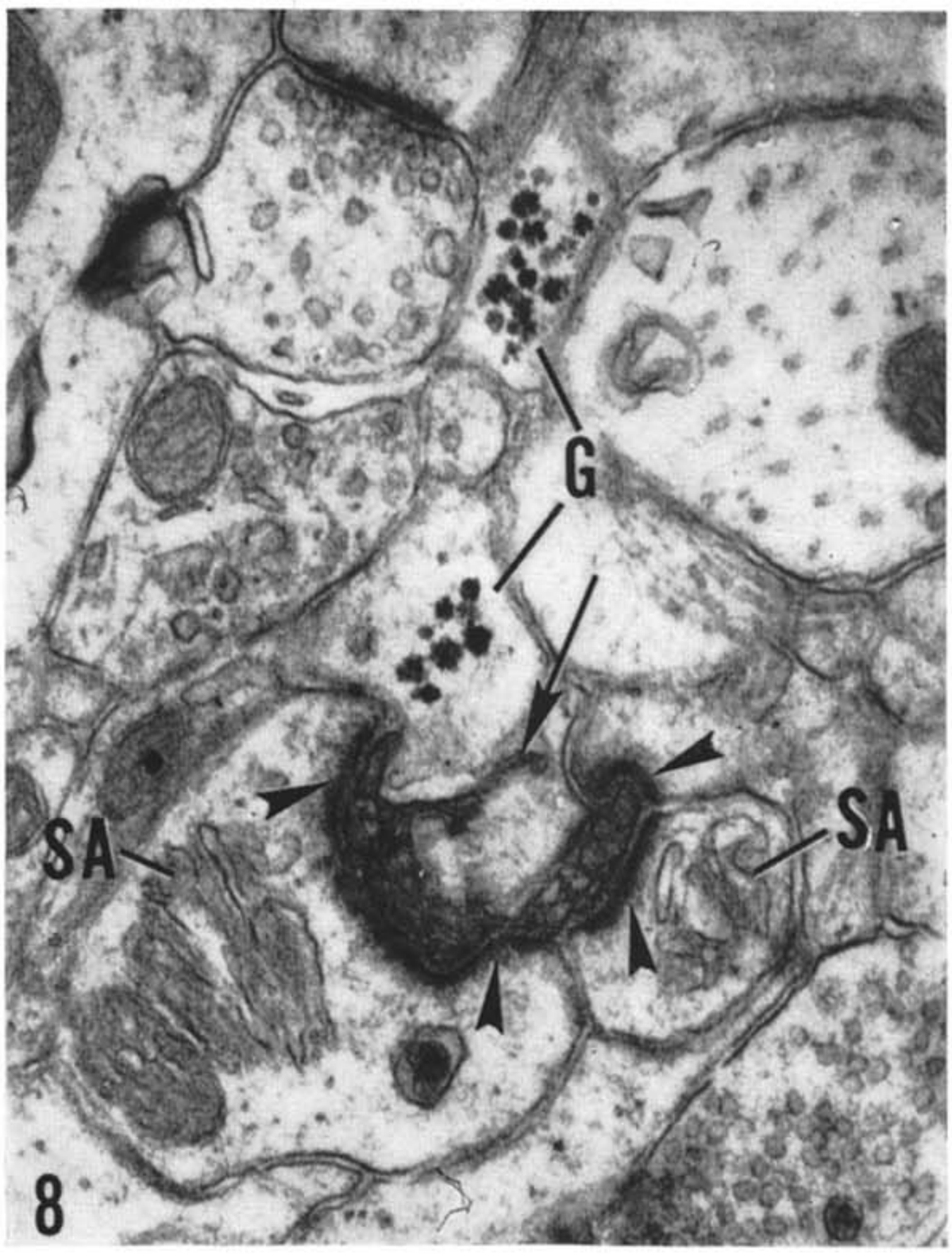
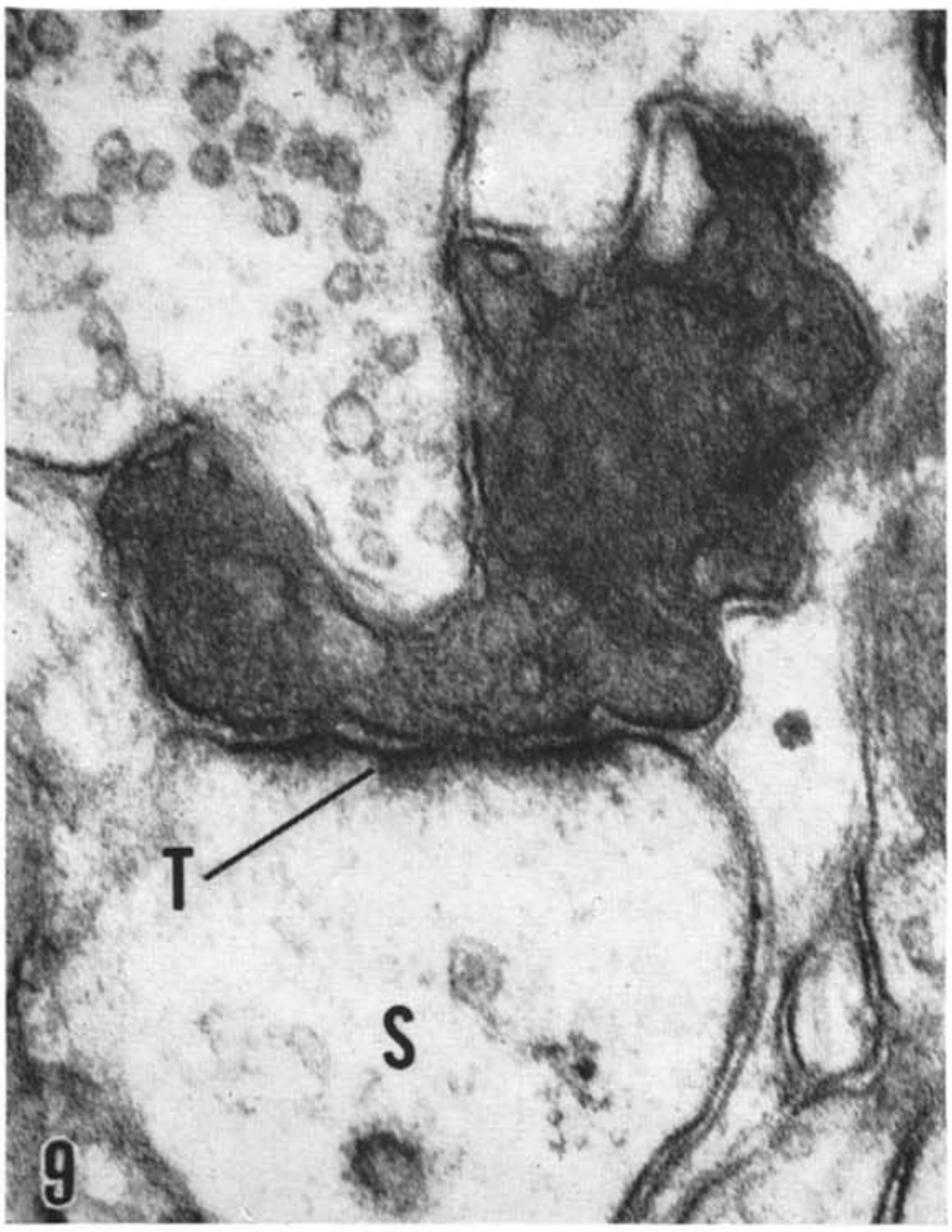


FIGURE 6. Two degenerating axon terminals (arrows) ending in relation to dendritic spines (S) in the deeper aspect of layer III following a lesion of the contralateral somatic sensory cortex. Layer III can be recognised by the presence of large apical dendrites (D) and relatively few myelinated axons (M). The superficial aspect of the brain is towards the left. × 10000. *Inset*: an enlarged view of the upper of the two degenerating axon terminals showing the asymmetrical synaptic thickening (T) and the spine apparatus (SA) in the postsynaptic profile. × 70000; lead citrate stain.







