THE INTRINSIC, ASSOCIATION AND COMMISSURAL CONNECTIONS OF AREA 17 OF THE VISUAL CORTEX

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CONTENTS

An experimental neurohistological study has been made of the intrinsic connections of the cortex of area 17 of the monkey, of the commissural connections of the visual cortex of the cat and monkey and of the association fibres passing into area 17 of the cat. In light microscopic studies the axonal degeneration method of Nauta has been used, and the site and mode of termination of the degenerating fibres has also been determined with the electron microscope.

After narrow slit lesions through the depth of the cortex of area 17 degeneration of the intrinsic fibre connections does not extend beyond 5–6 mm: this extent is asymmetrical, being 1–2 mm further on one side of the lesion than on the other. In all layers there is intense fine degeneration in a width of 200 μm on each side of the lesion and in layer IV no degeneration extends beyond this distance. In all the other layers there is moderate fibre and terminal degeneration for up to 2 mm on one side and 1 mm on the other; in the stria of Gennari fibre degeneration continues for a further 1–2 mm from the lesion, and these fibres probably terminate within the stria and in the immediately adjoining parts of layer IIIb superficially and in layer IV deeply. After a small focal lesion in layers I and II fine degeneration is found in these layers over a total extent of 2–3 mm, and a few fibres pass down into layer III. When the damage extends into layer III, in addition to the horizontal degeneration in this layer there is a moderate degree of fibre degeneration in the stria, in layers V and VI and a few fibres pass into the underlying white matter. If the lesion extends deep enough to involve the stria dense horizontal fibre degeneration appears in it and this extends to a maximum width of 5–6 mm. Similar degeneration in the stria has been

found after small lesions restricted to it or within layer IV, indicating that most of the horizontal fibres in the stria arise within the cortex and probably in layer IV (or V and VI). When the lesion reached down to layer V there was an increase in the density of degeneration in layer V itself, in layers II and III, and more degenerating fibres entered the white matter; these observations suggest that many of the fibres in layer V arise in that layer, that there is a recurrent projection from layer V to layers II and III and that most of the efferent fibres from area 17 arise in the deep layers of the cortex. Degenerating fibres which pass vertically up or down from a small lesion in the cortex were confined to a narrow band lying above or below the lesion. Electron microscopic observations are in good agreement with the light microscopy both with respect to the extent of the degeneration and with the variation in the different laminae. The degenerating axon terminals formed only a small proportion of the total number of terminals present, and there was a marked decrease in their number beyond 1 mm from the lesion. The majority (90 %) of the terminals had asymmetrical membrane thickenings and most made contact with dendritic spines; others formed synapses upon dendrites and cell somata of stellate cells. Degenerating terminals with symmetrical membrane thickenings formed 10 % of the total and the post-synaptic profiles related to these were complementary to those of the asymmetrical terminals, 78 % ending on dendrites of both pyramidal and non-pyramidal cells. A small number ended on cell bodies and on initial segments.

The degeneration of commissural fibres was studied only at the boundary of areas 17 and 18. With the light microscope it was found that all layers were affected by degeneration in area 18 but that layer IV was clear in area 17. This was confirmed with the electron microscope and it was found that all of the terminals had asymmetrical membrane thickenings and the majority made synaptic contact with dendritic spines. The association fibre connections passing from area 18 into area 17 of the cat were found to terminate only in the lateral part of area 17 and that layer IV was left clear of fragmentation. These fibres have asymmetrical terminals and the majority end on dendritic spines.

Introduction

Physiological studies of the sensory areas of the cerebral cortex by the method of single unit recording have made important contributions to our understanding of their functional organization. In these cortical areas it has been shown that the cells are arranged in functional columns, in the somatic sensory area on the basis of the peripheral receptors which have been stimulated (Mountcastle 1957) and upon the cellular responses to one or other eye or upon receptive field orientation in the visual area (Hubel & Wiesel 1962). The cells in different layers of the cortex (Hubel & Wiesel 1968; Whitsel, Roppolo & Werner 1972) or in the various cytoarchitectonic subdivisions of the main areas (Powell & Mountcastle 1959; Hubel & Wiesel 1965) have been found to differ in the form of the stimulus required for activation. The anatomical basis for these differences is far from clear, but certain important details about the origin and termination of the afferent fibres to these areas from the thalamus have been defined.

The differences in functional properties between the cells in various laminae of the cortex have been shown most clearly in area 17 of the visual cortex of the monkey (Hubel & Wiesel 1968), perhaps in part because of the well-marked structural lamination of this area. In layer IV the majority of the cells are activated by stimulation of one eye only and by the simplest form of stimulus, whereas the neurons in the more superficial and deep layers are binocularly related and require more complex stimuli. The precise termination of thalamocortical fibres has also been determined in most detail in this area as the level of termination in the cortical laminae has been established for the small and large cell layers of the lateral

geniculate nucleus and also the mosaic distribution of the fibres from those layers of the lateral geniculate nucleus related respectively to one or other eye (Hubel & Wiesel 1969, 1972; Wiesel, Hubel & Lam 1974). In addition, there is some evidence from electron microscopic studies about the types and parts of neurons with which the axon terminals of the geniculocortical fibres make contact (Colonnier & Rossignol 1969; Garey & Powell 1971).

Little is known, however, of the short fibre connections which pass between the layers of the cortex and particularly those which interconnect cells of different functional properties. This is a formidable problem, and is but one aspect of the larger question of the principles underlying the intrinsic anatomical organization of the neocortex. Several histological and physiological techniques are available to investigate this problem, but each has definite limitations. In the present study the methods based upon the degeneration of axons and their terminals in experimental material have been used at the light and electron microscopic level in area 17 of the monkey. With these methods it has been possible to determine the origin and distribution of some of the intrinsic fibre connections in terms of the cortical laminae, but they give little information about the various types of cells from which the fibres arise or upon which they end. In addition, the termination of the other cortical connections, from the opposite hemisphere and adjoining cortical areas, have been studied with the same methods. A preliminary account of the findings has been published (Fisken, Garey & Powell 1973).

Material and methods

Nineteen young adult Macaque monkeys and five cats were used in this investigation. The intrinsic connections of the cortex of area 17 were studied in the monkey, the commissural connections of the visual cortex in both the monkey and cat, and the termination of association fibre connections in area 17 in the cat. The operations were done under Nembutal anaesthesia and with aseptic precautions.

For the study of the intrinsic connections of area 17 of the monkey the lateral surface of the occipital lobe on one or both sides was exposed. The lesions were placed with a needle or fine knife, or with a tungsten microelectrode (Hubel 1957). A dissecting microscope was used and care was taken to insert the instrument between vessels so as to minimize the degree of vascular damage. Preliminary experiments showed that the extent of axonal degeneration was limited to a few millimetres on either side of the lesion, and, as it is known that area 17 neither sends nor receives commissural fibres, in the later experiments several small lesions were placed on each side of the brain. In the early experiments two types of lesion were made: either a slit, some 3–4 mm long through the whole depth of the cortex, made by inserting a needle or fine scalpel blade to a depth of 1–2 mm, or an electrolytic lesion at a particular depth within the cortex. In the case of microelectrode lesions, considerable care was taken to try to place lesions at known depths within the cortex; localized lesions of approximately 100–200 μm diameter were found in individual laminae after passing a current of 5–10 μA for 5–10 s, but it was clear that in some cases the traverse of the electrode through the more superficial layers had caused a certain amount of degeneration, which made interpretation of the findings difficult. The procedure for making an electrolytic lesion was later changed so that, after the introduction of the electrode to a particular depth in the cortex, the current was turned on and allowed to run while the electrode was slowly withdrawn to the surface. In order to identify the individual lesions *post mortem* they were positioned with the aid of a stereotaxic apparatus at known distances

from certain landmarks such as the lunate sulcus anteriorly and the medial margin of the hemisphere medially; accurate drawings were made at the time of operation, and the lesions at adjoining points were deliberately placed at distinctly different depths. With the exception of two lesions, all the observations were made on that part of area 17 on the dorsolateral surface of the hemisphere containing the representation of the central ten degrees of the visual field (Talbot & Marshall 1941; Daniel & Whitteridge 1961); no attempt was made to place lesions within the cortex of that part of area 17 which is buried within the walls of the calcarine sulcus, since in order to do so it would have been necessary to pass through the cortex and white matter lying superficial to it. After a survival period of 1–6 days the animals were again anaesthetized, and for light microscopy were perfused through the ascending aorta with 0.9 % saline followed by 10 % neutral formalin. The brain was removed and stored in fixative for several weeks. For electron microscopy, anaesthetized animals were cooled to 25 °C and perfused with a buffered salt solution followed by a mixture of 1 % glutaraldehyde and 4 % paraformaldehyde in phosphate buffer at pH 7.0–7.3; after several hours of further fixation, the brain was removed and stored in fixative at about 4 °C.

For the study of degeneration with the light microscope, the occipital lobe was cut off just in front of the superior temporal sulcus and put into a solution containing 30 % sucrose for 7–10 days, before being sectioned on a freezing microtome at 25 μm in the coronal or sagittal plane. All sections were collected and a 1:20 series was stained by either the method of Nauta & Gygax (1954), or of Fink & Heimer (1967) or of Wiitanen (1969). The sections were examined for the presence of lesions and an alternate series was stained by the same or a different method, this process being repeated until all the lesions had been found and could be examined on closely adjoining sections stained by more than one method. In certain cases, serial sections through a microelectrode lesion were stained and examined.

For electron microscopy slices of cortical tissue approximately 10 mm long and 0.5 mm thick were cut at right angles to slit lesions; each slice was then divided into blocks approximately 2 mm × 2 mm, beginning at the edge of the lesion and extending for 3–4 mm on either side. Blocks were bevelled and separately numbered so that the position and orientation of each block relative to the lesion could be known. In the case of microelectrode lesions, the procedure was to cut out a slice of tissue 0.5 mm thick which contained the lesion and then to trim this down to a single block; in a number of cases this consisted of the lesion and the cortex 1 mm to either side of it. The blocks were rinsed briefly in 10% sucrose in phosphate buffer, post-fixed in osmium tetroxide and dehydrated (with block staining by uranyl acetate at the 70% alcohol stage); they were embedded in Epon–Araldite. In order to identify the exact region required for thin sections, a 'thick' section of 1–2 μm was taken from the whole block face and stained with a mixture of methylene blue and Azure II (Richardson, Jarett & Finke 1960); an appropriate area for thin sections was chosen and the block trimmed. Thin sections were cut and mounted on a film of Formvar on copper grids with a single hole 1 mm × 2 mm, and stained on the grid with alkaline lead citrate (Reynolds 1963) and uranyl acetate (5 % solution in 50% ethanol).

Detailed electron microscopic maps of perpendicular sections of the cortex were made to obtain information about the distribution of degenerating terminals in the different laminae at varying distances from a particular lesion. The region to be surveyed was usually of the order of 2 mm (the approximate depth of the cortex) × 3 mm, but the section for survey could not be larger than about 1.5 mm × 0.75 mm because larger sections were difficult to cut and to

mount on the grid, and also took so long to survey that there was danger of the section rupturing. It was therefore necessary to divide up the face of the whole block into areas for thin sections so that the region to be surveyed could be covered without any appreciable gaps between the individual areas; the block was trimmed to several areas in succession, and at each stage the size of the area and its position relative to the edges of the whole block face were recorded by means of a drawing made with the aid of a dissecting microscope fitted with an eyepiece micrometer. Each section was surveyed in the electron microscope with a conventional 'square search' procedure: the stage micrometer coordinates of the corners of the section were recorded and then the section was examined systematically, the position and features of any degenerating terminals found being recorded. Finally, a representation of each area, with its degenerating terminals, was plotted out on graph paper and the 'maps' so formed fitted together to form a representation of the whole region occupied by the block.

For the investigation of the commissural connections in the monkey, most of the superomedial parts of the striate and peristriate cortex on the lateral surface of the brain were removed. The lesions were made by suction and as far as possible the cortex of the whole of the pre-lunate gyrus and of both walls of the lunate sulcus was removed. After survival periods of 3–5 days the animals were again anaesthetized, cooled and perfused with buffered saline followed by a mixture of 1% glutaraldehyde and 4% paraformaldehyde. Blocks of tissue were taken for electron microscopy from the posterior bank and wall of the lunate sulcus of the opposite hemisphere. The terminal degeneration of the commissural fibres was studied with the electron microscope only at the boundary of areas 17 and 18, and not at the other sites of such degeneration in the peristriate cortex. As the extent of cortex at the 17/18 boundary which contains degeneration is only a few millimetres wide, it was important to know the precise relationship of the small blocks taken for electron microscopy to this boundary. A thin slice of tissue was cut, in the sagittal plane, from the posterior bank and wall of the lunate sulcus and this included the anterior part of area 17, the 17/18 boundary and area 18. Blocks through the whole depth of the cortex and 1 mm square were taken and numbered in strict order from anterior to posterior (that is, from area 18 through to area 17). Another slice of tissue of the same antero-posterior extent was then cut from immediately medial or lateral to that from which the first was taken, sectioned on a freezing microtome at 25 μm and the sections were stained by the Fink–Heimer method. In this way the position of the maximum degeneration at the 17/18 boundary was determined and the blocks taken from the corresponding position of the first slice were used for study with the electron microscope. Maps of the distribution of the degeneration in the cortex were made with the electron microscope and the regions surveyed were strips 0.5 mm wide through the depth of the cortex. The procedure for mapping individual sections was the same as that described earlier for the study of the intrinsic connections of area 17.

Five cats were used in the investigation of the commissural connections of the visual cortex and in three of these animals material was also studied from the cortex of area 17 of the operated hemisphere for association connections. In two animals, used only for the study of commissural connections, the whole of the cortex of areas 17, 18 and 19 was removed by suction and in the remaining three animals small lesions were made with a needle in area 18 on the lateral gyrus, care being taken not to encroach upon adjoining areas. After survival periods of 2–5 days the animals were again anaesthetized, cooled and perfused with aldehyde mixture for electron microscopy. The brain was removed and 1 mm coronal slices of the lateral gyrus were taken from each hemisphere at the level of the lesion. From these, small blocks 1 mm

square through the depth of the cortex were taken from area 17 on the ipsilateral side of the three animals with small lesions in area 18 and from the boundary region of areas 17 and 18 of the opposite side of all five animals. The degeneration of commissural fibres was studied only in this 17/18 boundary region and not at the other sites which receive such connections. As in the monkey, coronal slices of the lateral gyrus 2–3 mm thick were taken for light microscopy from immediately next to those taken for electron microscopy, and the procedures for mapping the degeneration were the same as those which have been described for the monkeys' brains.