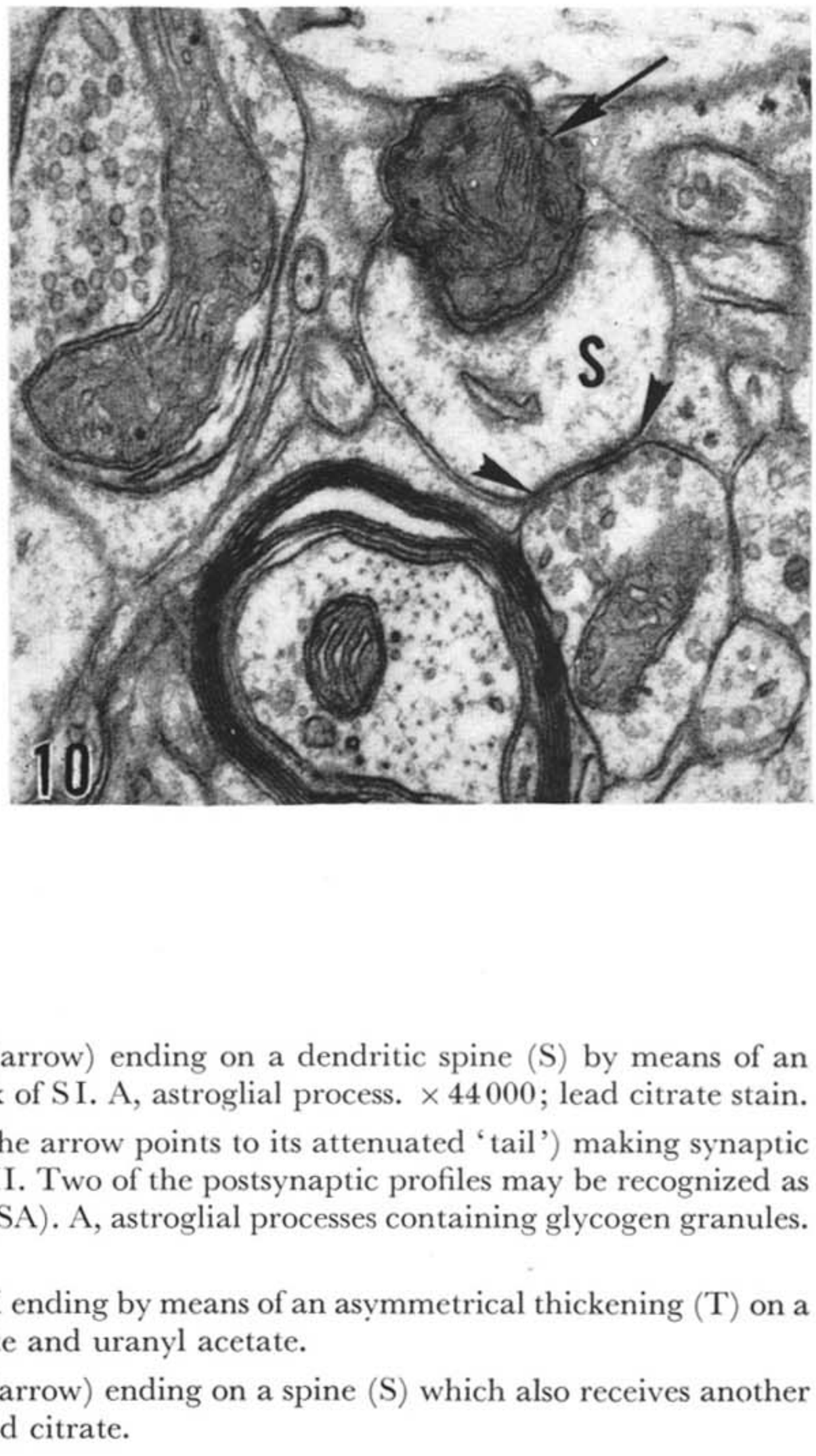
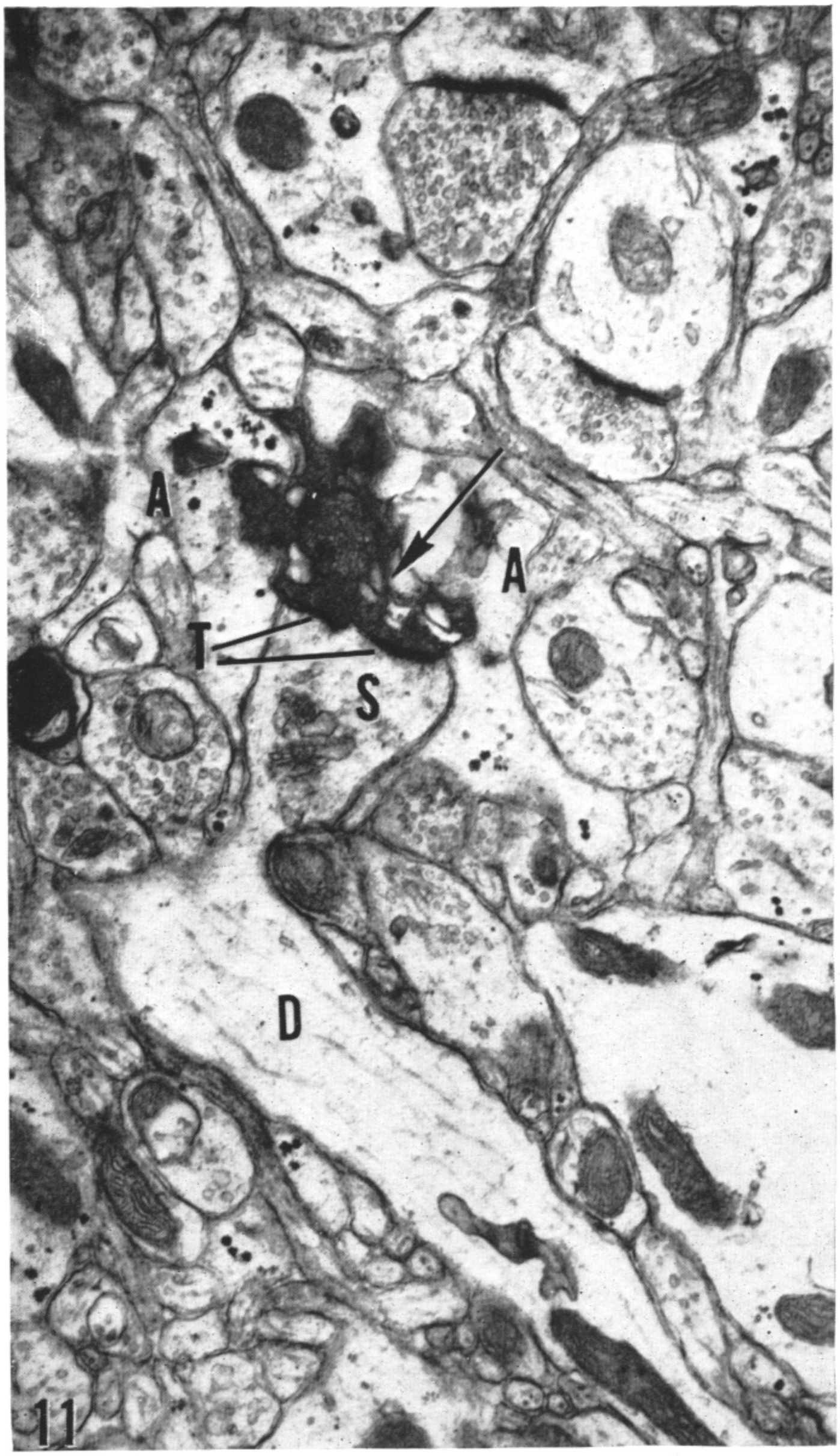


FIGURE 7. A degenerating commissural axon terminal (arrow) ending on a dendritic spine (S) by means of an asymmetrical thickening (T) in layer I of the cortex of SI. A, astroglial process. ×44000; lead citrate stain.

FIGURE 8. A degenerating commissural axon terminal (the arrow points to its attenuated 'tail') making synaptic contact (arrow heads) with three profiles in layer III. Two of the postsynaptic profiles may be recognized as dendritic spines by the presence of spine apparatus (SA). A, astroglial processes containing glycogen granules. ×44000; lead citrate and uranyl acetate stain.

FIGURE 9. Degenerating commissural axon terminal in SI ending by means of an asymmetrical thickening (T) on a dendritic spine (S). Layer IV. ×84000; lead citrate and uranyl acetate.

FIGURE 10. A degenerating commissural axon terminal (arrow) ending on a spine (S) which also receives another normal axon terminal (arrow heads). ×40000; lead citrate.



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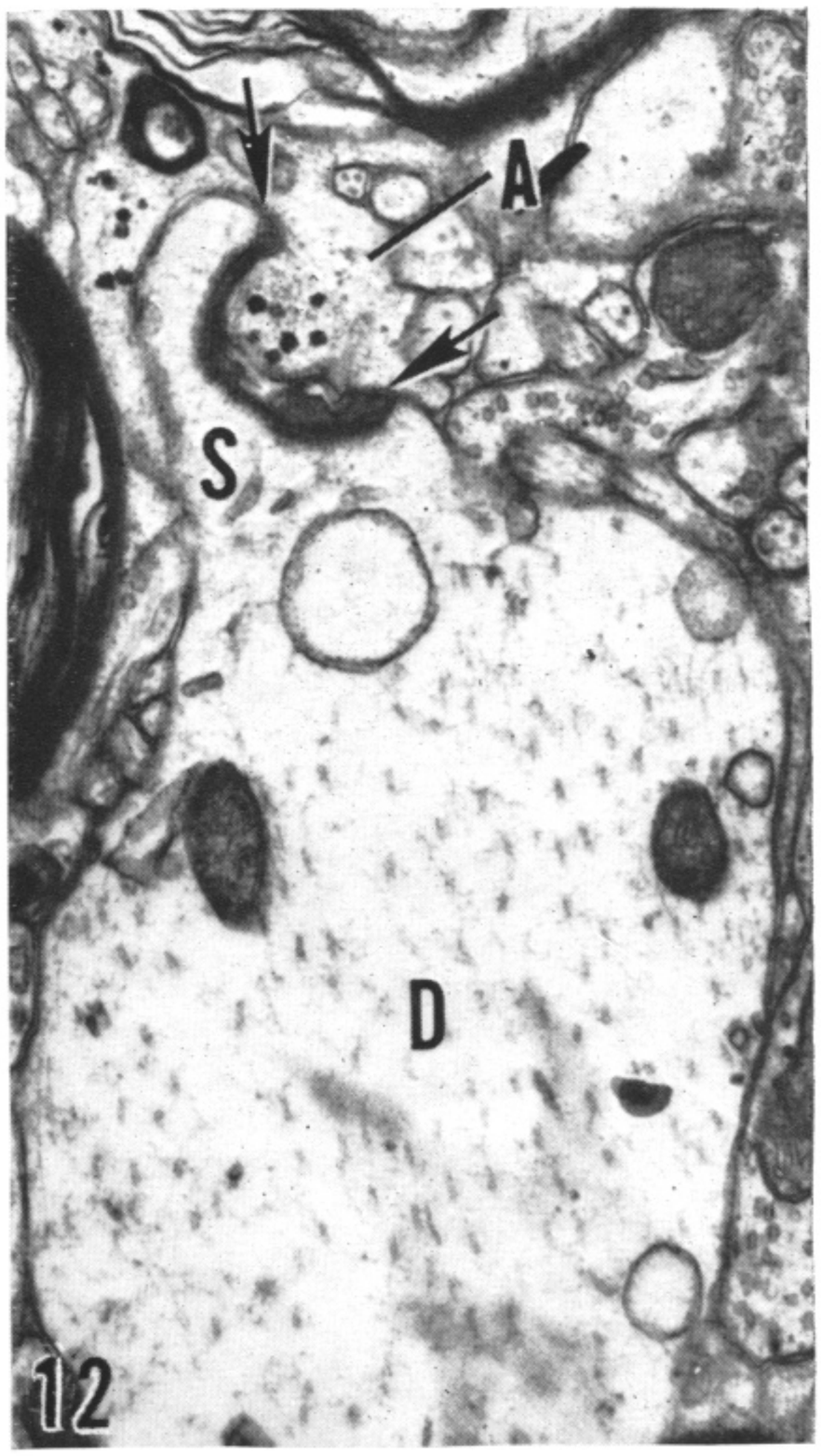

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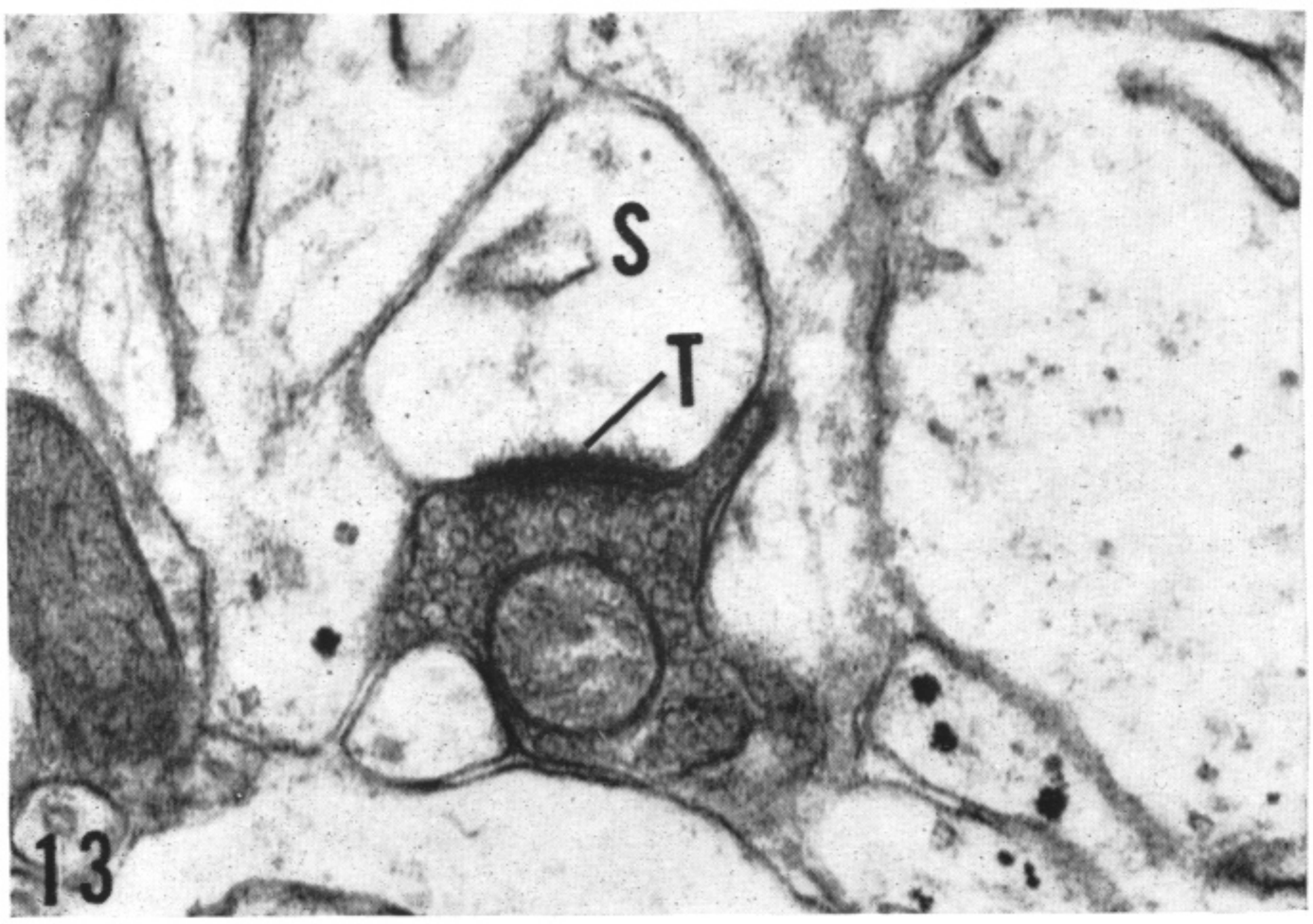

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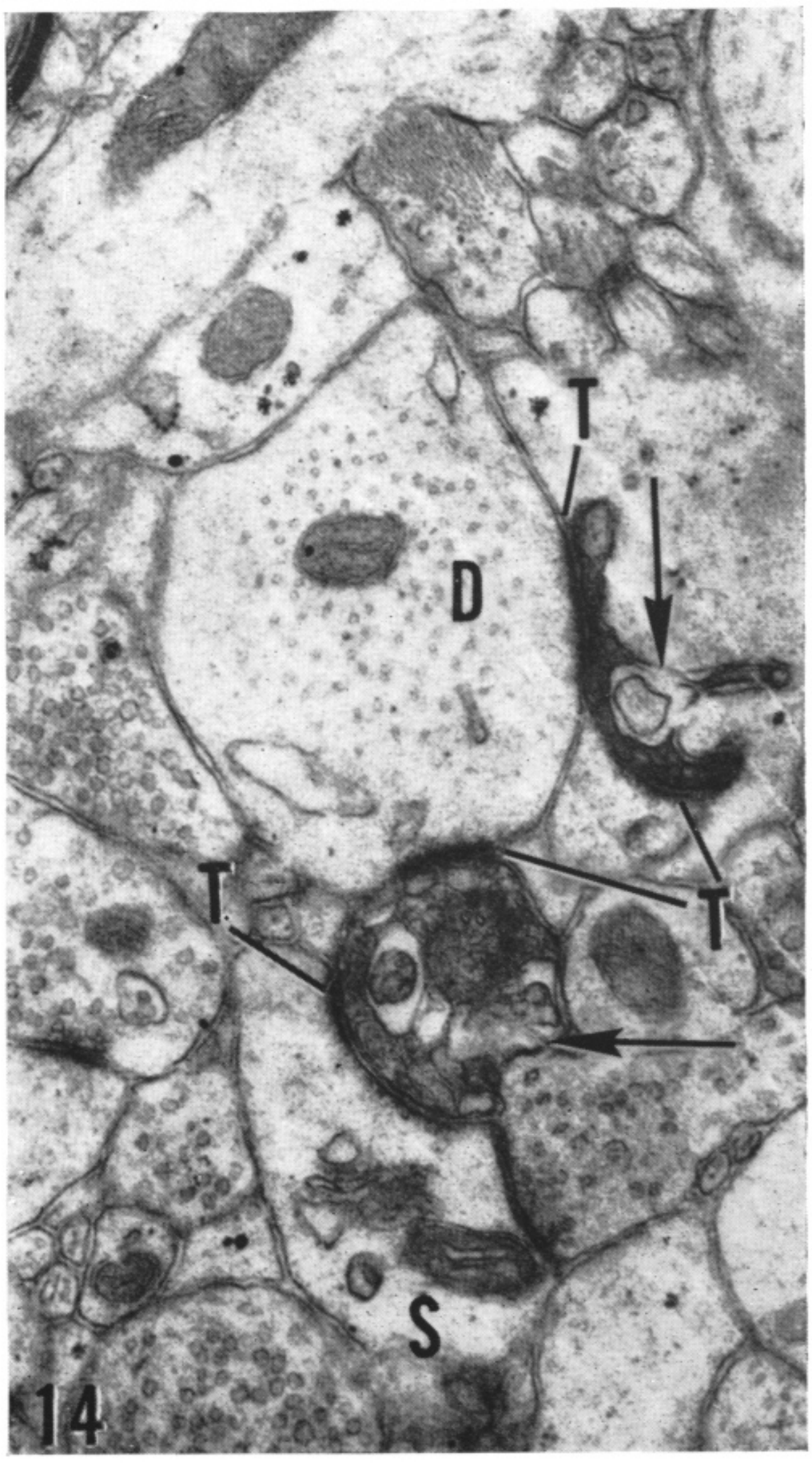

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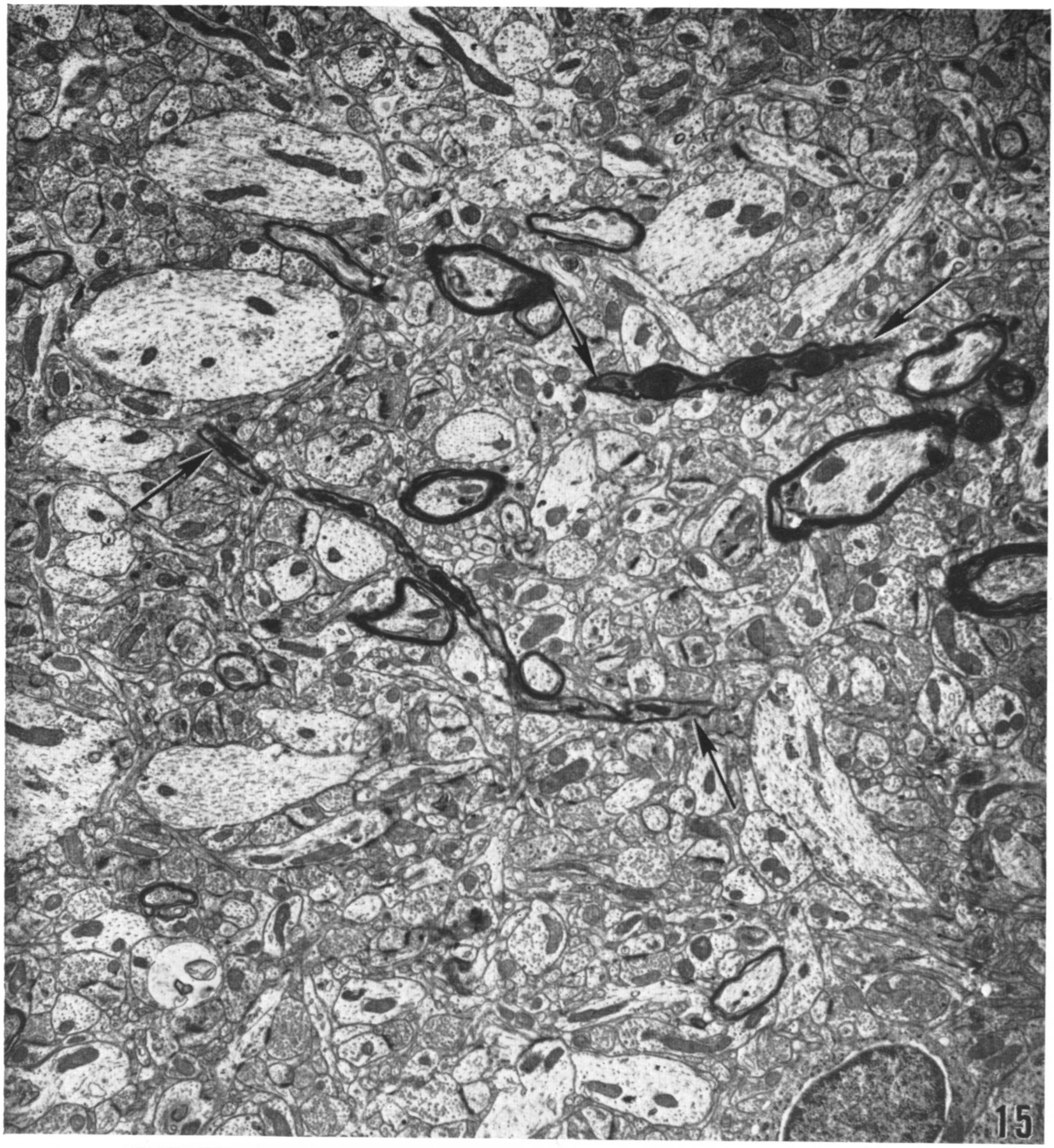


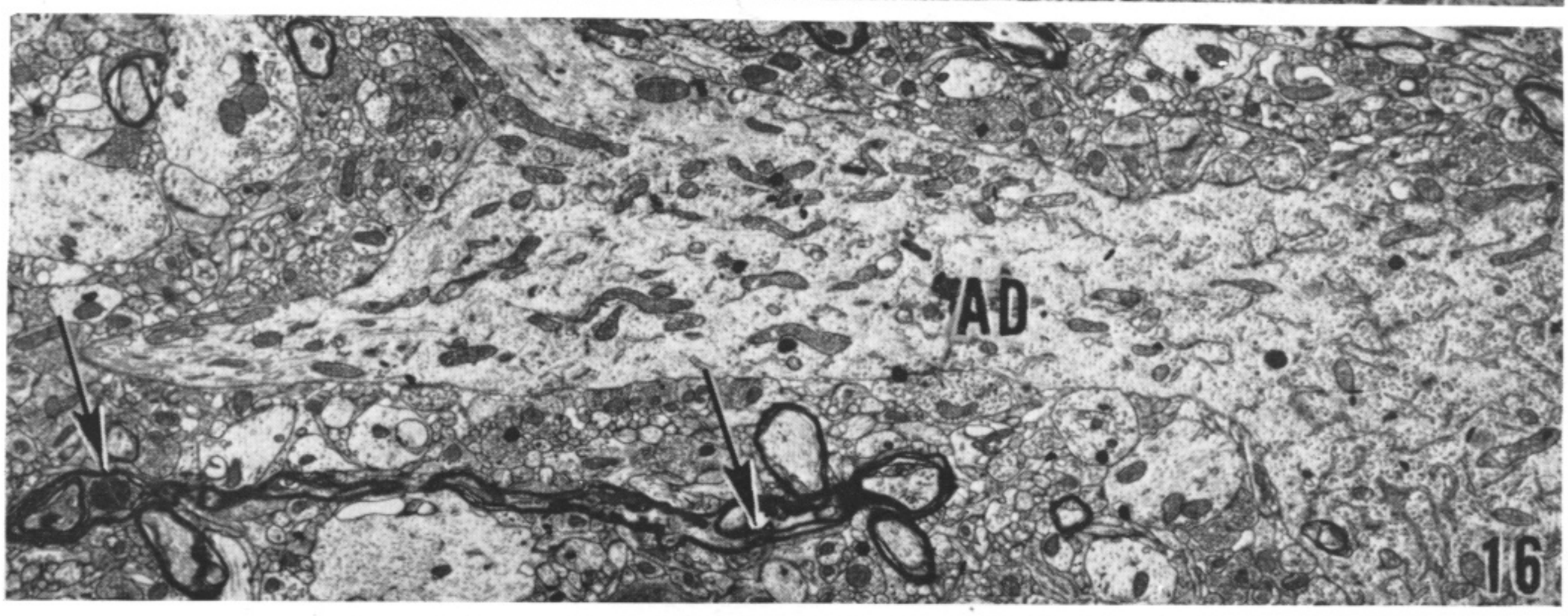


FIGURE 15. Two degenerating commissural nerve fibres ascending through the deep aspect of layer III. The fibres (arrowed) are thinly myelinated. The superficial aspect of the brain is to the left. × 8000; lead citrate and uranyl acetate.