Results

Light microscopy of the intrinsic connections of area 17 of the monkey

The study is based on the degeneration observed after 67 lesions, of different depths, in the cortex of area 17 on the exposed lateral surface of the hemisphere, and upon two in the same architectonic area on the banks of the calcarine sulcus on the medial surface. Fifty-one of these lesions have been found to be useful, the remaining 16 being discarded because of poor impregnation, excessive sideways spread of the lesion or undue extension into the underlying white matter. The experiments will be divided into groups, depending upon the depth of the lesion and the laminae involved; the depth of the lesions will be described in terms of those laminae, from the surface. Although the sections have been examined as carefully as possible to determine the maximum depth of the lesions, such an assessment is bound to contain an element of uncertainty, and where a lesion encroached on the superficial margin of a lamina we have tended to assume that the lamina was involved.

Preliminary experiments showed that the extent of axonal degeneration was limited to a few millimetres on either side of the lesion, and as it is known that most of area 17 neither sends nor receives commissural fibres, in later experiments several small lesions were placed on each side of the brain. It should be emphasized, however, that the lesions were always sufficiently separated to prevent confluence of the degeneration, which, indeed, was never found on the sections. The lesions could be identified individually by comparing their appearance in the sections with the records made at operation of their exact positions and depths.

Three different versions of the Nauta technique were used to stain adjoining sections of most of the lesions, and as the study progressed it was found that the use of more than one of these staining techniques was extremely valuable. Each of them had certain advantages and disadvantages in that, for example, the original Nauta–Gygax method (1954) showed the degenerating axons very clearly but was less useful for the finer, terminal degeneration, whereas the Fink–Heimer technique had the opposite characteristics; the particular advantage of the Wiitanen method, in our hands, was that in addition to staining the degeneration, it permitted such remarkably clear delimitation of the laminae that there was no need for the staining of adjoining sections by the Nissl method, which was important because the lesions were frequently so small that it was necessary to stain all sections over their extent for fibre degeneration.

As many of the lesions were very small and localized, and as in most experiments the degeneration was limited to a few millimetres in extent, certain points may be mentioned regarding the validity of the observations. In each experiment, all of the sections of the occipital lobe were kept, in order, and repeated series of sections over the extent of the lesions were stained by two or three of the different techniques. Furthermore, the sections were examined carefully for the

possibility of any small incidental lesion or focal necrosis due to involvement of small pial vessels. Finally, the results of a few experiments using the method of injection of labelled L-leucine (Cowan *et al.* 1972) are in general agreement with the observations made on material impregnated for axonal degeneration.

To facilitate the description of the results of individual experiments, a brief account of the cytoarchitecture of area 17 will be given. A recent analysis by Hassler & Wagner (1965) divides the cortex of area 17 into six major laminae of which two, the main pyramidal cell layers III and V, are further subdivided. The important new feature of their classification as compared with that of von Bonin (1942) is that Hassler & Wagner consider that the sublayer containing the stria of Gennari (which in the monkey separates the layers receiving geniculocortical afferents (Hubel & Wiesel 1969, 1972; Garey & Powell 1971)) should be thought of as the deepest subdivision of layer III, called by Hassler & Wagner layer IIIc, rather than as the superficial part of layer IV (layer iva of von Bonin). Layer I is the molecular layer containing a few stellate cell somata, while layer II is a layer of predominantly small pyramidal cells with some scattered small stellate cells. Layer III is wide and is divisible into a superficial lamina of small and medium-sized pyramidal cells and a deeper band of larger, darker pyramids. Deeper still the cell density decreases noticeably, the pyramidal cells continuing to be present but in reduced numbers, and a considerable number of small and medium-sized stellate cells appearing between them. It is this heterogeneous, sparsely cellular band which contains the overwhelming majority of the fibres of the stria of Gennari and which is designated layer IIIc. Layer IV proper (ivb of von Bonin) stands out remarkably at low magnification as a dark band of closely packed large and small stellate cells, and the superficial, more loosely packed part of this layer also contains the deepest fibres of the stria of Gennari. Layer V is again much lighter and is a narrow strip of small pyramidal cells with a few very large dark pyramidal cells, the cells of Meynert, on its deep aspect. Layer VI is composed of deeply staining, medium-sized pyramidal and fusiform cells and presents the appearance of a further dark band, with a more sparsely celled zone on its deep aspect. Meynert cells are also found in that part of layer VI adjacent to layer V. Fuller descriptions of the structure of the visual cortex have been given recently by Garey (1971), Lund (1973), Szentágothai (1973) and Lund & Boothe (1975).

Group A

In the first group of 13 experiments, all made with the needle or fine scalpel, the damage extends through most of the depth of the cortex, either without involvement of underlying white matter (4 cases) or with slight extension into it (9 cases).

As an example of the first type of lesion, that in experiment 126R-1 (figure 1; figure 9, plate 1) will be described. It is situated in the lateral part of area 17, aproximately 10 mm behind the lunate sulcus and about 4 mm medial to the inferior occipital sulcus as it turns backwards. In the sagittal sections of this hemisphere the lesion is seen as a narrow, well defined slit reaching to the deep part of layer VI; over no part of its extent does it involve the underlying white matter. Its mediolateral extent is approximately 2 mm, and it remains remarkably constant in both width and depth. (It is possible to define the anterior limit of area 17 in these sections both by the change in the laminae and by the sudden appearance of a few unusually large cells at the margin of layers III and IV; the lesion is approximately 5 mm behind this boundary.)

In the sections stained by the Fink–Heimer method degeneration can be seen throughout the depth of the cortex, but for a surprisingly limited extent on each side. Except for approximately

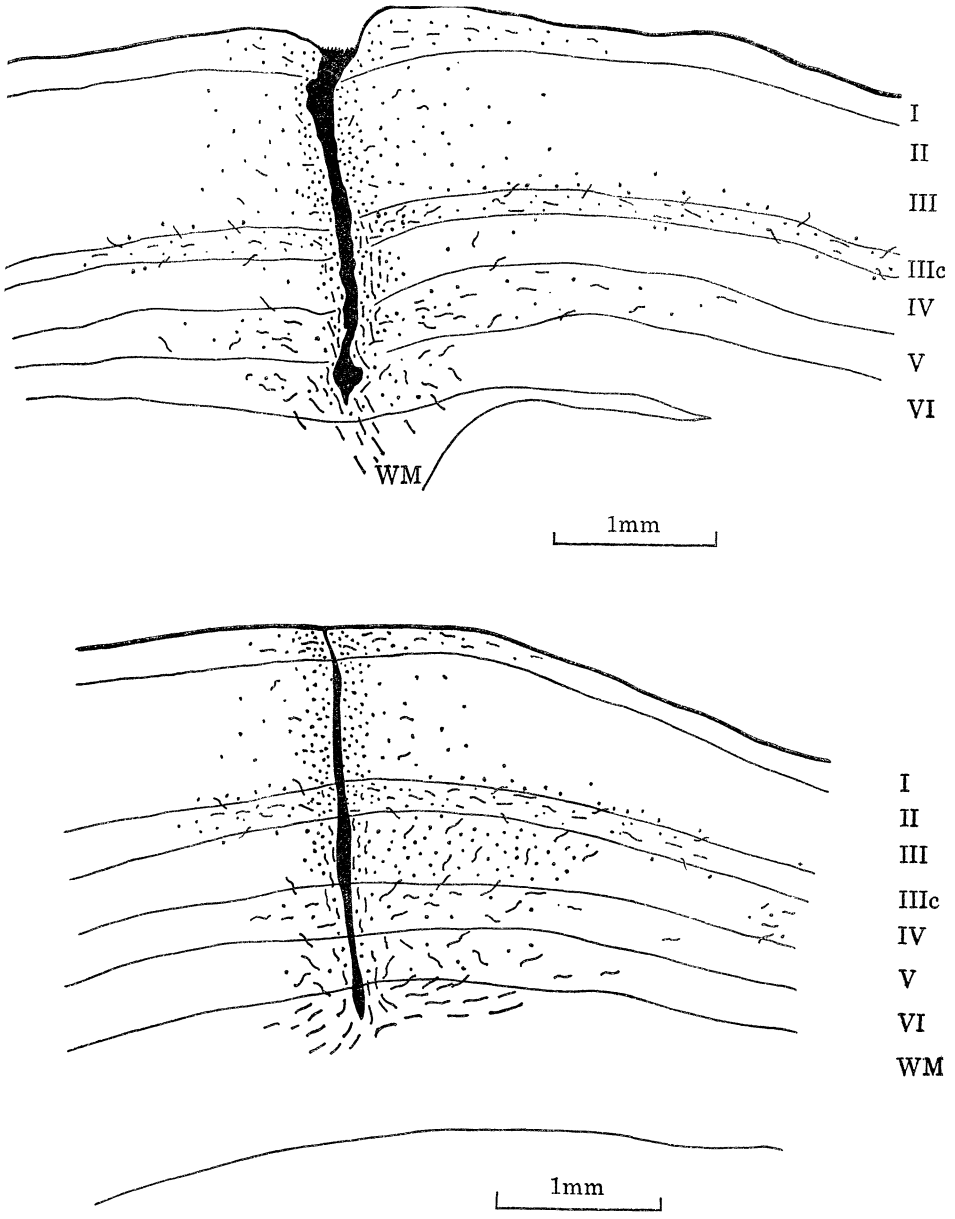


FIGURE 1. The lesion and the resulting fibre degeneration in experiment 126R-1 (upper) and 117R-2 (lower). In this and subsequent figures the lesion is shown in solid black, the fibre degeneration by short lines and the terminal degeneration by fine dots. The laminae of the visual cortex are indicated by the Roman numerals on the right of the figure. The horizontal extent of the degeneration has been indicated as accurately as possible, and the scale of the figure is given by reference to the length of 1 mm shown below.

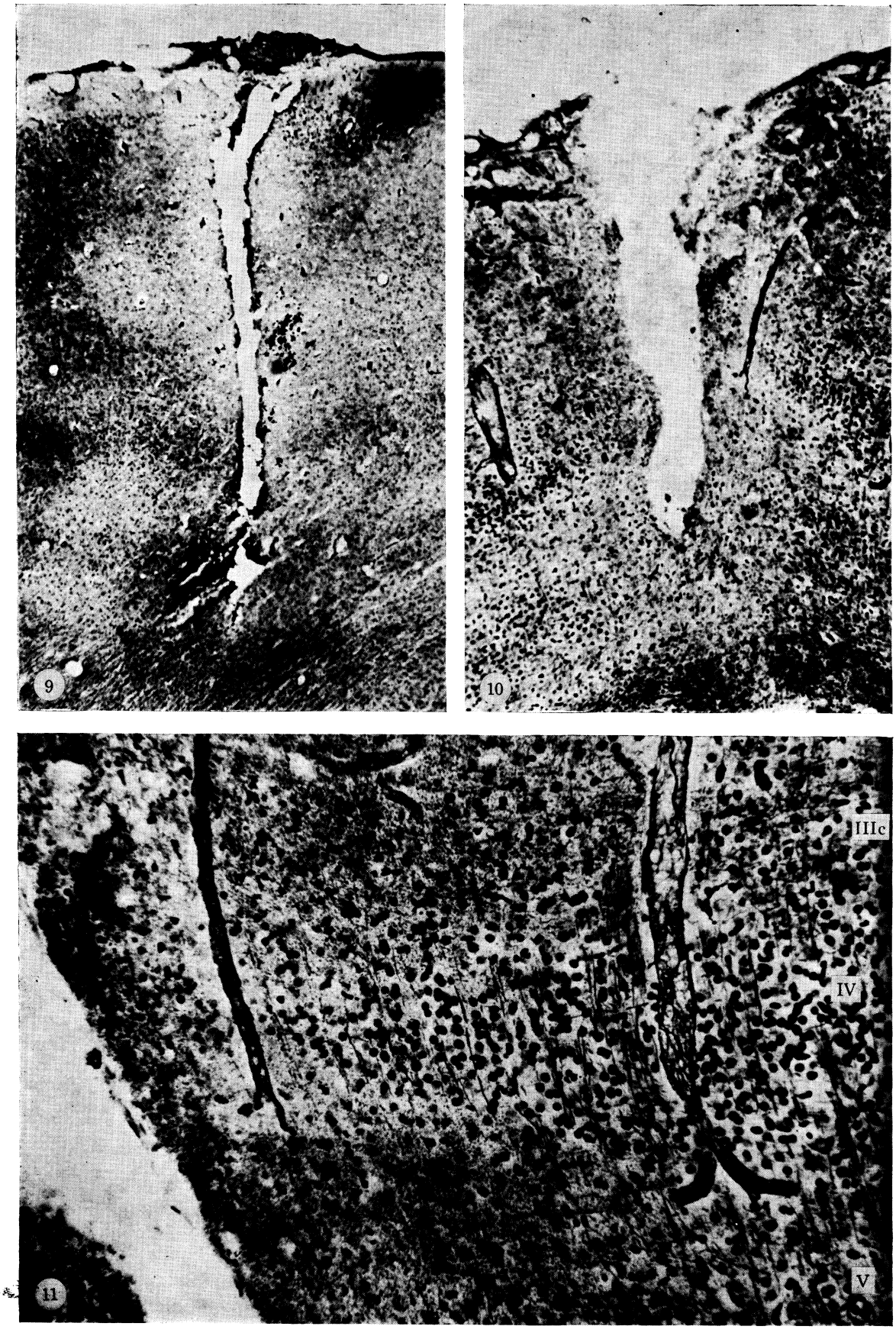
DESCRIPTION OF PLATE 1

All photomicrographs shown in the plates have been taken from area 17 of the visual cortex within 2 mm of the lesion in the cortex. Sections have been stained by either the Nauta–Gygax (1954) method, the Fink–Heimer (1967) or the Wiitanen (1969) modification of the Nauta technique.

FIGURE 9. The slit lesion in the cortex of area 17 of experiment 126R-1. The lesion is strictly confined to the cortex and does not invade the underlying white matter. Fink-Heimer stain. (Magn. × 50.)

FIGURE 10. The slit lesion in experiment 110L-2. The slit is wider than in the previous experiment, but does not extend deeper than layer V. Wiitanen stain. (Magn. × 75.)

FIGURE 11. Part of the previous figure at higher magnification, to show the absence of fibre and terminal degeneration in layer IV except in the immediate vicinity of the lesion. The absence of degeneration in layer IV is in marked contrast to the severe degeneration present in layers IIIc and V. (Magn. × 180.)



FIGURES 9–11. For description see opposite.

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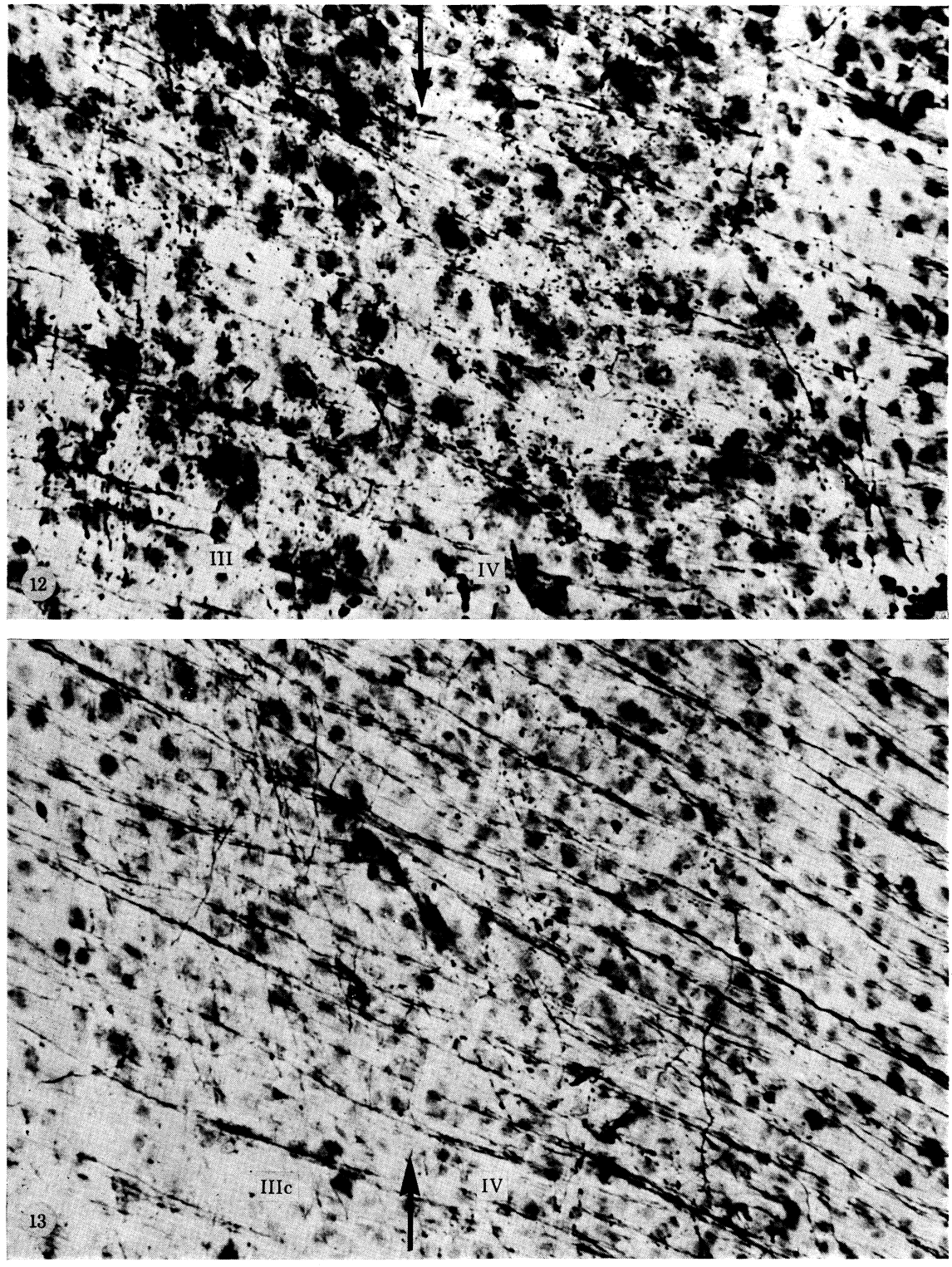


FIGURES 12 AND 13. For description see opposite.

200 μm on each side of the lesion, where there is very dense, fine degeneration throughout all layers, there are distinct differences both in the appearance and in the extent of the degeneration in different laminae. In layer I there is a little fine granularity and some rows of granules indicative of fibre degeneration, but only distributed over a distance of 1–2.0 mm from the lesion. Layers II and III have a largely similar appearance to each other, with an even distribution of fine, granular degeneration. This is densest for 200 μm on either side of the lesion, then remaining more or less uniform throughout the depth of these layers for a distance of 1.5 mm or so, where it stops relatively suddenly. The extent of spread is different on the two sides, being slightly greater towards the boundary of area 17. In the deep part of layer III much sparser degeneration of slightly coarser granules can be seen extending for a further 1–2 mm, being continuous on its deep aspect with much heavier degeneration in the stria, from which an occasional degenerating fibre can be seen passing into this layer. A notable feature of the degeneration in layers II and III is the marked paucity of obvious fibre degeneration, and in only a few cases can granules be seen to be arranged in rows as fragments of obliquely disposed fibres. The degeneration in layer III is directly continuous with degeneration in the stria of Gennari, but that in the latter is somewhat coarser, is intermingled with more fibre degeneration and clearly extends for a greater distance. On the side towards area 18 the degeneration, although gradually diminishing, reaches for 3.5–4.0 mm, i.e. almost up to the 17/18 boundary, whereas on the opposite side it extends for 1.5–2 mm. Except for approximately 200 μm immediately to the side of the lesion, where there is dense, fine granularity in layer IV, the deep aspect of the stria is clearly delimited by the relatively clear appearance of layer IV; beyond the immediate vicinity of the lesion there is only very sparse granular degeneration and an occasional, vertically disposed, fragmenting fibre in this layer. This lack of degeneration in layer IV, in contrast to that on its deep and superficial aspects, is very striking and makes the layer stand out even at relatively low magnifications (figures 10 and 11, plate 1). The appearance of layers V and VI are similar to each other, except that the quantity of degeneration in layer VI is somewhat less. The terminal, granular degeneration is coarser in these layers as compared with layers II and III, and the number of degenerating fibres is much greater; the latter are also quite coarse, are seen to run in all directions and are perhaps more numerous in layer V. In the latter layer there is also a greater proportion running horizontally, in about the middle of the layer, giving a general appearance of degeneration affecting the inner band of Baillarger; although there is a marked decrease in the number of these degenerating fibres at about 1 mm away from the lesion, sparse degeneration can be traced for almost the same distance as that in the stria.

In sections over this lesion stained with the Nauta–Gygax method there is less impregnation of the fine, granular degeneration, but more of coarser fragmenting fibres. The degenerating

Description of plate 2

Figure 12. The fibre and terminal degeneration in the stria (IIIc) and in layer IV in experiment 117R-2. The arrow demarcates layer IIIc from layer IV, and it should be noted that the superficial aspect of the cortex is to the left of the figure and the deep margin to the right. (Magn. × 400.)

Figure 13. To show the degeneration of afferent thalamo-cortical fibres in layer IV beyond the point at which degeneration is present in the stria (IIIc) in experiment 117R-2. The arrow demarcates layer IIIc from layer IV and the disposition of the cortex is as seen in figure 12. It can be seen that the stria in layer IIIc is free of fragmentation. (Magn. × 400.)

fibres in layer I are seen more clearly, and because of the diminished granularity of layers II and III, the fibre degeneration in the stria of Gennari stands out more prominently as a horizontal band. In layer V the tendency of the horizontally disposed fragments to be collected together in the position of the inner band of Baillarger can be seen more definitely. A further point brought out in these sections is that in the two deepest layers the degenerating fibres close to the lesion are predominantly vertically arranged, giving the appearance of a 'cuff' around the slit-like lesion, whereas further out the fibres are equally disposed in all directions. In the three other lesions of this group the findings are essentially the same, and in particular the asymmetric spread of the degeneration on the two sides of the lesion is seen in each case. Only a few additional points need to be mentioned: in one of the experiments, 117L-8, the horizontal fragments in layer V are clearly seen to be disposed in three or four rows in the position of the inner band of Baillarger; in another lesion, 117L-2, which only partially involved layer VI, the vertically arranged degenerating fibres in the deeper part of this layer, which are passing into the white matter, are concentrated in a narrow band in the direct line of the lesion. Another feature of this last experiment, in which the lesion is situated near the anterior edge of area 17, is that the terminal degeneration in layer IV extends appreciably further anterior to the lesion than it does posteriorly, and more than would be expected from the asymmetry found in the other lesions: posterior to the lesion the degeneration in this layer, as in the experiment described in detail, extends for only 200 μm or so, but anteriorly it is distributed for almost a millimetre; this difference is no doubt due to the part of the lesion in layers V and VI having interrupted the thalamocortical fibres which must have entered at this point, as the lesion is at the anterior margin of the underlying white matter.

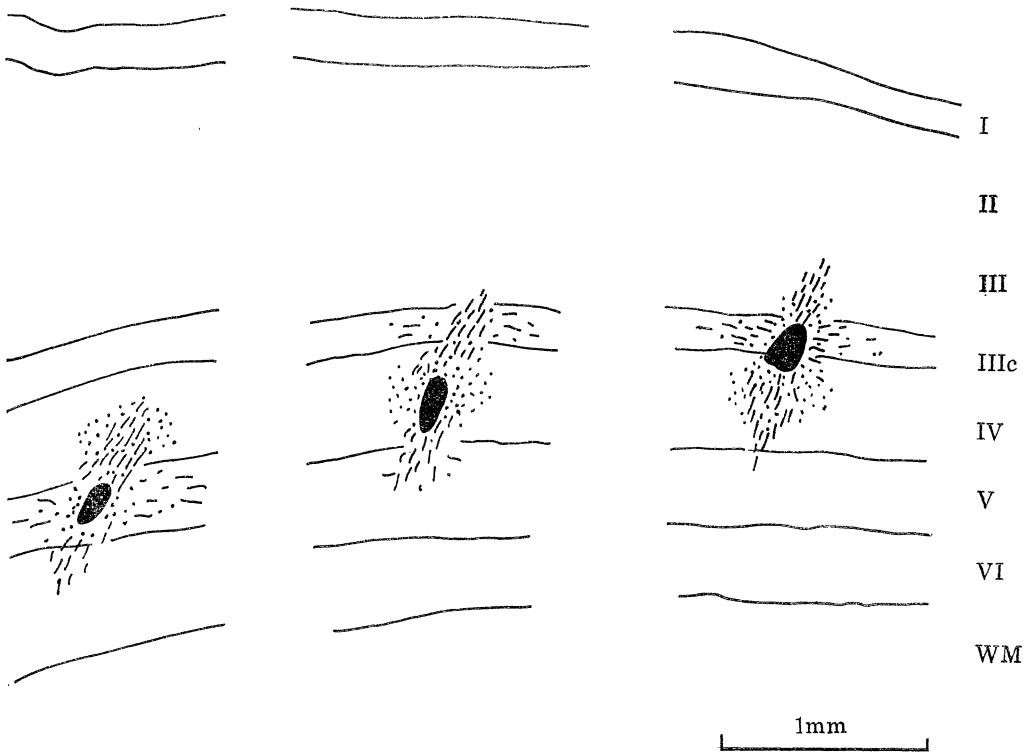


FIGURE 2. The site of the damage and the resulting fibre degeneration in experiment 120R in which the lesion appeared at different depths on adjoining sections. It should be noted that the fibre degeneration superficial and deep to the lesion is of approximately the same width as the lesion itself.

In the nine lesions in which the underlying white matter was involved to a small extent, certain slight differences were found in the pattern of degeneration (117R-2, figure 1). More degenerating fibres were found in layers V and VI, some of which were quite long and could be seen to take a very oblique course away from the lesion. The second notable feature was the difference in the amount of degeneration in layer IV on the two sides of the lesion: on one side it was similar to that seen after lesions confined to the cortex, in that there was granular degeneration in the immediate vicinity of the lesion, but beyond this it was relatively clear. On the other side, however, the degeneration extended further (figures 12 and 13, plate 2) and was accompanied by some fibre degeneration which could be seen entering it from the deeper layers. It is almost certain that this difference is due to the interruption of some thalamocortical fibres in their subcortical course, as the side more extensively affected was always that which would be predicted from a knowledge of the course of the incoming thalamic fibres, that is, anterior or medial to the lesion. The suggestion that this involvement of thalamocortical fibres occurred in the white matter and not within the cortex is supported by the findings in one experiment (120 R) in which the lesion was made electrolytically and barely encroached on the white matter. The sections happened to be cut at an oblique angle to the line of the track; consequently the lesion was seen as a small focus of necrosis at different depths on succeeding sections (figure 2). It was striking that, when the lesion was in the middle portions of the cortex, the major fibre degeneration, both above and below the lesion, was in a band the width of the lesion and the fibres were vertically disposed; on either side of the lesion some fibres passed out horizontally and these were more obvious when the lesion was at the level of the outer or inner band of Baillarger in layer IIIc or layer V. The finding of degenerating fibres superficial to the lesion over a width only approximately equal to that of the damage suggests strongly that the thalamocortical fibres run vertically for most of their intracortical course, and this is supported by the finding of no obvious asymmetry in the terminal degeneration in layer IV. No significant qualitative difference was seen in the layers superficial to layer IV after lesions involving the white matter, for the degeneration in these layers was so dense after lesions confined to the cortex that whatever slight increase there might have been in the amount of degeneration when the white matter was also involved was not noticeable.

Group B

The first group of experiments have shown the maximum extent and the total pattern of fibre and terminal degeneration after lesions of the cortex but they have given little information about the origin of the fibres in the individual laminae. In the experiments of this and the subsequent groups the lesions affect differentially two or more laminae and provide some information about the laminar origin of these fibres. In this second group of three experiments the lesion is confined to layers I and II. (We have no lesion which is restricted to layer I.) The three lesions are similar in that each is only 0.3–0.5 mm in diameter (figure 3). In the sections stained with the Fink–Heimer and Wiitanen methods, fine fibre and granular degeneration is seen in layer I and, while densest in the immediate vicinity of the lesion, it extends out for 1 or 2 mm on either side (figure 3; figure 23, plate 6). In layer II there is dense, very fine granular degeneration surrounding the lesion, but this granularity rapidly diminishes in amount away from the site of damage (figures 14 and 15, plate 3); vertically, sparse degeneration extends into layer III but does not extend deeper than IIIa, as there is a clear area between the deep margin of the degeneration and the stria in IIIc. No degeneration can be seen deep to the

superficial part of layer III, and no fibres can be seen passing vertically out of the cortex or running horizontally in the stria. In the Nauta–Gygax preparations a few degenerating fibres are seen running down into the upper part of layer III.

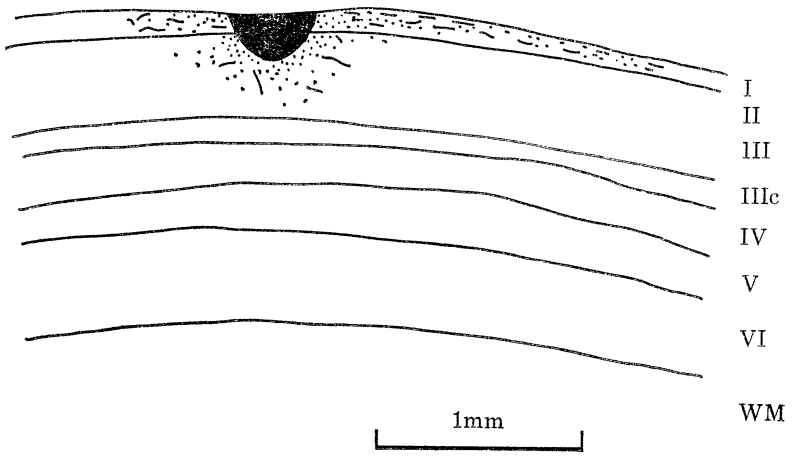


FIGURE 3. The extent of the damage and the resulting degeneration in experiment 126R-2, in which only laminae I and II were involved.