FIGURE 16. A further small degenerating commissural fibre (arrows) ascending through layer V in association with the apical dendrite (AD) of a large pyramidal neuron. Orientation as above. × 5000; lead citrate and uranyl acetate.

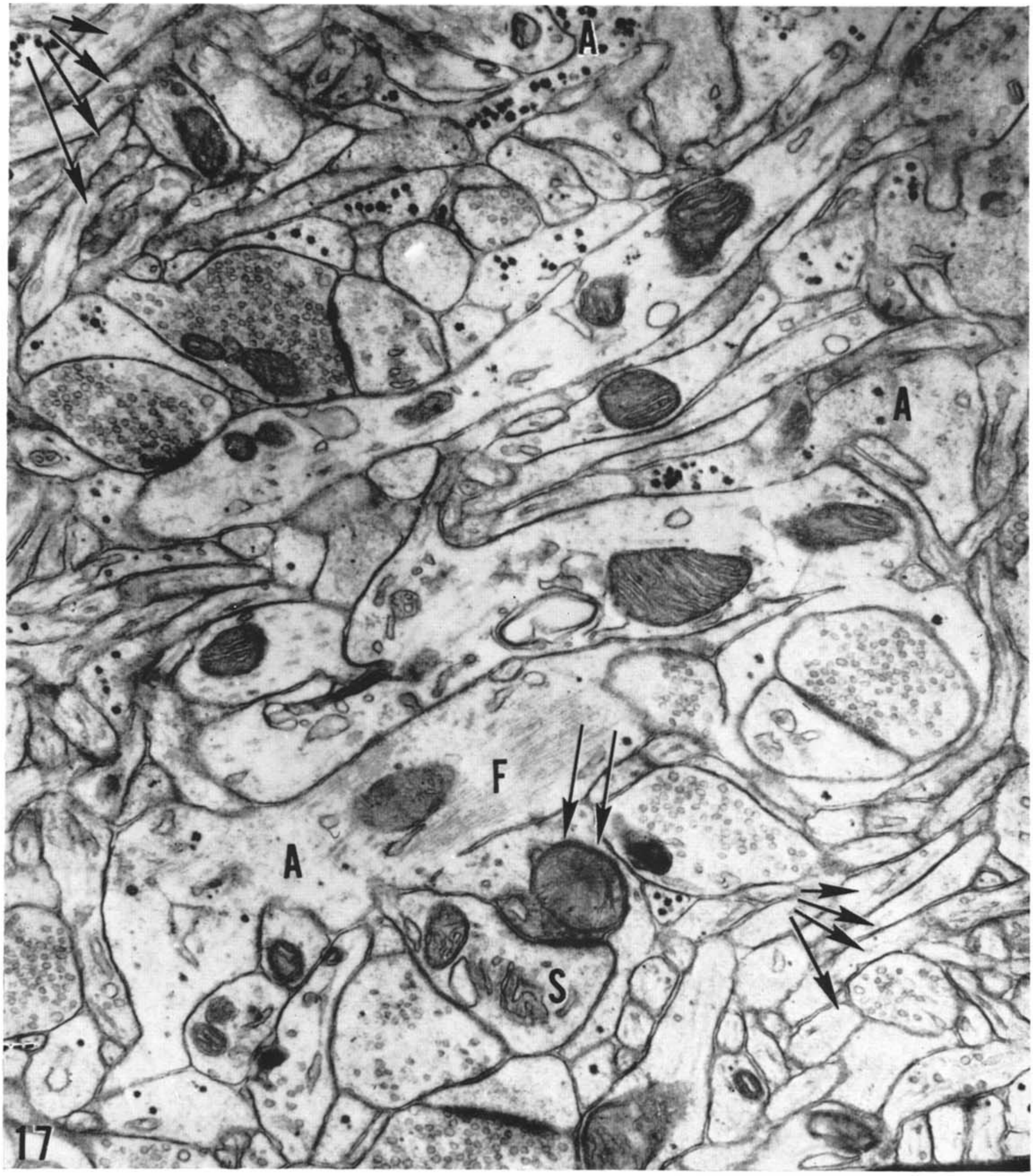
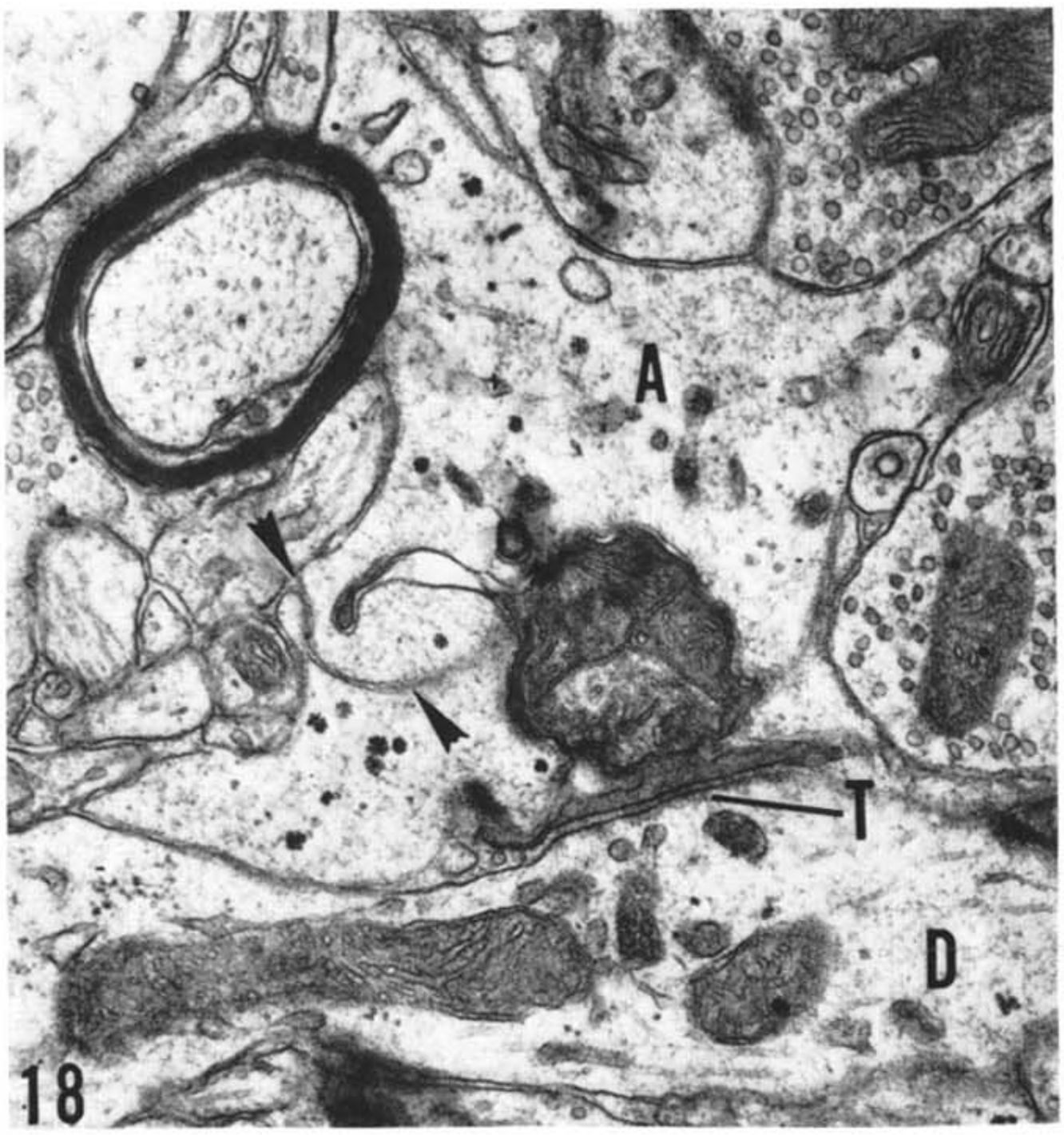
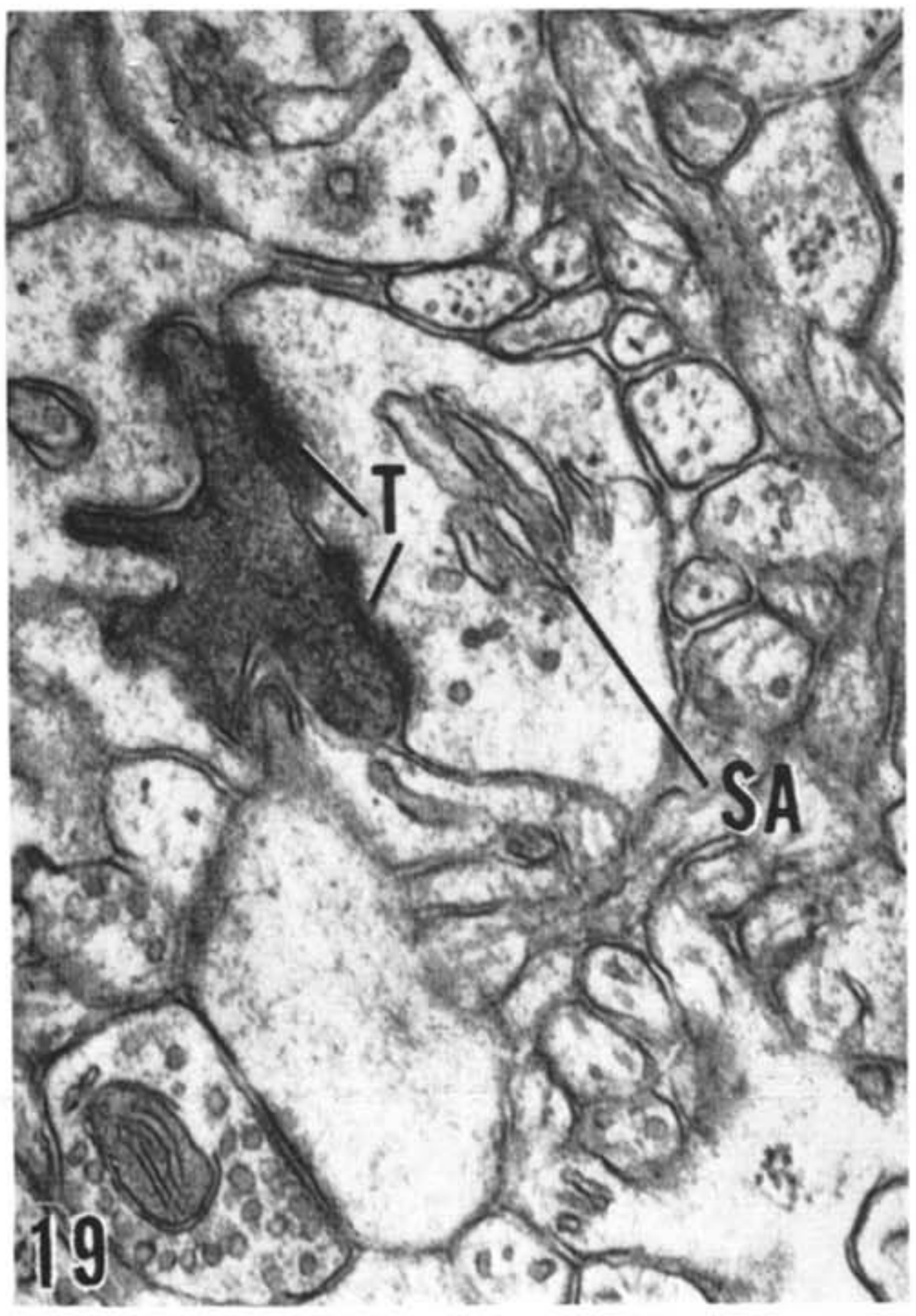
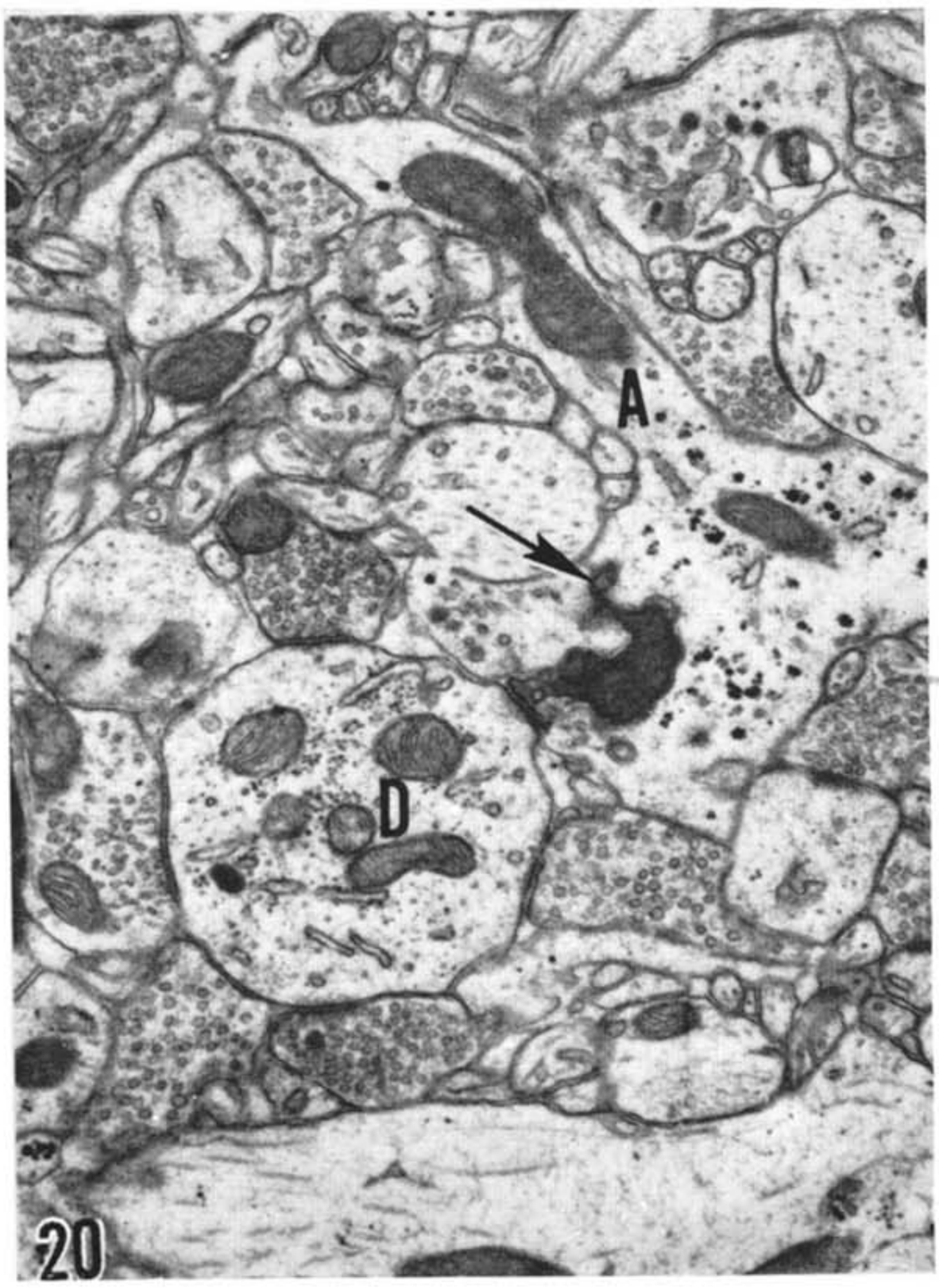