Group C

This group is made up of nine lesions which, in addition to damaging layers I and II, have involved layers IIIa and IIIb but not IIIc, in which the stria runs. It has not been possible in this material to distinguish with certainty between involvement of the subdivisions a and b of layer III.

The first experiment to be described in this group is experiment 139R-3. The lesion was produced electrolytically and forms a small area of necrosis, approximately 500 μm in diameter, in layers I, II and the superficial part of layer III (figure 4). The Wiitanen sections are exceptionally well stained and show both the degeneration and the laminae very clearly. There is dense, fine granular degeneration immediately around the lesion in each of the affected layers. From this narrow zone of dense degeneration a few fine degenerating fibres can be seen radiating outwards, and there is a moderate amount of terminal degeneration scattered among them; in layer I this degeneration extends outwards for almost 1.5 mm on one side and for 2 mm on the other, but in layers II and III it reaches less far. Although it is difficult to be certain about small differences in the density of degeneration in different experiments, it is probable that the amount of terminal degeneration in layer III due to small lesions reaching down only to this layer is less than after one extending through the deeper layers as in the first group. Deep to the lesion, in the deep half of layer III and the underlying stria, there is moderate granular degeneration, but the major feature is a narrow band of fragments of degenerating, vertically disposed fibres; these fragments are slightly larger than the fibres around the lesion. The side-to-side extent of the degeneration in the deep half of layer III, including the stria, is no wider than at the level of the lesion, and both in the stria and throughout the depth of layer III above it there is only an occasional degenerating horizontal or obliquely disposed fibre. In layer IV the vertically disposed degenerating fibres can be clearly seen over a relatively narrow side-to-side extent; interspersed among them is a little fine granularity. In layer V there is a slight increase in the fine terminal degeneration, together with

a little degeneration of the horizontal fibres in the inner band of Baillarger. A few degenerating vertical fibres continue through layer VI to enter the white matter, and in this layer there is also a little granular degeneration. The number of degenerating fibres in layer VI is considerably less than the number passing through the stria and layer IV.

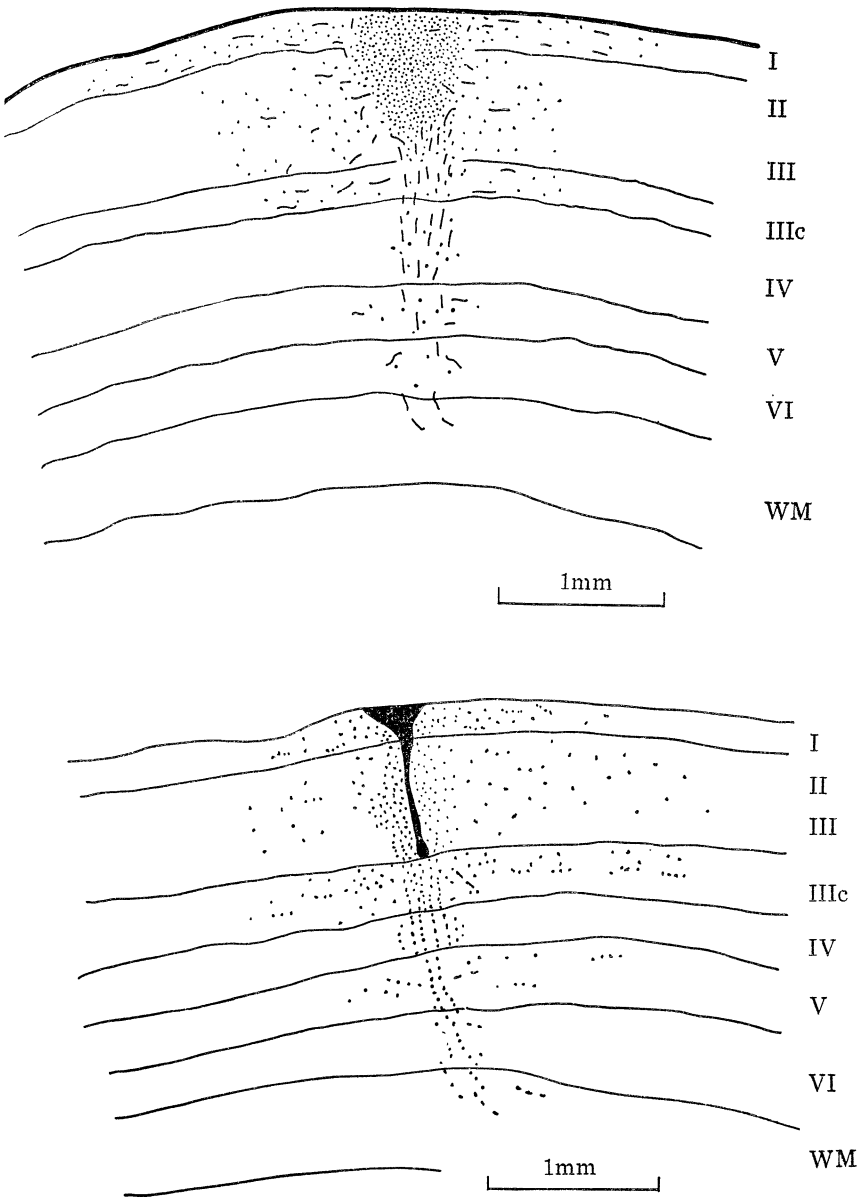


FIGURE 4. The lesion and degeneration in experiment 139R-3 (upper) and 117L-5 (lower). In experiment 139R-3 the extent of the lesion is indicated by the dense stipple.

In experiment 117L-5 (figure 4) the lesion extends to the deep margin of layer IIIb but does not encroach on the stria lying in IIIc; it provides a closer comparison with the experiments described in the first group, because it is in the form of a well-defined, narrow needle track no more than 50 μm in width. The pattern of degeneration in the different laminae is similar to that in the previous experiment, but because of the narrowness of the lesion certain

features are well displayed. In the stria and in layer IV the restricted extent of the vertical degenerating fibres is quite definite, and in the latter of these there is a sharp diminution in the amount of degeneration on either side. In layer V the degeneration in the inner band of Baillarger is well impregnated (figure 19, plate 4) and can be seen to extend more widely than the degeneration in layer IV, being almost as wide as that in layer III. The decrease in the number of fragmented fibres and in terminal degeneration in layer VI is again quite definite.

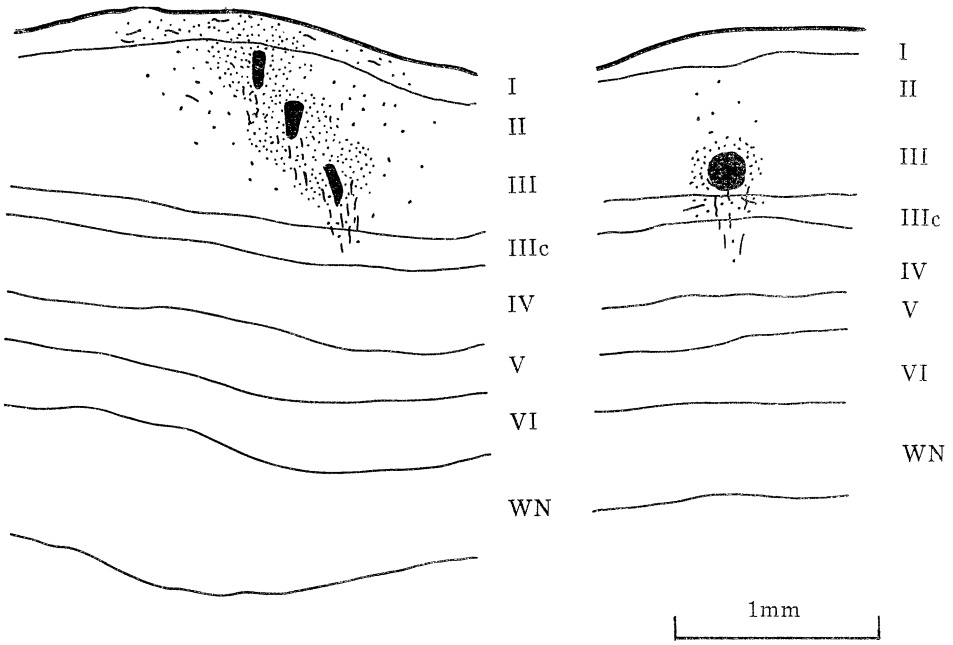


FIGURE 5. The lesion and degeneration in experiment 126R-3 (left) and 114R-3 (right). In 126R-3 three small focal lesions were made at different depths along the same penetration, and all were found on the same section.

Two further experiments will be described together as they illustrate, in different ways, the same points (figure 5). In experiment 114R-3 the lesion was made by passing a current of a few microamperes during the traverse of the needle through the superficial layers. The sections were cut obliquely to the lesion; consequently portions of the latter at different depths appear on different sections as small foci a few hundred micrometres in diameter. The deepest extent of the lesion is in IIIb immediately above the stria (figure 17, plate 3). The interesting point is that, on the individual sections, on which the lesion appears in layer II and the superficial part of layer III on the one hand, and in the deep part of layer IIIb on the other, the fine granular

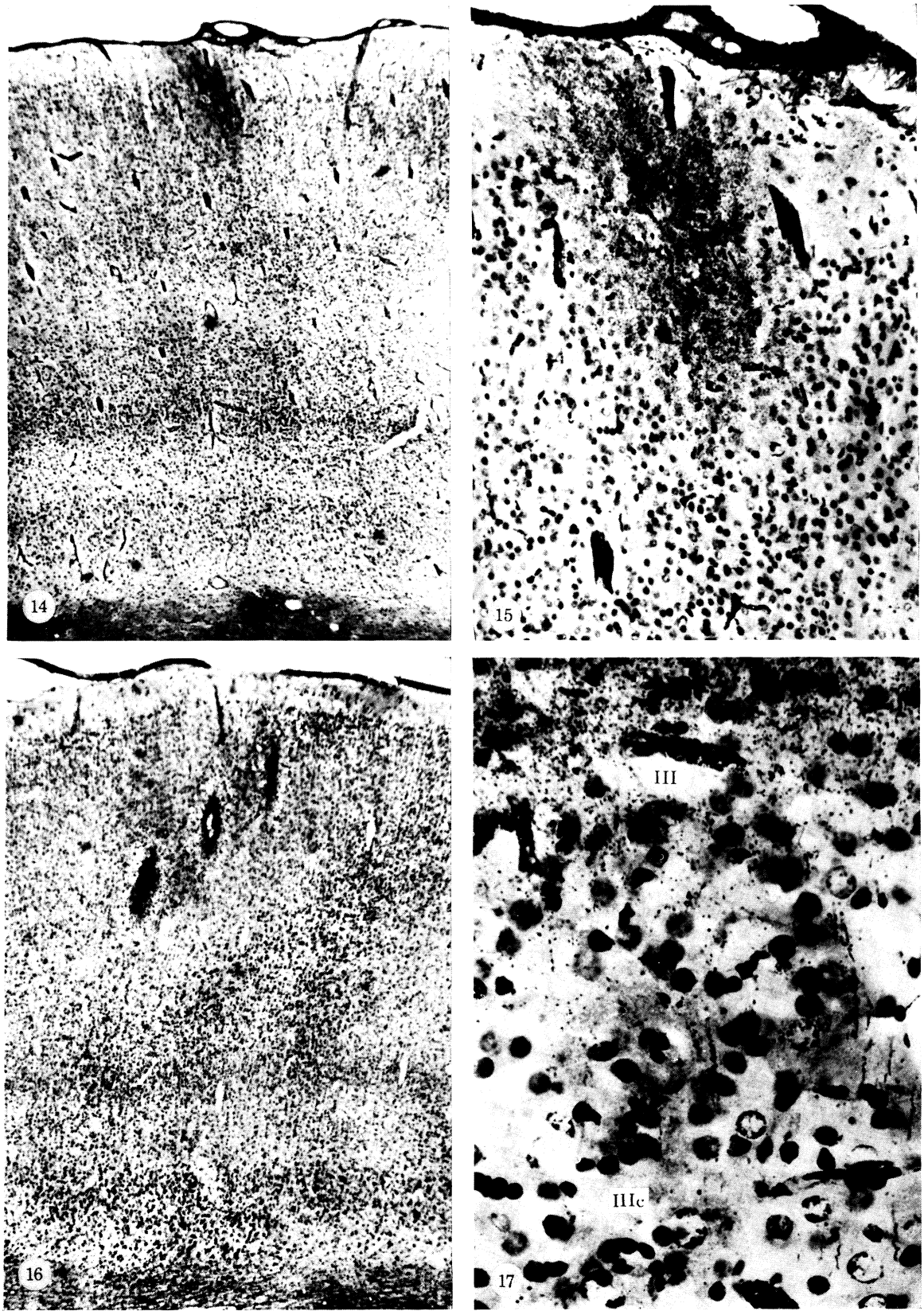
DESCRIPTION OF PLATE 3

FIGURE 14. The small lesion in layers I and II in experiments 114R-2. (Magn. × 50.)

FIGURE 15. The same lesion as in the previous figure, at a higher magnification. (Magn. × 150.)

FIGURE 16. The three small lesions in layers II and III in experiment 126R-3. (Magn. × 50.)

FIGURE 17. To show the small number of fibres running vertically downwards through layer IIIc from the deep aspect of the lesion in experiment 114R-3. The lesion is indicated by the dense granularity at the top of the figure. (Magn. × 450.)



FIGURES 14–17. For description see opposite.

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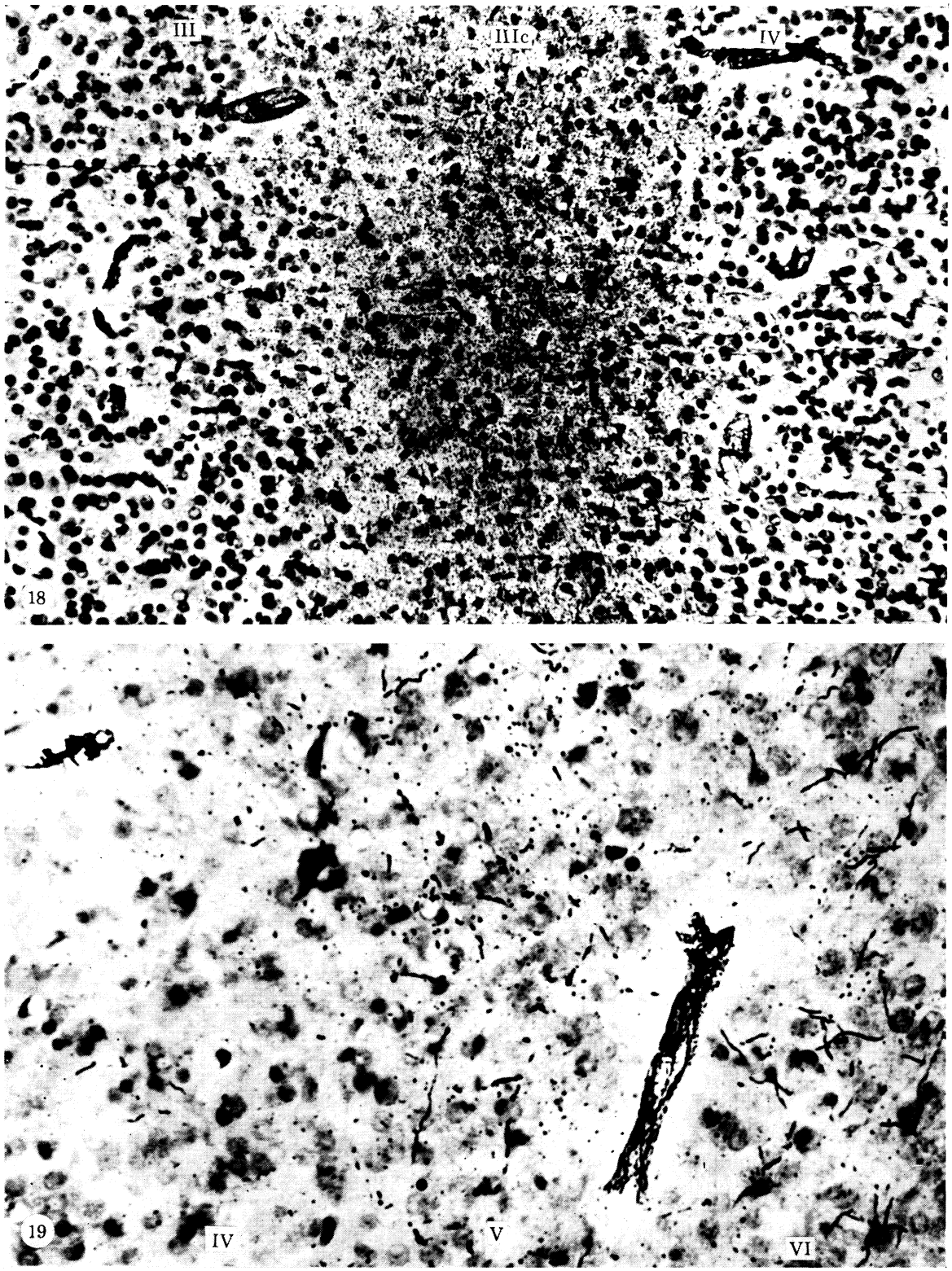

FIGURES 18 AND 19. For description see opposite.

degeneration in layer III is more or less restricted to the vicinity of the lesion, and it is worth noting that the width of the degeneration in layer IIIc is no greater than that in IIIa and b. In the other experiment, 126R-3, three small foci, each about 50 μm wide, were made at different depths along the same oblique needle track and the three foci have been found on the same section (figure 16, plate 3); they are all within the region of layers II and IIIa and b. Again there is a definite appearance of three circular areas of fine degeneration, one around each, with the superficial and deep margins continuous. The narrow bands of vertically disposed degenerating fibres from each of these are clearly separated and the number of fibres from each focus increases progressively with its depth.

Group D

In this group of ten experiments, in which the lesion has extended to involve the stria of Gennari in layer IIIc, an important new feature of the pattern of degeneration appears, namely that the fibre degeneration in the stria is more severe and extensive than in the previous groups of more superficial lesions. There are two types of lesion in this group: the first is similar to those which have already been described in that all of the affected layers have been damaged more or less equally by a needle stab or by the current being passed from a microelectrode during its entire traverse, whereas the second is a small focus of necrosis strictly confined to layer IIIc, with no appearance in the superficial layers suggestive of damage due to the passage of the fine electrode.

In the experiments with the first type of lesion (117L-4, figure 6), the resulting degeneration in the layers superficial and deep to the stria is similar, in both appearance and extent, to that in the previous group with small lesions. In the stria itself, however, the pattern is distinctly different: there is more fragmentation of fibres and a large proportion of these are clearly running horizontally: although the intensity of this degeneration is maximal for a few hundred micrometres on either side of the lesion, it extends out on both sides to beyond the limit of the fine granular degeneration occupying most of the depth of layers IIIa and b. In all of the experiments the degeneration is clearly asymmetrical in extent and is usually present for 1–2 mm more on one side than the other; although the number of degenerating fibres diminishes away from the lesion, undoubted fragments can be seen over a total extent (from end to end) of 5–6 mm. From this degeneration in the stria fibres can be seen passing both superficially into the deep part of layer IIIb, and deeply into the superficial, loosely cellular half of layer IV; in these layers a little coarser terminal degeneration is present over the extent of the degeneration in the stria.

In experiment 111L-4 (figure 6; figures 21 and 22, plate 5) the damage is in the form of a small, flask-shaped focus of necrosis approximately 150 μm in width and is confined to the stria and the immediately adjoining part of layer IIIb; its deep margin is certainly within the limits of the stria. There is no sign of the electrode track passing through the more superficial parts

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DESCRIPTION OF PLATE 4

FIGURE 18. The lesion in the stria (IIIc), as indicated by the very dense granular degeneration in experiment 110R-6. There is very little degeneration in layer III superficial to it and in layer IV deep to it. The surface of the cortex is to the left and the deep aspect to the right. (Magn. × 200.)

FIGURE 19. The degenerating fibres passing horizontally in layer V, due to the lesion in experiment 117L-5. The surface of the cortex is to the left and the deep aspect to the right. (Magn. × 450.)

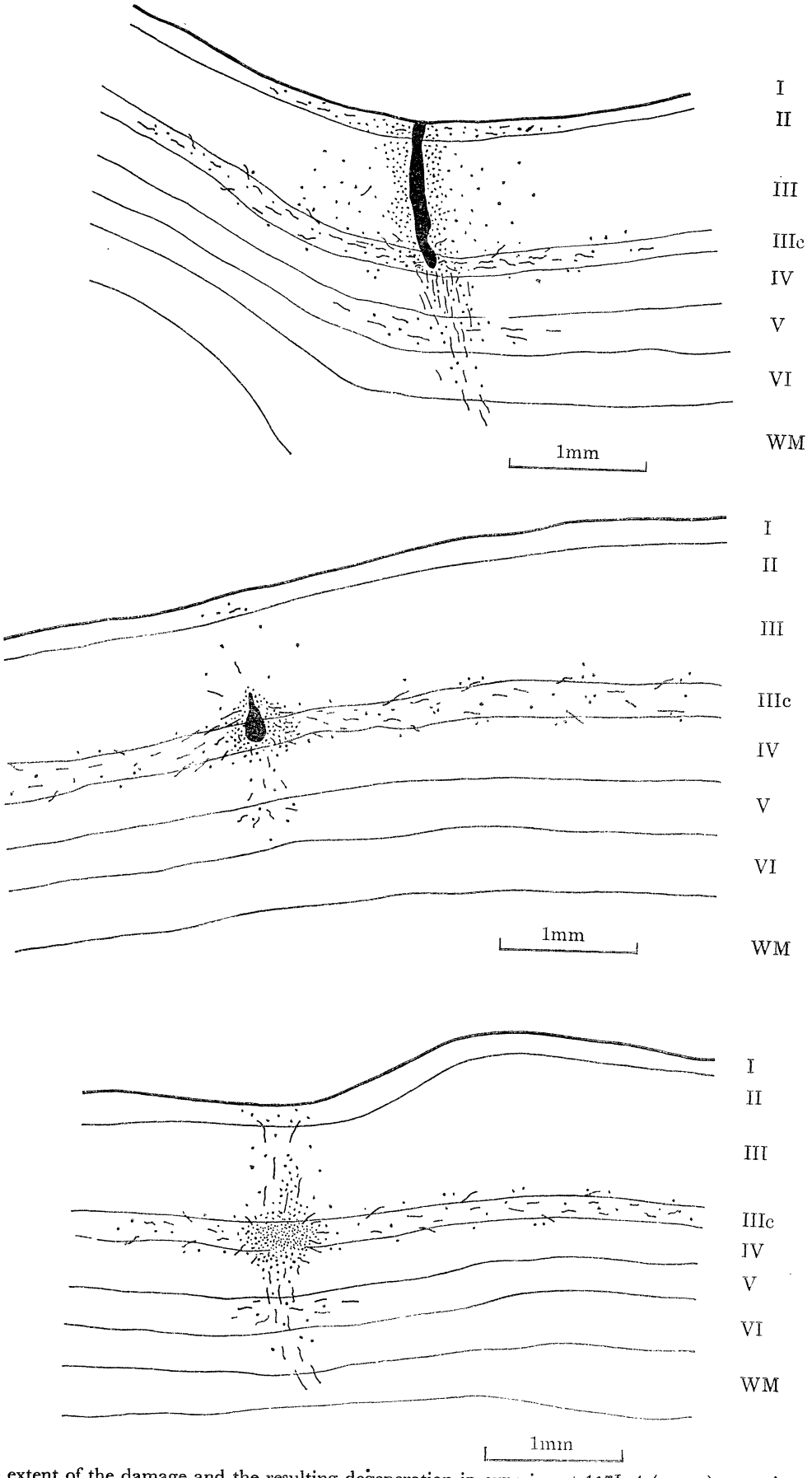

FIGURE 6. The extent of the damage and the resulting degeneration in experiment 117L-4 (upper), experiment 111L-4 (middle) and experiment 110R-6 (below). In each of these experiments the damage extended down to involve the stria in lamina IIIc. In experiments 111L-4 and 110R-6 there was very little degeneration in the superficial layers due to the passage of the electrode. Note the patchiness of the terminal degeneration associated with fibres in the stria on the right-hand side of experiment 111L-4.

of the cortex, even on adjoining serial sections, and this is in accord with the small amount of fine, granular degeneration in these layers. From the site of damage degenerating fibres can be seen running in the stria, and on each side, in addition to those running horizontally, there are some fibres diverging obliquely down to the superficial half of layer IV. There is again a little terminal degeneration in this part of layer IV and in the deep part of layer IIIb over the extent of the degeneration in the stria, and beyond 1 mm from the lesion this tends to be concentrated into patches of about 200 μm in width, alternating with relatively clear areas. Even after this small, focal microelectrode lesion the degeneration in the stria extends over a distance of some 6 mm from end to end, and is again clearly asymmetrical. The amount of degeneration, both of fibres and of terminals, in layer V appears to be appreciably less after this lesion than after those, of this and previous groups, in which there was damage to the layers superficial to the stria; this difference is almost certainly not technical because the sections are very well impregnated.

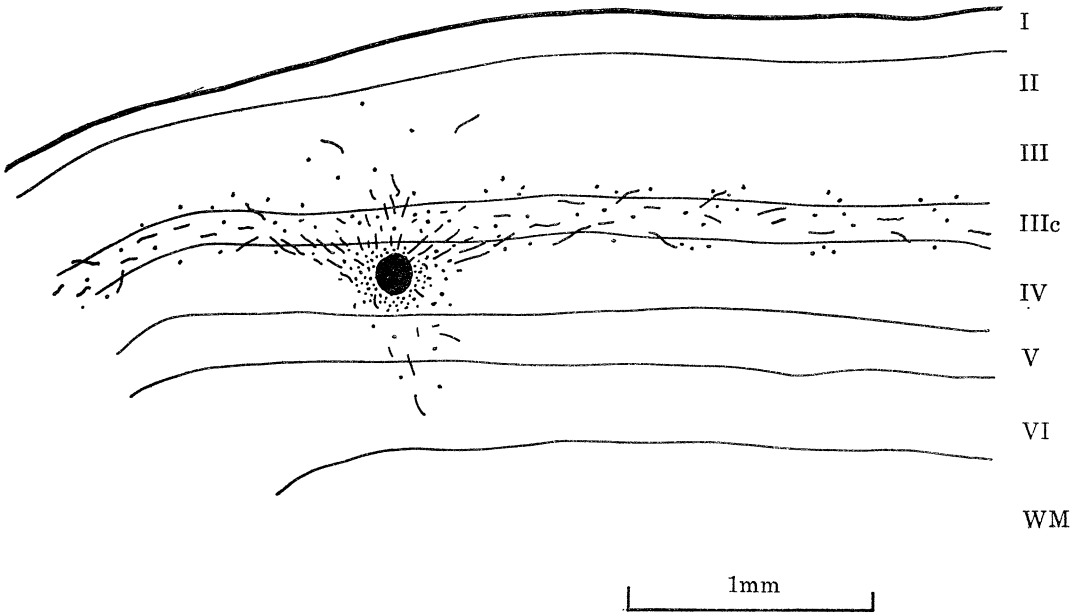

FIGURE 7. The small focal area of damage within lamina IV and the ensuing degeneration, mainly in the stria, in experiment 111R-9. In this experiment also there was very little degeneration in the more superficial layers due to the passage of the electrode. The terminal degeneration is aggregated in narrow bands away from the lesion on the right-hand side.

In experiment 110R-6 (figure 6; figure 18, plate 4) a small micoelectrode lesion is mainly within the stria of Gennari, but has encroached upon the superficial half of layer IV. Again there is no sign of an electrode track in the superficial layers, and only a little sparse degeneration is present superficial to the site of damage. The additional involvement of layer IV has not resulted in any significant difference in the pattern of degeneration as compared with a lesion restricted to the stria.

As far as can be judged, the degeneration resulting from a focal area of damage of comparable size, but confined within layer IV, is also similar in distribution (experiment 111R-9, figure 7; figure 20, plate 5). Immediately around the small focus of damage in the middle of layer IV in this experiment there is granular degeneration throughout the depth of layer IV, and, superficially, degenerating fragmented fibres can clearly be seen to enter the stria. The

oblique direction and divergence of these fibres on either side of the lesion as they pass into the stria of Gennari is quite obvious. Away from the neighbourhood of the lesion terminal degeneration is seen only in the superficial part of layer IV and in the part of layer IIIb adjoining the stria, and again this is mainly in narrow patches with clear areas in between. The only further points that need be emphasized about these experiments is the surprising intensity of fibre degeneration in the stria after such a small amount of damage (figure 24, plate 6) and that the spread of degeneration is of the same order as after larger lesions, partly, no doubt, because the sections were fortunately very well impregnated.