FIGURE 17. A degenerating thalamo-cortical axon terminal (double arrows) ending on a dendritic spine (S) in the junctional region between layers III and IV. This region is characterized by a dense 'feltwork' of thin unmyelinated axons (arrows). A, astroglial processes containing filaments (F) and glycogen granules. × 30 000; lead citrate.







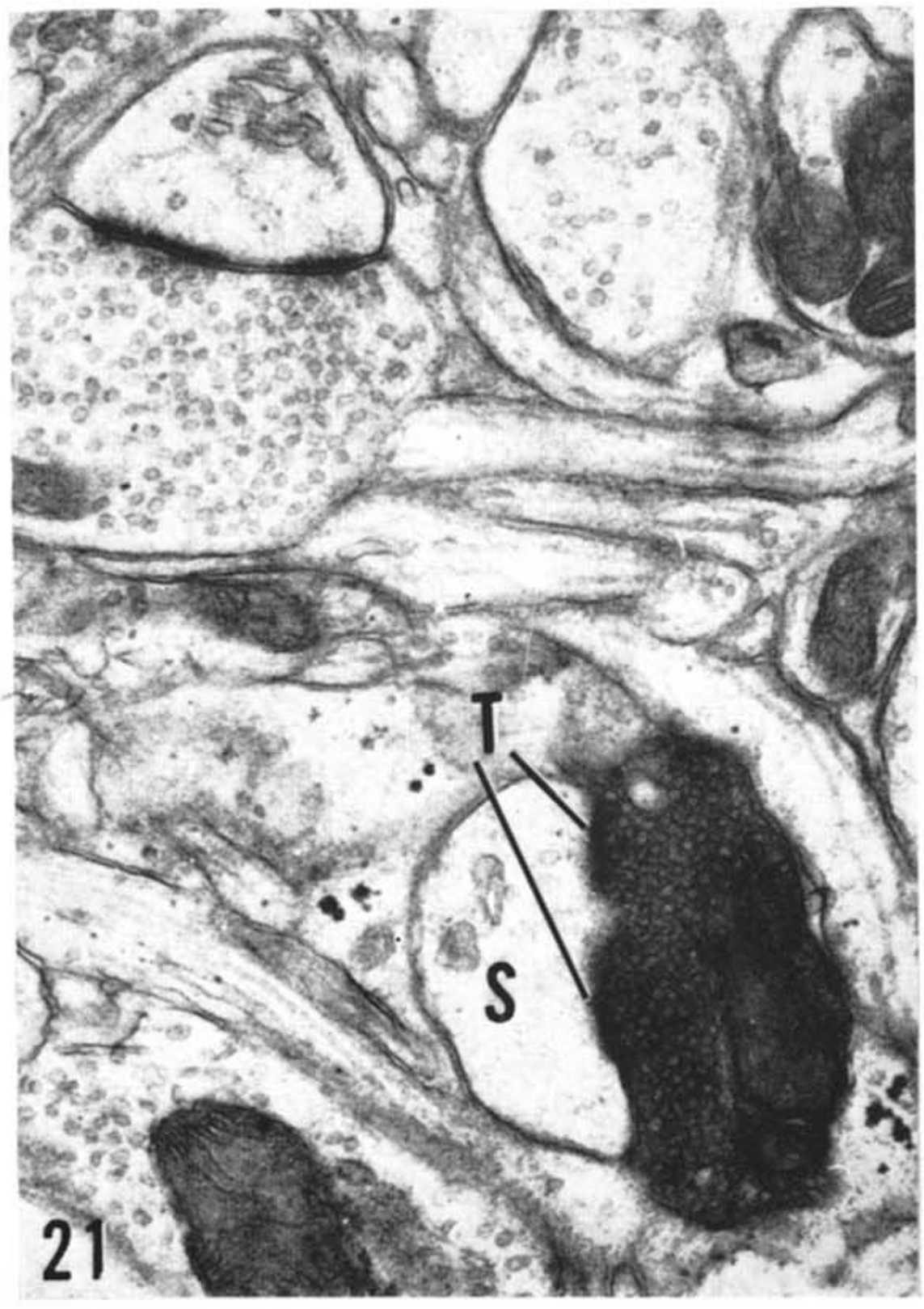
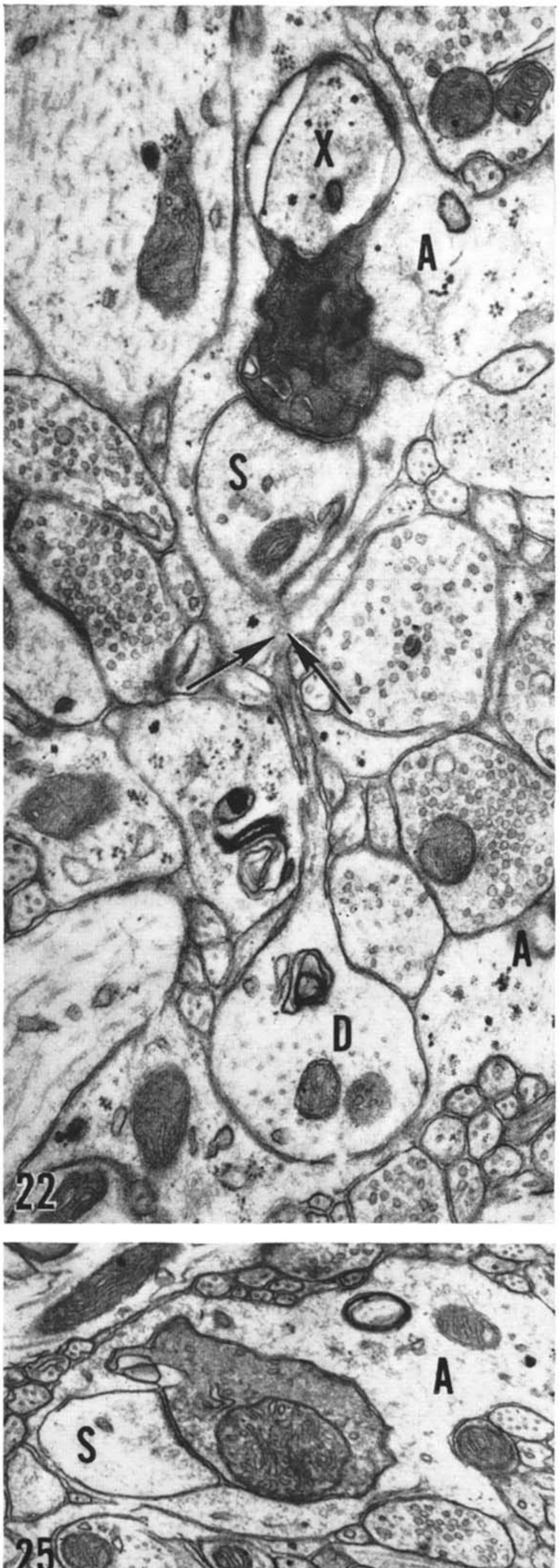