Group E

In the final group of ten experiments the lesions penetrate the cortex to the depth of layer V. Most of these lesions are in the form of narrow slits, some of which are at quite an oblique angle to the surface of the cortex. In the latter there are a number of degenerating, vertically disposed fibres in the layers superficial to the lesion; these probably represent the degeneration of afferent fibres and of axon collaterals of cells in the deeper layers. This increase in fibre degeneration is the only difference seen in layer III in these experiments as compared with the previous ones. The intensity and spread of the degeneration in the stria does not appear to be any different after involvement of layer V, but in layer IV there are somewhat coarser granules of terminal degeneration and of fragmented fibres; however, this degeneration does not extend for more than 100–200 μm on either side of the lesion. In layer V, however, the number of degenerating fibres in the inner band of Baillarger is greater than after lesions reaching down only as far as layer IV, but are still much fewer than those in the stria. The extent of spread of these fibres in layer V is essentially the same as that of fibres in the stria, but those in layer V are numerous only for about 1 mm from the lesion, at which there is a sharp reduction in density and the fibre degeneration is very sparse thereafter. There is also an undoubted increase in the number of degenerating, vertically disposed fibres passing through layer VI to enter the white matter. In these experiments there is less granular, terminal degeneration and far fewer obliquely arranged fibres, in both layers V and VI, than in the first group (Group A) in which the damage involved layer VI; consequently it has been possible to define more clearly the disposition and spread of the degenerating fibres in the inner band of Baillarger.

In one experiment (135-L, figure 8) a narrow slit lesion was made within a couple of millimetres of the lateral part of the lunate sulcus; the slit was 2–3 mm long, ran parallel to the sulcus and was close to the junction of the representations of the horizontal and vertical meridians. On the sections the lesion was found to be at the junction of areas 17 and 18 and extended slightly into the underlying white matter. The pattern and distribution of the degeneration in area 17 is similar to that found after the comparable lesions described earlier in group A, and the intensity of the degeneration within the stria and the inner band of Baillarger is particularly

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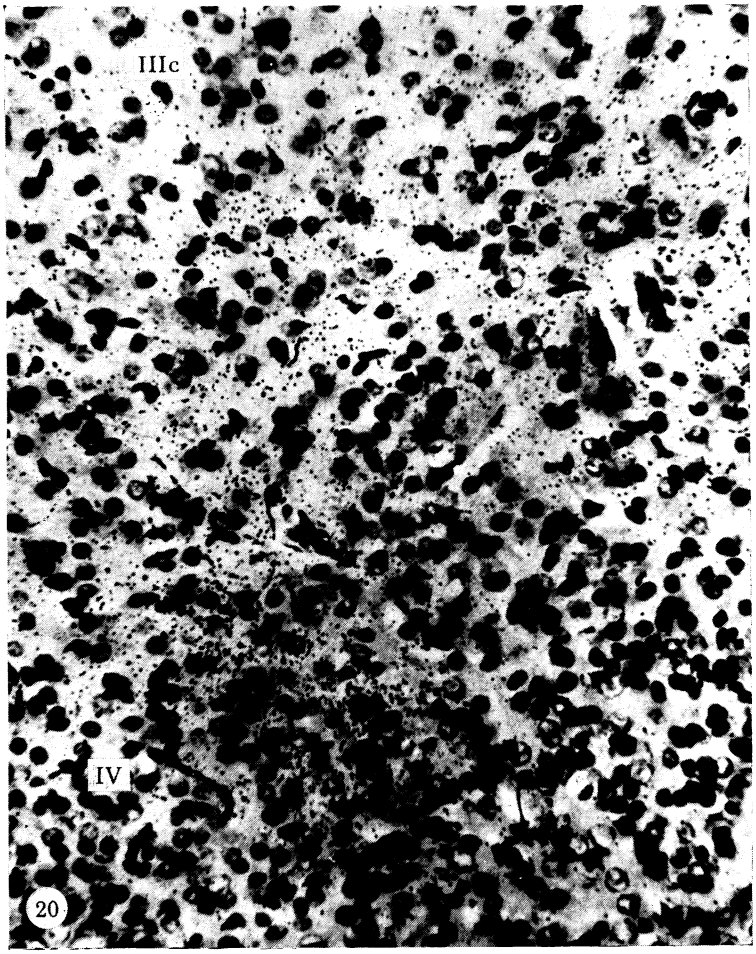
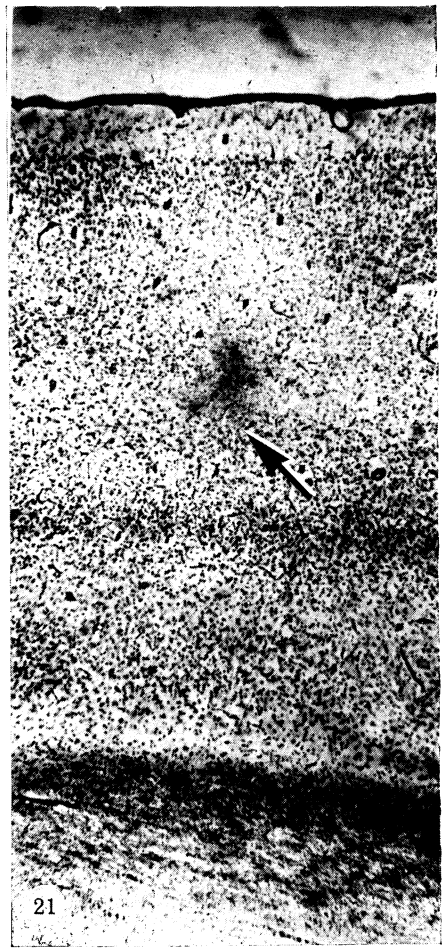
DESCRIPTION OF PLATE 5

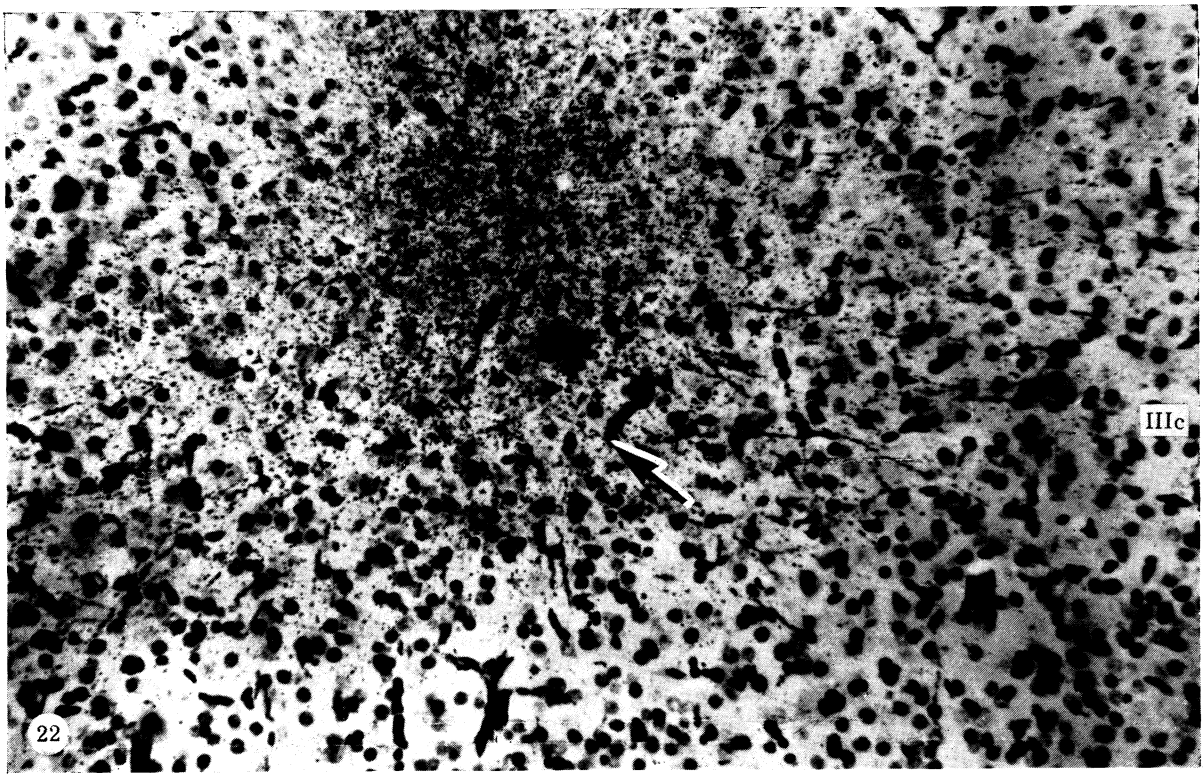
FIGURE 20. The lesion in layer IV in experiment 111R-9, shown by the focus of granularity in this layer. The degenerating fibres due to this lesion can be seen extending superficially into the stria in layer IIIc. (Magn. × 300.)

FIGURE 21. The small focal lesion in the deep part of layer IIIb and in IIIc in experiment 111L-4. (Magn. × 40.)

FIGURE 22. The deep aspect of the same lesion at higher magnification, and the degenerating fibres resulting from this can be seen extending horizontally into the stria (IIIc) on either side. (Magn. × 240.)







FIGURES 20–22. For description see opposite.

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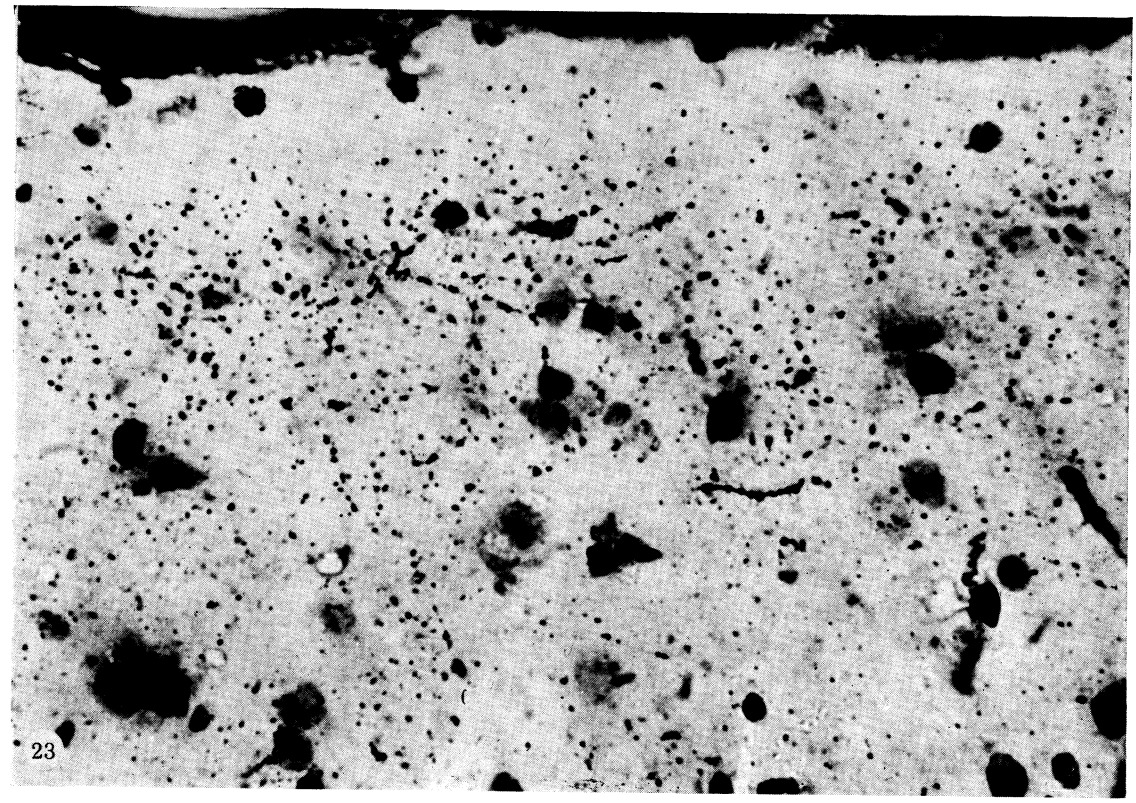
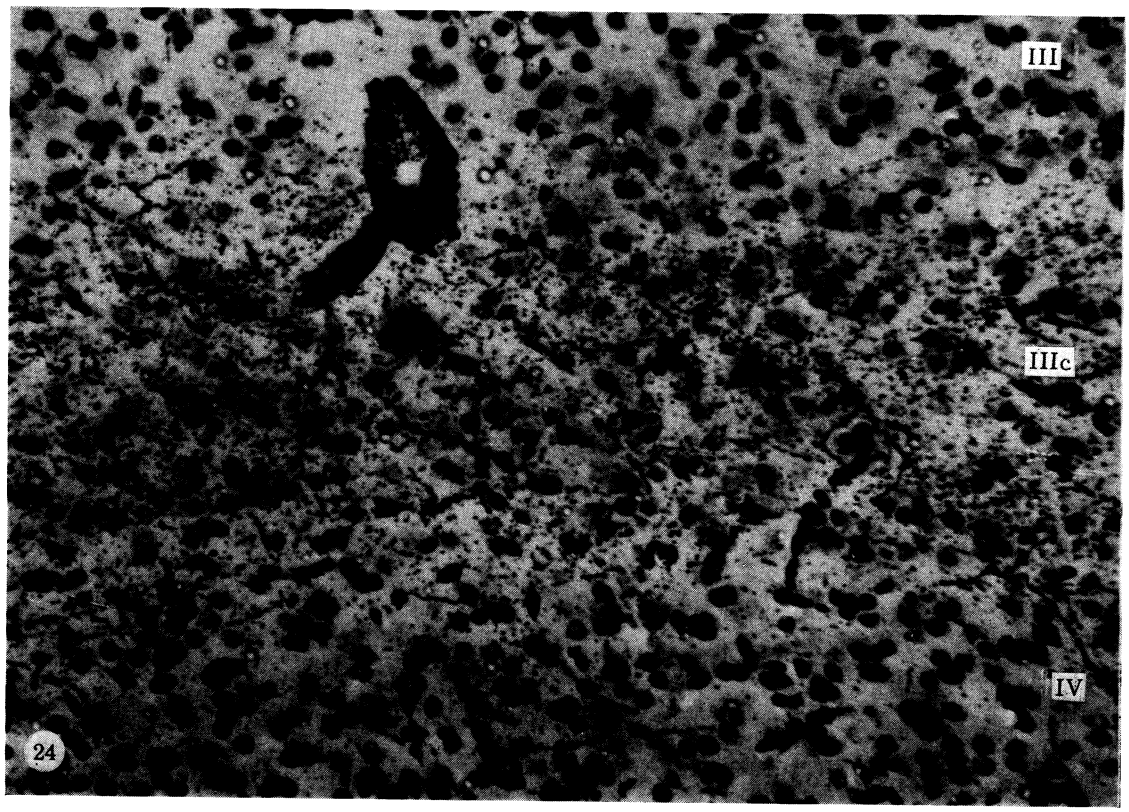




FIGURES 23 AND 24. For description see opposite.

severe in these well impregnated sections; consequently the relative absence of degeneration in layer IV beyond the immediate vicinity of the damage stands out prominently. On the opposite side of the lesion, in area 18, there is degeneration of approximately the same intensity throughout all layers of the cortex, with more fragmenting fibres in the deeper layers but with no appreciable concentration in the positions corresponding to the stria and inner band of Baillarger. The degeneration on this side of the lesion extends for a few millimetres into area 18, and is due partly to the interruption of afferent fibres in the underlying white matter. There is well stained degeneration in other portions of the peristriate cortex, but as this is not relevant to the present investigation, it will not be described in detail.

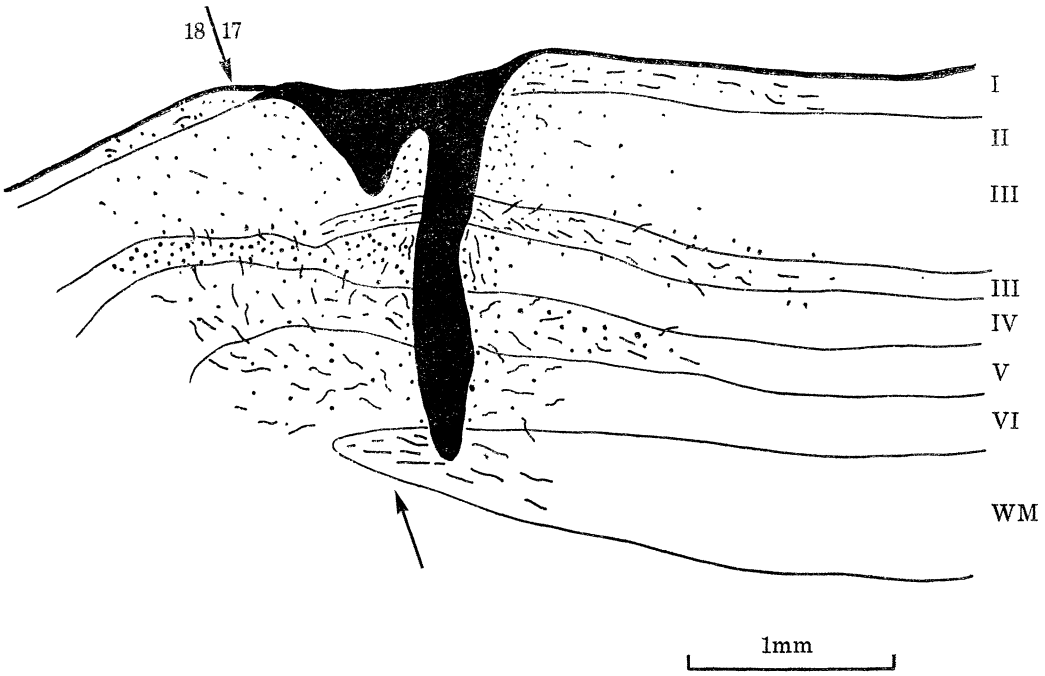


FIGURE 8. The lesion in the cortex of area 17, close to the boundary of areas 17 and 18, and the resulting fibre and terminal degeneration in experiment 135-L. Note the different pattern of degeneration in area 17 on the right-(in which lamina IV is almost devoid of degeneration beyond the immediate vicinity of the damage) as compared with that in area 18 on the left, in which there is the same intensity of degeneration throughout all layers of the cortex (partly due to interruption of afferent fibres in the underlying white matter).

Group F

Lesions in all of the groups which have been described so far have been in that part of area 17 which is on the exposed lateral surface of the hemisphere, and they therefore lie within the representation of the more central parts of the retina (Talbot & Marshall 1941; Daniel & Whitteridge 1961). In two experiments small lesions were placed in the cortex of area 17 on the anterior bank of the inferior ramus of the calcarine sulcus, which should be in the representation of

DESCRIPTION OF PLATE 6

FIGURE 23. Terminal and fibre degeneration in layer I of the cortex 1.5 mm away from the small superficial lesion of layers I and II, in experiment 114R-2. (Magn. × 700.)

FIGURE 24. The dense degeneration in the stria in layer IIIc, 0.5 mm away from the focal lesion in layer IV in experiment 111R-9. (Magn. × 320.)

part of the visual field 15–20° out from the macula (Daniel & Whitteridge 1961). The histological sections show that both lesions are within area 17, that one of them extends as far deeply as the stria and that the other passes through the entire thickness of the cortex to involve slightly the underlying white matter. The degeneration after each of these lesions is comparable to that found after lesions of similar depth in the part of area 17 involved in the previous groups. In the lesion in which white matter was involved there is severe terminal degeneration in layer IV, and close to the lesion, where this merges with that in the stria, the granules are seen to be coarser than those in the stria; this degeneration of thalamocortical fibres extends further towards area 18 than does the degeneration in the stria, and as a result its bilaminar distribution, in the deep part of layer IIIb and in layer IV, on either side of the clear stria, is quite distinct.

Electron microscopy of the intrinsic connections of area 17 of the monkey

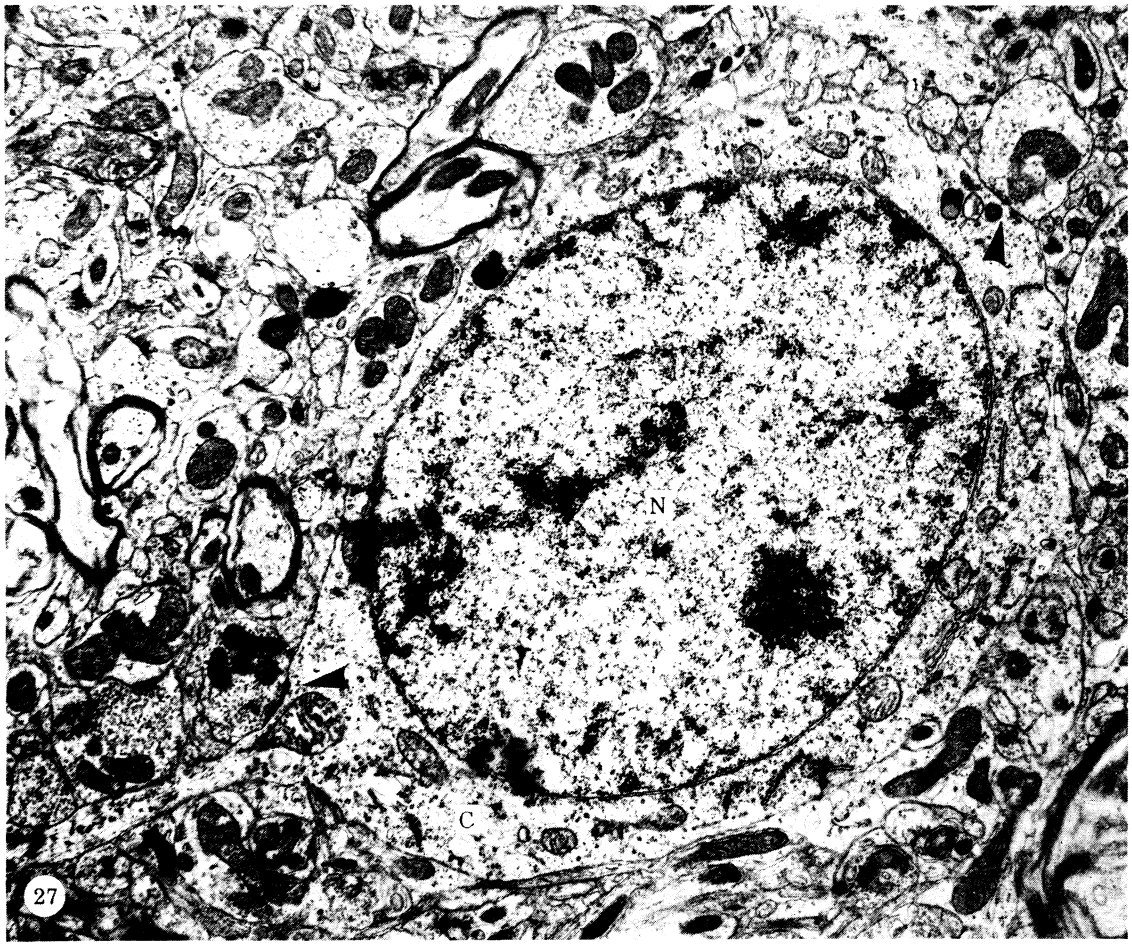
Before presenting the experimental results it may be useful to describe briefly the main ultrastructural features of the cortex of area 17 (a fuller account is given by Garey 1971). The two main neuron types, pyramidal and non-pyramidal, can readily be distinguished. The pyramidal cell, which typically possesses a large apical dendrite into which the cell soma tapers, has a rather light cytoplasm with few organelles, and its nucleus often has a single indentation. Rather few synapses are seen on the cell soma and proximal parts of the dendrites and such as are present are all of the symmetrical type (type II of Gray 1959), with flattened or pleomorphic vesicles. The non-pyramidal neurons may be divided into at least two types. The cell body of the first of these, the 'large stellate', can be recognized by the relatively large number of mitochondria and the considerable amounts of both rough and smooth endoplasmic reticulum. This density frequently makes the cell difficult to define at low magnification, as it merges readily into the surrounding neuropil. The other characteristic feature of such cells is that the cell soma and proximal dendrites receive a large number of synapses, some of which are of the asymmetrical type, with spherical vesicles (type I of Gray). The dendrites of such cells are frequently varicose or tortuous in outline and bear variable numbers of spines. The second type of nonpyramidal neurone has been described in the sensorimotor and visual cortex of the monkey (Sloper 1973*a*; Tömböl 1974), and has been called the 'small stellate'. The cell soma is round and 8–12 μm in diameter. The nucleus is dark, with dense clumps of chromatin, and is frequently indented; in the cytoplasm there is a small number of organelles, although the Golgi apparatus is often prominent (figures 27 and 28, plate 7; figure 29, plate 8). The soma receives few synapses, usually less than three in a single section, but these may be of either type. The dendrites of these cells are usually very varicose, often having an initial constriction,

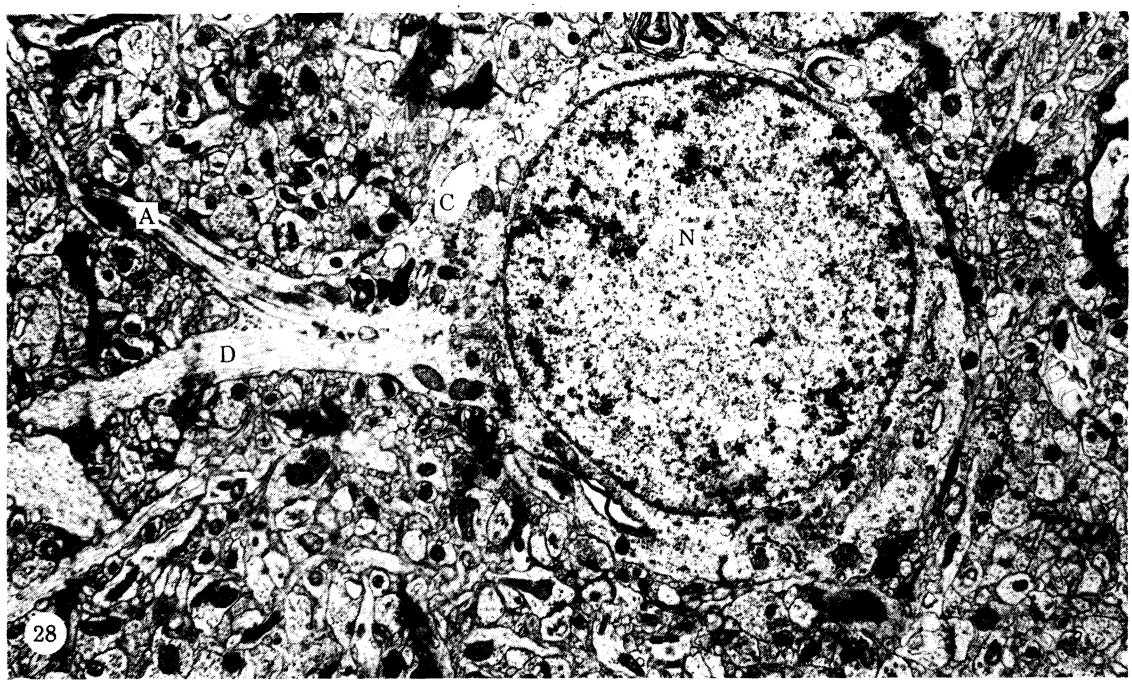
Description of plate 7

All of the micrographs are from area 17 of the visual cortex of the monkey and are of material taken within 2–3 mm of a lesion in the cortex.

Figure 27. A small stellate cell in layer III of area 17 of the visual cortex. The cell has a rather dark nucleus (N), with prominent chromatin clumps, while the cytoplasm (C) is sparse and pale. Synapses upon the cell (arrowheads) are few in number. The cell gives rise to a rather narrow dendrite. (Magn. × 8400.)

Figure 28. A small stellate cell in layer III of the visual cortex. The nucleus (N) shows chromatin clumps and the cytoplasm (C) is sparse with relatively few organelles. The cell gives rise to a dendrite (D) from the root of which the axon initial segment (A) can be seen arising. (Magn. × 6000.)





FIGURES 27 AND 28. For description see opposite.