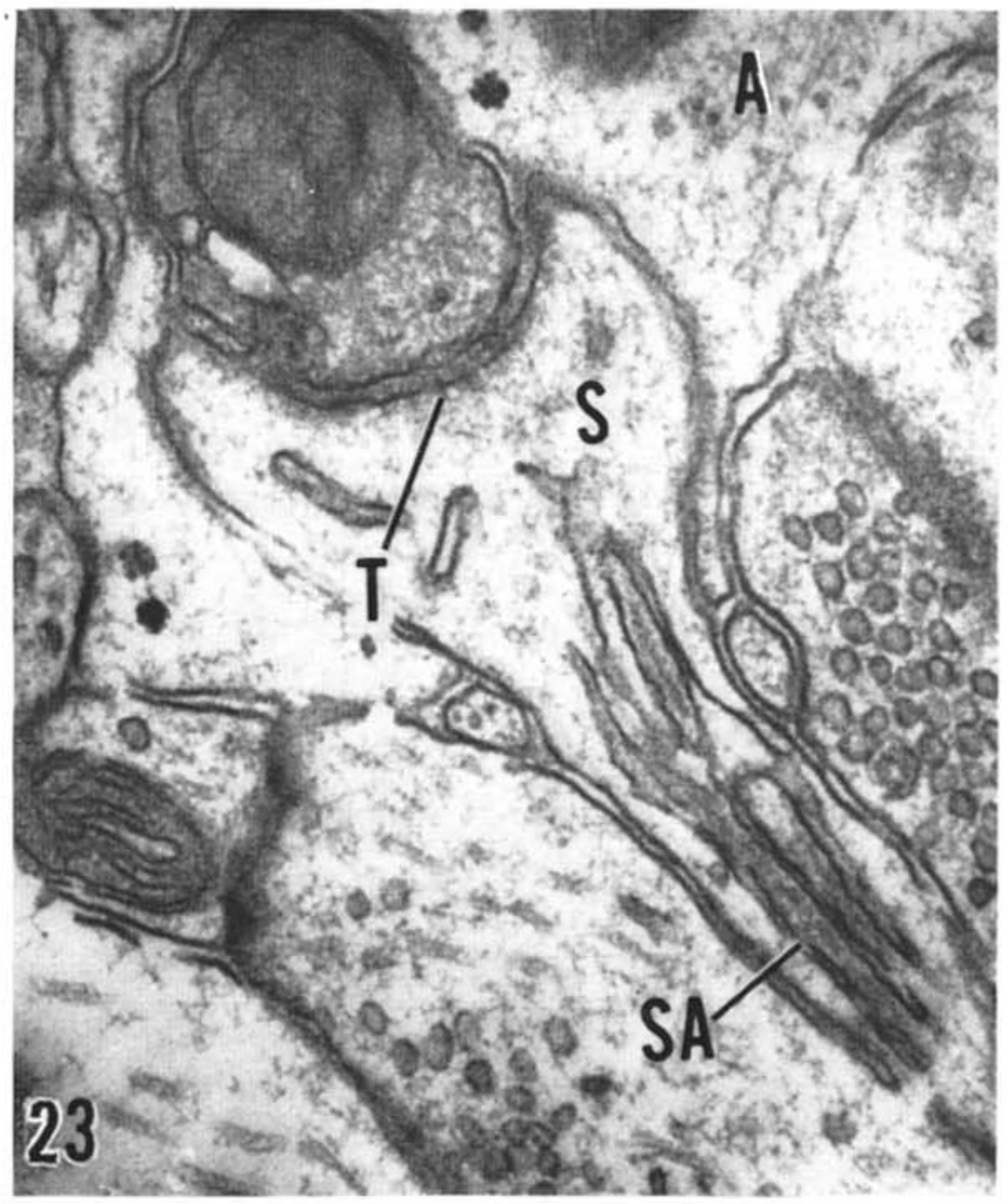
FIGURE 18. A degenerating terminal of a thalamo-cortical axon ending (T) on a small dendrite (D) in layer IV of SI. Note the manner in which the astroglial process (A) has enfolded itself (arrow heads) around the 'tail' of the terminal. × 33000; lead citrate.

FIGURE 19. Degenerating thalamo-cortical axon terminal ending by means of a double synaptic contact (T) on a dendritic spine. The spine apparatus (SA) of the latter is particularly well shown. × 41000; lead citrate and uranyl acetate.

FIGURE 20. A degenerating thalamo-cortical axon terminal (arrow) making synaptic contact with a small dendrite (D) which also receives at least 4 other (normal) axon terminals. Note the reactive astroglial process (A) containing glycogen granules and folding around the degenerating terminal. × 20000; lead citrate.

FIGURE 21. A thalamo-cortical axon terminal at a very early stage of degeneration. There is a little shrinkage of the terminal but synaptic vesicles are still obvious. The terminal contacts a dendritic spine by means of a double synaptic thickening (T). × 29000; lead citrate and uranyl acetate.





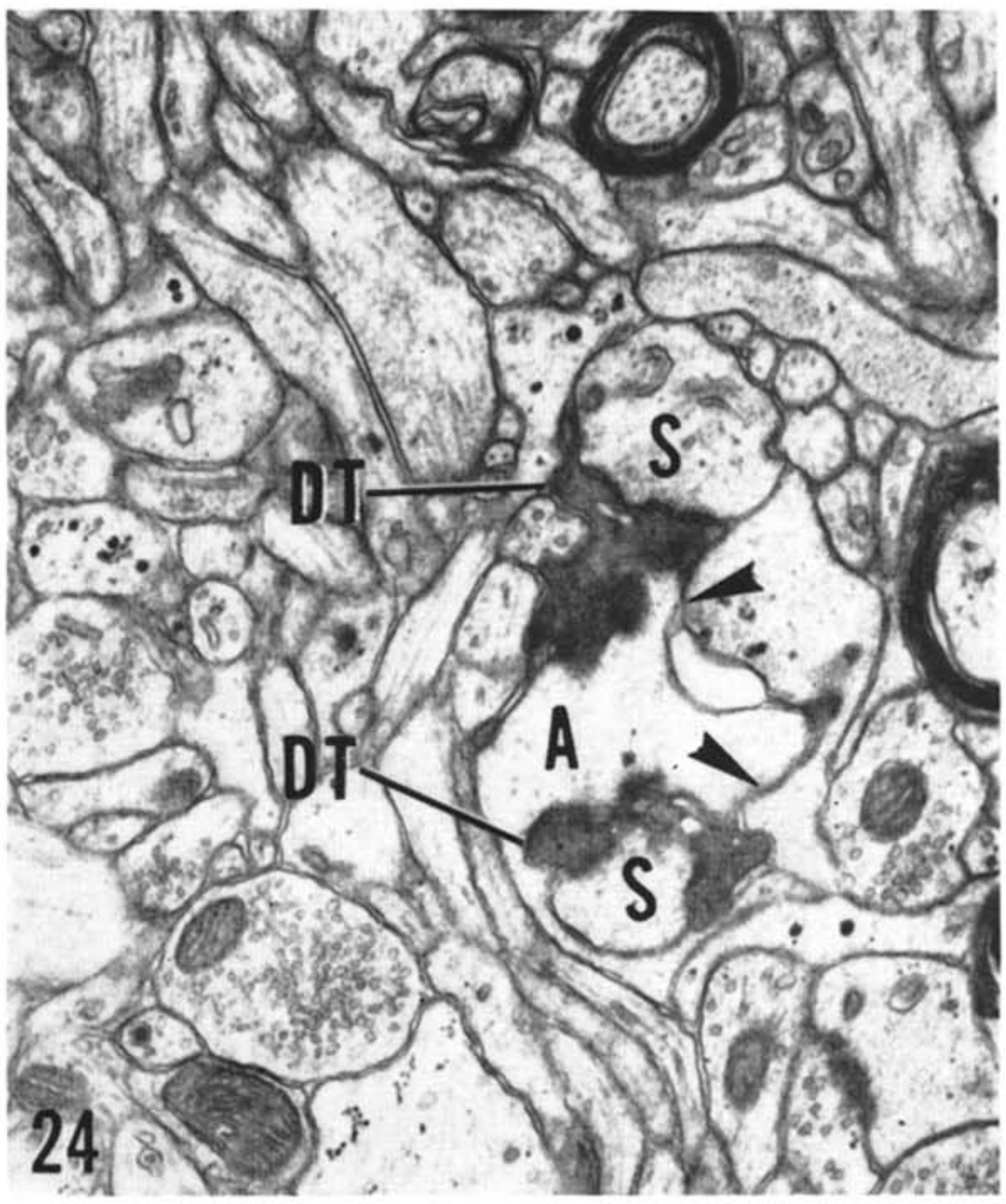
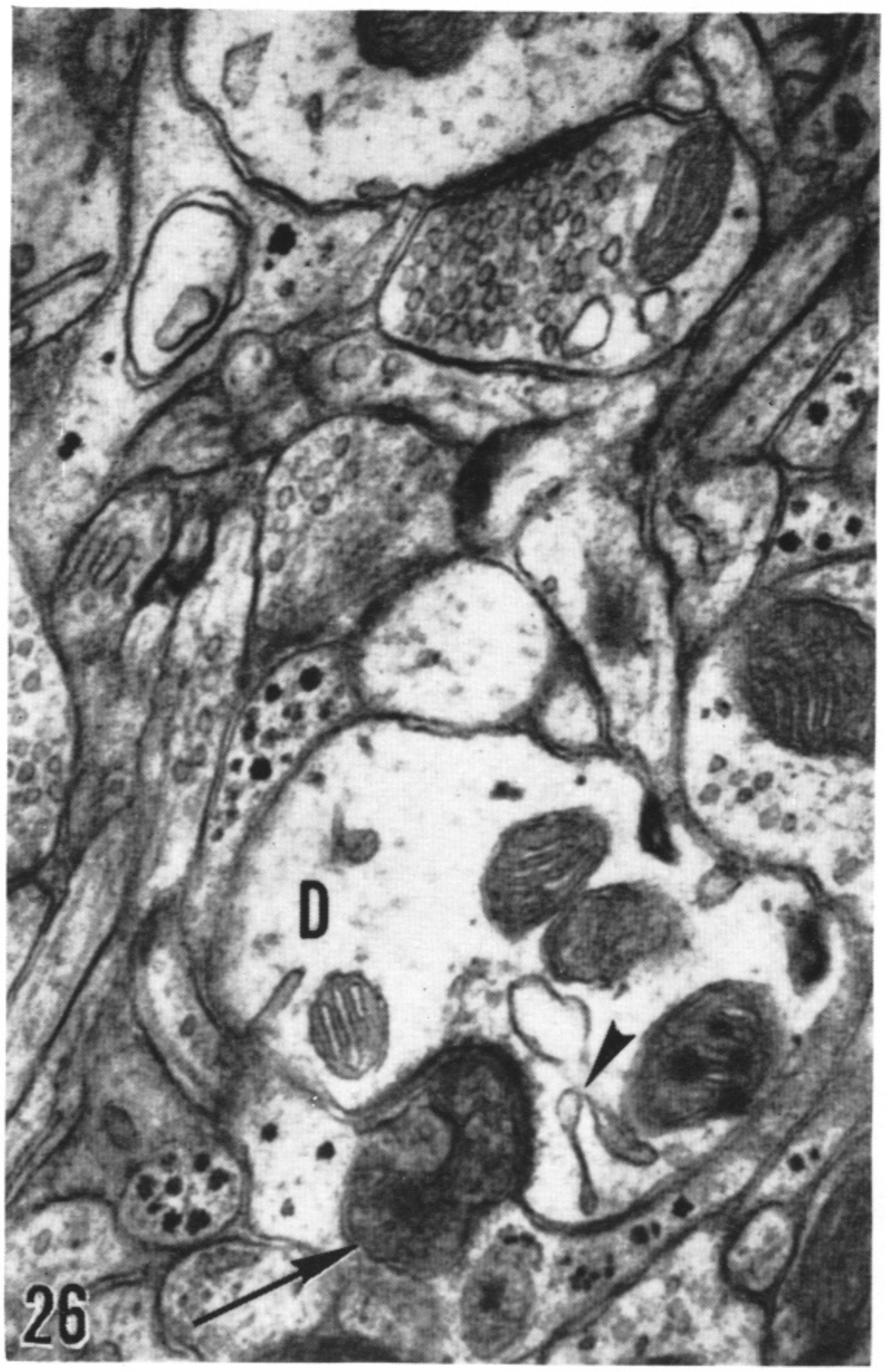


FIGURE 22. A degenerating thalamo-cortical axon terminal making synaptic contact with a dendritic spine which is in turn attached by a narrow pedicle to a small dendrite. Note how the astroglial process (A) has not only pierced the degenerating terminal (X) but has also wrapped itself around the attachment of the spine to its pedicle (arrows). × 30000; lead citrate.

FIGURE 23. A degenerating thalamo-cortical terminal ending on a dendritic spine which contains spine apparatus (SA) in its pedicle. × 66000; lead citrate.

FIGURE 24. Two degenerating thalamo-cortical terminals (arrows) which appear to be ending on adjacent dendritic spines (S) and which are joined by a narrow sliver of degenerating axoplasm (arrow heads) around which the astroglial process has wrapped itself. × 23000; lead citrate.

FIGURE 25. A degenerating thalamo-cortical terminal and the spine upon which it terminates both enwrapped by an astroglial process. Layer I of the cortex. × 29000; lead citrate.



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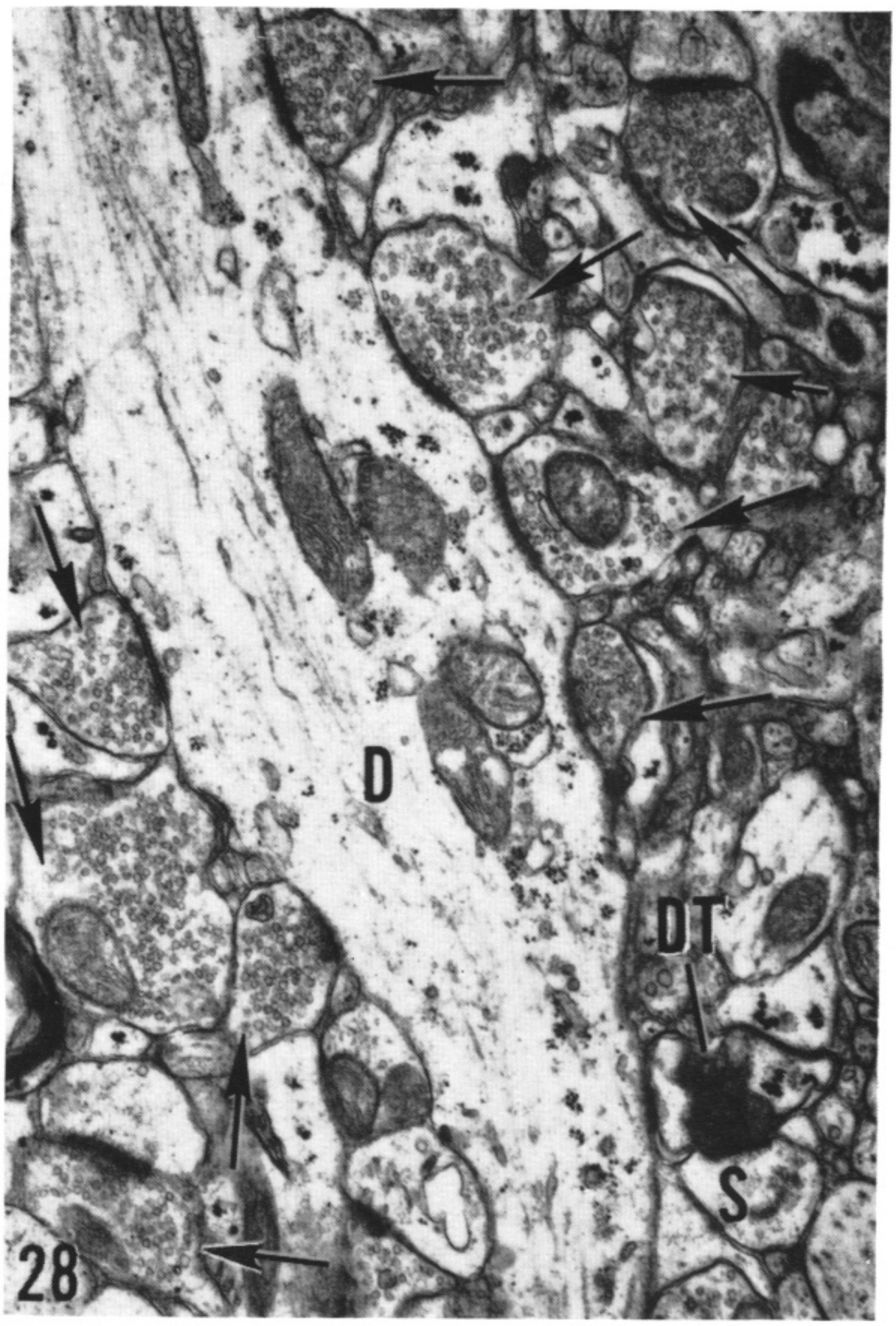

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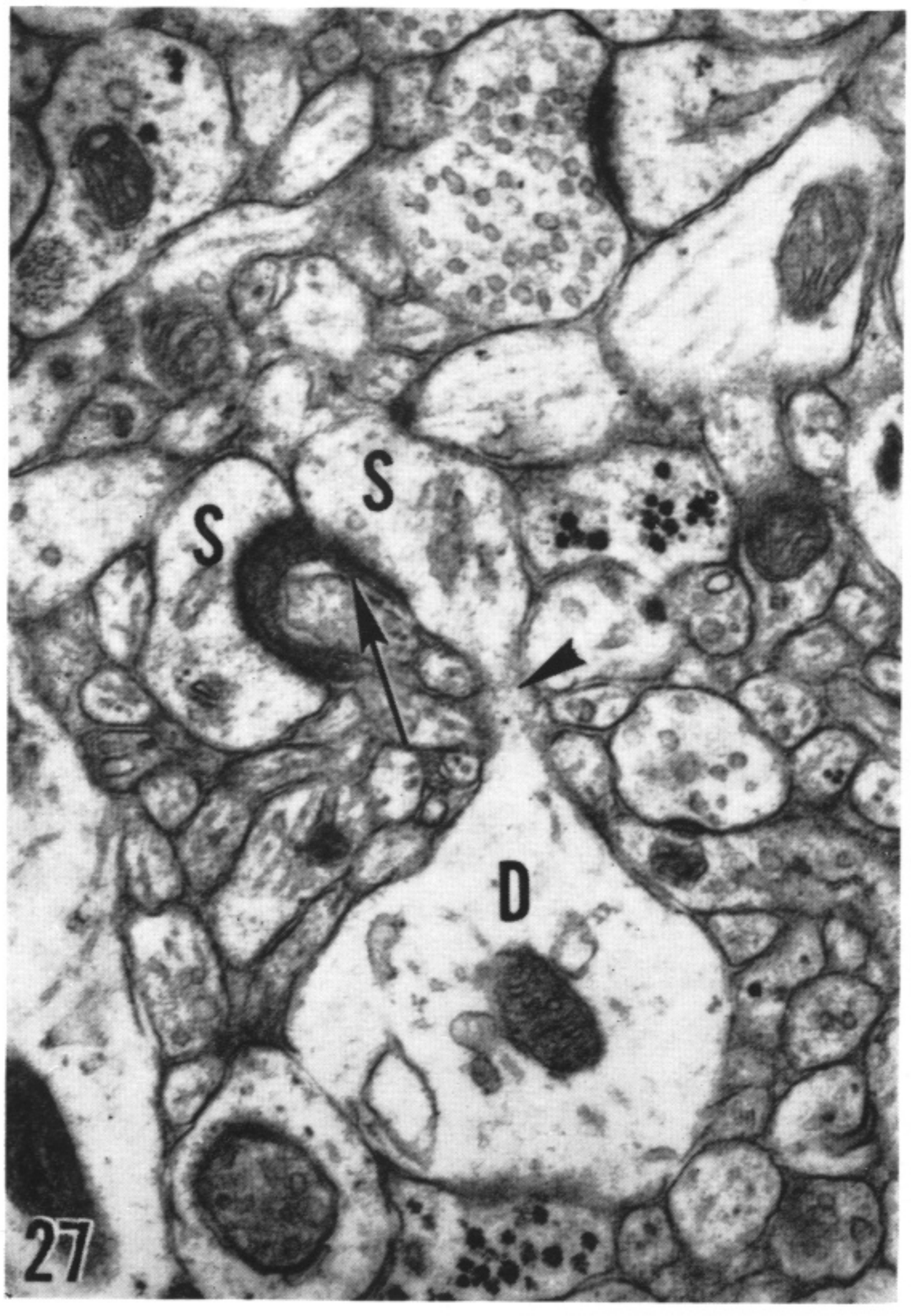

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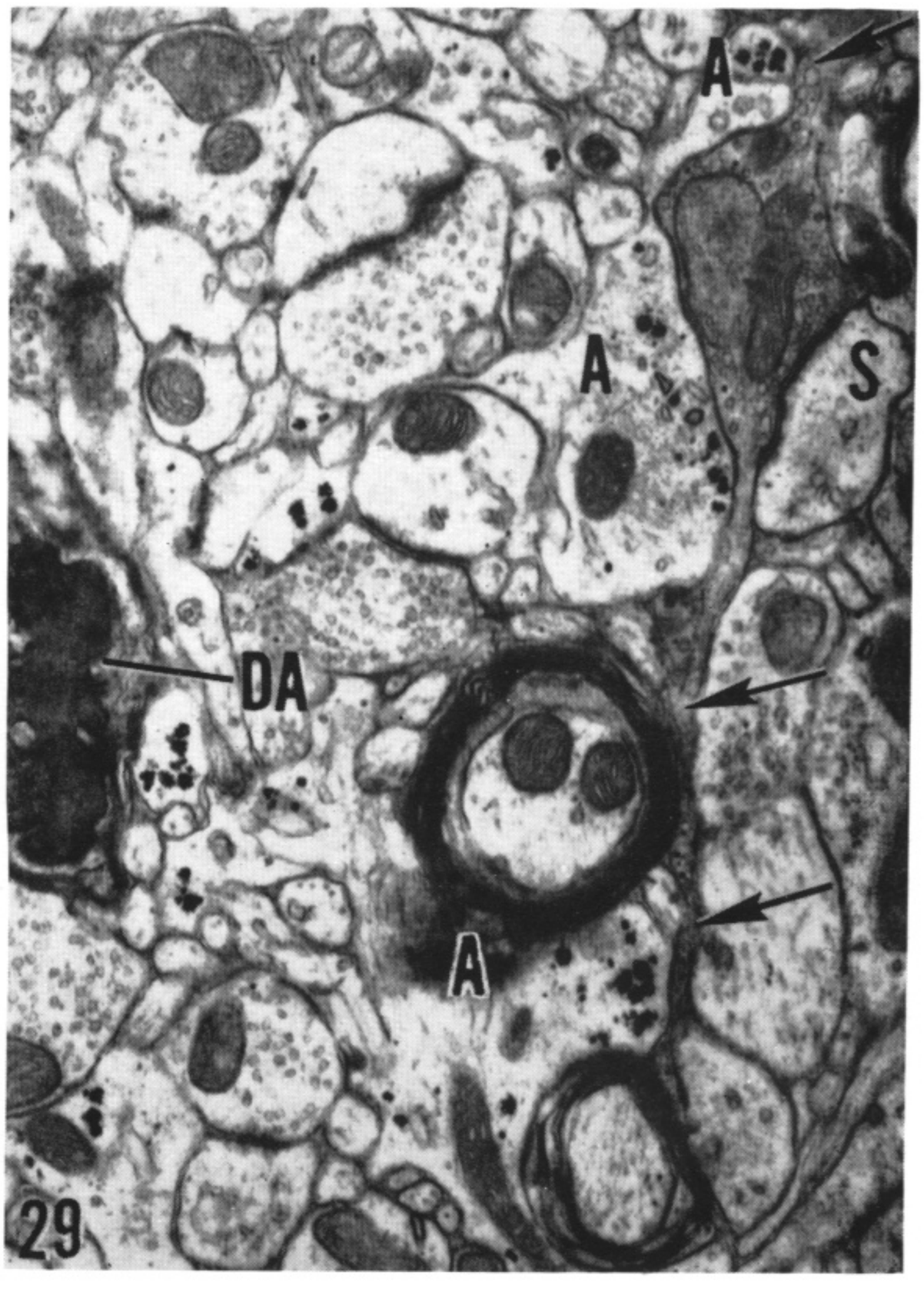

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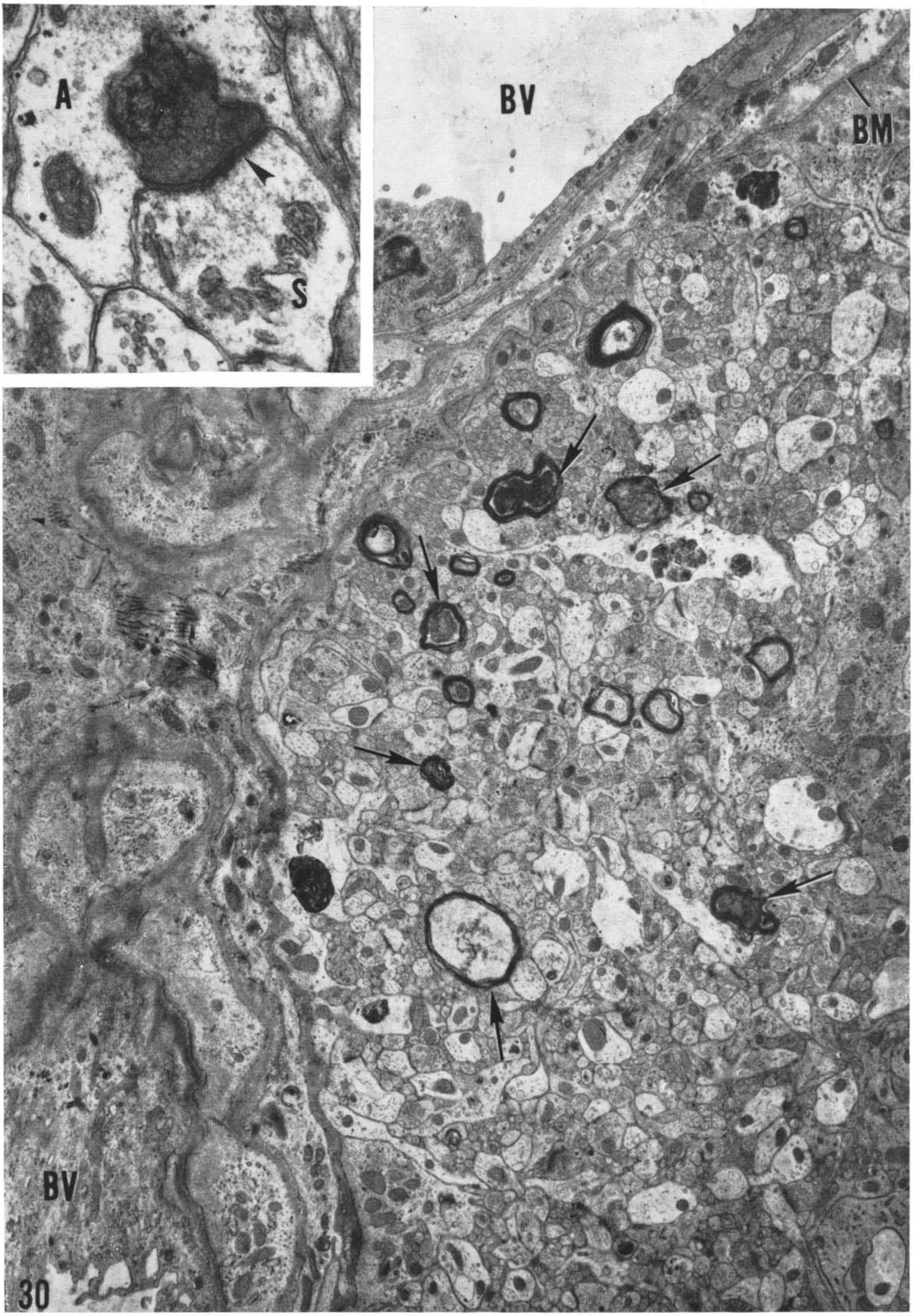

FIGURE 30. The superficial aspect of the cortex at the point of entry of a small blood vessel (BV). The surface is towards the top. The basement membrane (BM) which constitutes the most superficial layer of the brain substance is indicated. A small bundle of degenerating small myelinated axons (arrows) lie immediately deep to the surface. These arise from one of the knife cuts in the brain in which the hindlimb subdivision of SI was isolated and spread out in all directions in this position. × 9000; lead citrate. *Inset*: a degenerating axon terminal ending on a dendritic spine in layer I of SI following a lesion of the ipsilateral SII. The synaptic contact zone is indicated (arrow head). × 54000; lead citrate.

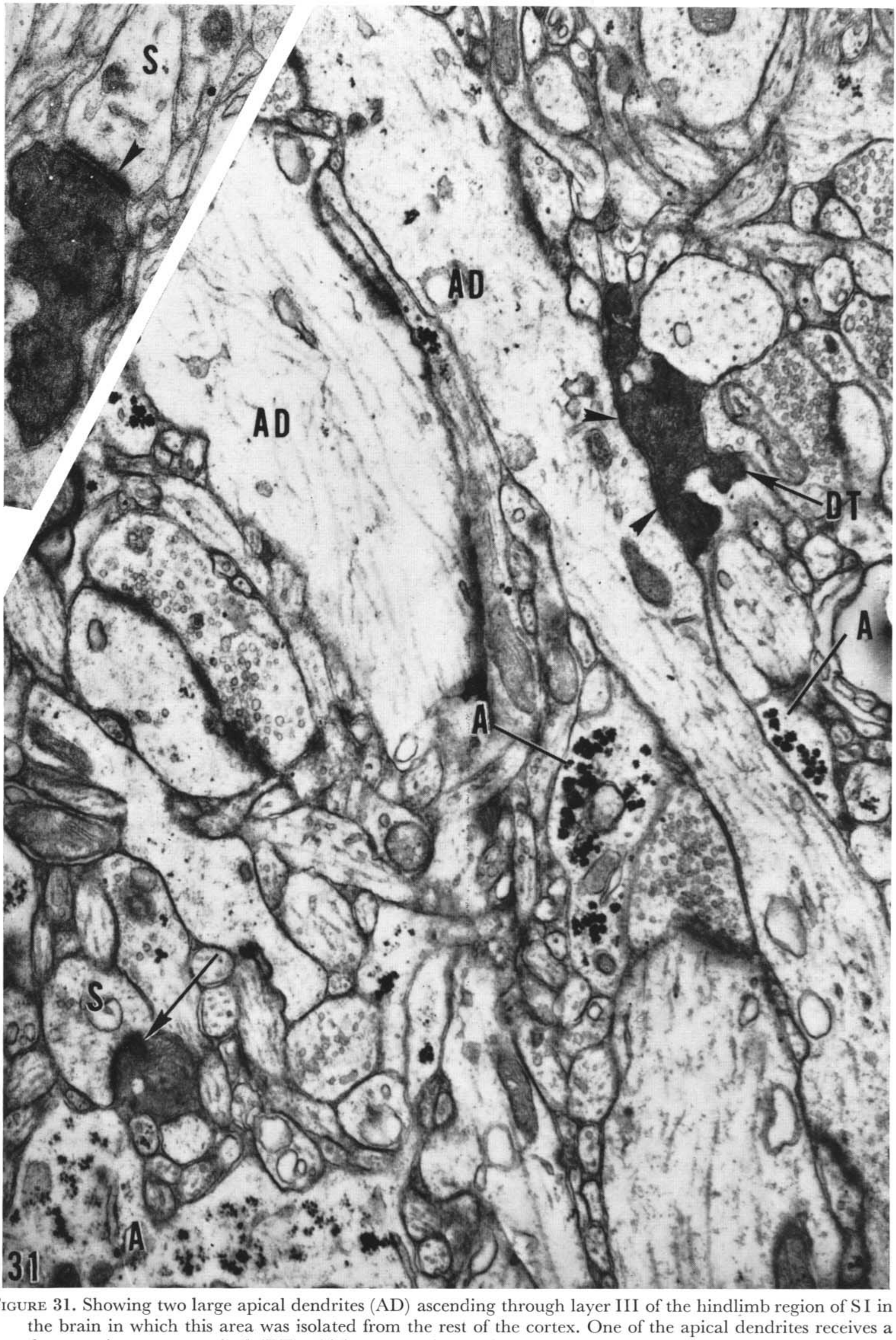

FIGURE 31. Showing two large apical dendrites (AD) ascending through layer III of the hindlimb region of SI in the brain in which this area was isolated from the rest of the cortex. One of the apical dendrites receives a degenerating axon terminal (DT) which apparently terminates in a symmetrical thickening (arrow heads). Another degenerating terminal is also present in the micrograph (arrow) ending on a dendritic spine. Note the very heavy accumulation of glycogen in the astroglial cytoplasm. × 31 000; lead citrate and uranyl acetate. *Inset*: a degenerating axon terminal making an asymmetrical synaptic contact with a dendritic spine in layer III of SI following a lesion in the ipsilateral SII. × 51 000; lead citrate and uranyl acetate.