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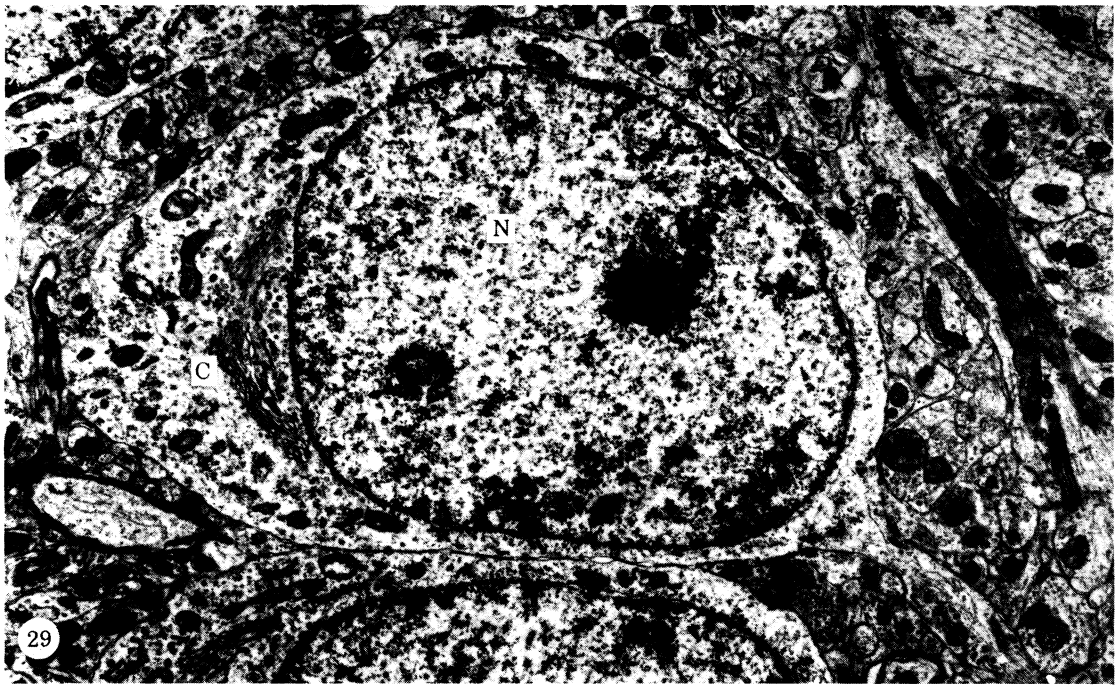

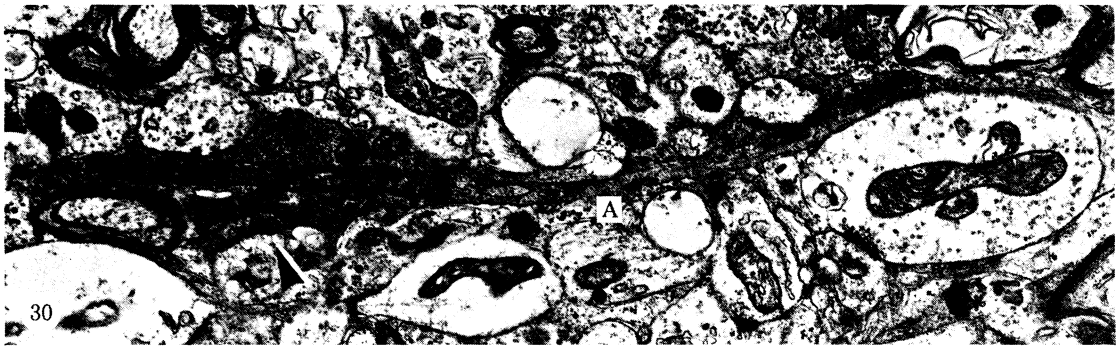

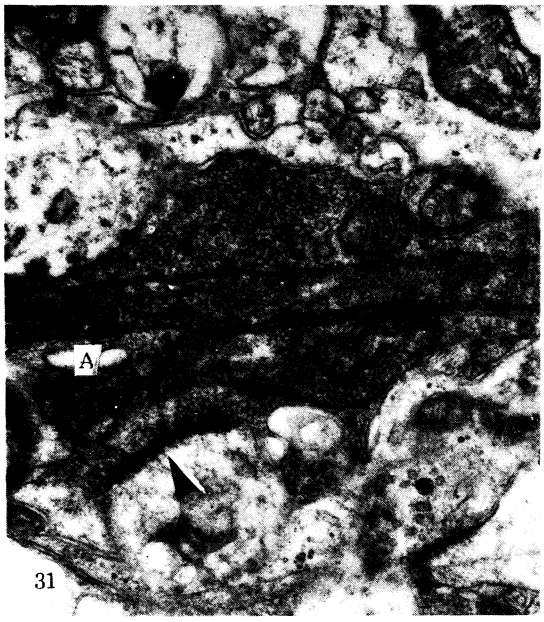

FIGURES 29–32. For description see opposite.

and they receive a moderate number of both types of synapses. An example of a stellate cell receiving a degenerating terminal after an intrinsic lesion is seen in figure 46, plate 11.

The neuropil of area 17 consists of dendrites, myelinated and non-myelinated axons, axon terminals and dendritic spines. Synapses are common, and almost all of them can be classified as being either asymmetrical (type I), in which the postsynaptic thickening is denser than the presynaptic and the synaptic vesicles appear round, and symmetrical (type II) in which the postsynaptic thickening is equal to or only very slightly thicker than the presynaptic and the vesicles appear flattened or pleomorphic. The synaptology of different parts of the neuron varies: a dendritic spine invariably receives one, and may receive two, asymmetrical synapses. In addition, some 10–20 % of spines receive a symmetrical terminal. Pyramidal cell dendrites probably receive a mixture of the two synaptic types; close to the cell soma, however, where their nature can more confidently be determined, they receive rather few synapses, almost all of which are symmetrical. Stellate cell dendrites, by contrast, receive a large number of synapses, up to half of which may be asymmetrical. Initial segments are characterized by the abrupt narrowing of the cytoplasm of the parent cell as they arise, by the presence underneath the membrane of a dark undercoating, and by the arrangement of the neurotubules in well defined bundles. Initial segments receive a few synapses and these are invariably of the symmetrical type.

Most of the results to be described were obtained from experiments in which lesions were placed throughout the whole depth of the cortex either in the form of a slit, made with a knife or a needle, or by allowing the current to run continuously during the downward and upward traverse of a microelectrode. Only material adjacent to lesions which involved most of the depth of the cortex but which did not penetrate the white matter was used for electron microscopic study, and these were selected after a careful examination of 'thick' sections of several blocks. This restriction was necessary for two main reasons: first, despite accurate measurements of the site of placement of small microelectrode lesions in relation to known landmarks, it proved more difficult than anticipated to determine their precise situation in order to include them in the small blocks necessary for electron microscopic study; and secondly, the density of degeneration even within a few millimetres of larger lesions proved to be surprisingly small. However, some results of the study of material in relation to partial lesions will be presented.

Blocks of approximately 0.5 mm thickness were cut in such a way as either to include the whole lesion and approximately 1 mm or so on each side (microelectrode lesions), or the edge of a lesion and 2–3 mm of the cortex on one side. Depending upon the orientation of the lesion, blocks were cut either in the sagittal or coronal plane, and, in agreement with the light microscopic observations, no obvious differences were found between sections from blocks cut

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Description of plate 8

Figure 29. A small stellate cell in layer IV. This cell is one of a group of similar cells. N, nucleus; C, cytoplasm. (Magn. × 10000.)

Figure 30. A degenerating intrinsic nerve axon (A) in the deep part of layer III, with a terminal *en passant* making an asymmetrical synapse (arrowhead). (Magn. × 9500.)

Figure 31. The terminal *en passant* of figure 30 and its asymmetrical synapse (arrowhead) at higher magnification. (Magn. × 23000.)

Figure 32. A degenerating large terminal in layer VI. The terminal appears to have three synaptic thickenings, two of which (the larger indicated by an arrowhead) make contact with a dendrite (D). (Magn. × 24000.)

in these different dimensions. In the 'thick' sections, the edge of the lesion was seen to be surrounded by a narrow zone, approximately 200 μm wide, which was densely stained and showed intense gliosis. Usually, this region was sharply demarcated from the rest of the section which appeared essentially normal; the neurons and their dendritic processes stained normally and were not separated by oedematous swelling. The pia mater was intact, which indicated that the aim at operation to minimize interference with blood supply by inserting the needle between blood vessels had been achieved.

In the thin sections used for electron microscopy these observations were confirmed. Except for the region of 200 μm immediately adjoining the lesion the tissue was remarkably well preserved; the overall appearance of the neuropil was no different from that of experimental material from brains in which lesions had been placed in a distant site, such as the lateral geniculate nucleus or, except for the degenerating terminals and glial reaction, from normal tissue. Within the 200 μm width immediately adjoining the edge of the lesion, however, the structure is different: the majority of profiles are enlarged and pale with widely dispersed organelles or are dark and shrunken. All parts of the neuron: soma, dendrites or axons and their terminals may show either of these two distinctly different appearances. In addition, there is a marked glial reaction with most of the processes being dark with large amounts of glycogen. In view of this severe degeneration of pre- and post-synaptic profiles no study of terminal degeneration has been made within this region, and all the results refer to the essentially normal tissue beyond it. In the latter, only a very occasional dark neuronal soma, dendrite or spine has been encountered, and the observation that most of these were found within the first millimetre strongly suggests that they represent parts of neurons directly damaged by the lesion.

All of the affected axon terminals showed the same type or process of degenerative change, in that, after the earliest sign of enlarged vesicles, they underwent a progressive darkening and shrinkage; no evidence of filamentous degeneration of any terminals at any survival period has been obtained. In order to determine whether there were any differences in pattern and density of degeneration with changes of survival period, comparable material was examined at 24 h intervals from 1 to 6 days. After 24 h there was early degeneration of relatively few terminals within 1 mm of the lesion, shown either by enlargement and irregularity of the synaptic vesicles, but without much change in the axoplasm, or by slight increase in density of the axoplasm, closer packing of the vesicles and slight shrinkage and irregularity of the outline of the terminal; glycogen granules may be present in terminals at these stages. Terminals showing the type of early degeneration described by Westrum (1973) and Bodian (1975) and characterized by pallor and a marked reduction in the number of vesicles were also present (see figure 43, plate 10, for a possible example). We were hesistant to consider such terminals as definite degeneration and did not include them in our quantitative data, because the changes are less marked than in the other dark stages of degeneration. In addition, in our material they could have been interpreted as being due to impaired fixation in the vicinity of the lesion; in the experiments of Westrum (1973) and Bodian (1975) this question did not arise because the lesion was at a distance from the site examined. Over the next few days there was a progressive increase in the number of terminals showing later stages of degeneration in the form of increasing degrees of shrinkage, disruption of vesicles and mitochondria and increased electron density. The final stages of the degenerative process were seen either as engulfment of the dense terminal and preterminal fibre by reactive glial processes, or as the presence of the remnant of the terminal as a dense sliver adjoining the postsynaptic membrane; occasionally, an exposed

postsynaptic thickening was seen with no evidence of a presynaptic structure remaining. At all intervals studied after the first 2 days, terminals at all stages of degeneration may be found, and even at 6 days an occasional terminal may be seen, usually a few millimetres from the lesion, showing the earliest signs of degeneration. The period at which there seemed to be the maximum number of terminals showing unequivocal signs of degeneration was 4 days; consequently, material from experiments with this survival period was used for the quantitative studies. Certain strict criteria were set for the acceptance or rejection of possible degenerating terminals seen with the electron microscope: first, only those dark profiles with synaptic membrane specializations polarized away from them have been accepted, for although axon terminals can be distinguished from dark dendrites by other means (in the early stages of degeneration by the presence of synaptic vesicles and in the later stages by the considerably greater electron density of the axon terminal), the appearance of the synaptic thickenings has been found to be the most reliable guide. Secondly, in regard to the classification of degenerating terminals into asymmetrical or symmetrical, only the characteristics of the membrane thickenings have been used, because the shape and size of the synaptic vesicles changes during degeneration. In the majority of cases it has been possible on this basis to classify terminals with a reasonable degree of confidence, but a certain proportion has been left unidentified.

Qualitative observations

Most of the degenerating terminals seen were undoubtedly of small size, but an occasional large terminal with asymmetrical membrane thickenings and several synaptic contacts (figure 32, plate 8) was observed. The majority of degenerating boutons appear to be true terminals, but examples of terminals *en passant* have been seen (figure 30, plate 8); however, these are not sufficiently numerous to permit conclusions to be drawn concerning their distribution within the cortex or in relation to particular types of cell. Axon terminals undergoing degeneration have been found to make synaptic contact with all the main parts of neurons: the soma, proximal and distal dendrites, spines and initial segments. Occasionally, within the first millimetre or so of the lesion, the postsynaptic profile, a small dendrite or spine, has been found to be dark and undergoing degeneration (figures 35 and 36, plate 9). Just as there was difficulty in some cases in the identification of the type of axon terminal according to its membrane thickening, so in respect of some of the smaller postsynaptic profiles there has been uncertainty about their identification as either small peripheral dendrites or spines.

The density of degeneration was greatest within the first millimetre or so of the lesion, but even here at the optimal survival period of 4 days the number of terminals which were degenerating formed a very small proportion of the total, and certainly not more than 5%. At a distance of 1 mm the density of degeneration showed a sudden and marked decrease, and beyond this level, up to the distance examined (3 mm), only an occasional degenerating bouton was found. Within the first millimetre the density was sufficient to permit valid comparisons between the laminae, and the most striking feature of this comparison is the virtual absence of degenerating terminals in lamina IV. In repeated surveys the only evidence of degeneration in this lamina was found in the first half millimetre from the lesion, and this finding agrees with the light microscopic observations. Laminae I and VI also showed relatively few affected axon terminals, whereas laminae II, III and V contained most of the degeneration. Within the areas of maximum degeneration there was some evidence of clustering of degenerating terminals (figure 45, plate 10), due in part to involvement of *en passant* and terminal boutons

of the same axon. Degeneration of myelinated fibres and non-myelinated preterminal axons was found in most layers of the cortex and was maximal close to the lesion. The myelinated fibres were mostly fine, varying in size from 0.5 to 1 μm, and in these sections, cut perpendicular to the surface, they are seen in transverse, longitudinal and oblique section.

Degeneration of asymmetrical terminals

In all the experimental material examined, either in general survey of sections or in the more systematic, quantitative studies, the vast majority of degenerating terminals had asymmetrical membrane thickenings and of these the majority were of small size. Although such terminals have been found to make contact with cell somata, dendrites and spines, the greatest proportion of postsynaptic profiles consisted of dendritic spines. Of the latter, all varieties of size and form were found to be related to terminals undergoing degeneration, but it may be significant that the largest proportion of the profiles of the spines were small and contained only an indistinct spine apparatus (figure 34, plate 9; figures 38–40). There were several examples of degenerating terminals making synaptic contact with two spines, which were either on opposite sides of the terminal (figure 37, plate 9; figure 45, plate 10) or immediately adjoined each other with their synaptic contacts on the same aspect of the terminal (figures 41 and 45, plate 10). Further examples of multiple synaptic contacts are those shown in figures 43 and 44, plate 10, where a degenerating terminal forms synapses upon two dendrites. A degenerating asymmetrical terminal may make contact with a spine upon which there is another normal terminal of either the asymmetrical (figure 42, plate 10) or symmetrical type, but there was no instance of a spine receiving two degenerating terminals. Degenerating preterminal axons with asymmetrical boutons *en passant* have been seen to end upon spines (figure 30, plate 8). The dark dendritic spines which have occasionally been seen may also receive a synapse from a degenerating axon terminal (figures 33, 35 and 36, plate 9). Degenerating asymmetrical axon terminals also make axodendritic synapses. The dendritic profiles may be of medium or small size, and those of medium size have always been found to have two or more other, normal, asymmetrical synapses close to the degenerating terminal, when the dendrite has been cut in either transverse or

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DESCRIPTION OF PLATE 9

FIGURE 33. Two spines (S) in layer III close to a lesion. One spine is dark and has an asymmetrical synaptic contact (arrowhead) with a degenerating axon terminal. (Magn. × 48000.)

FIGURE 34. A degenerating axon terminal in layer IV, making an asymmetrical synapse with a spine (S). Both processes are engulfed by the cytoplasm of a glial cell (G). (Magn. × 48000.)

FIGURE 35. A dark spine (S) close to a lesion; it has an asymmetrical contact with a degenerating nerve terminal (T) which is at a relatively early stage of degeneration. (Magn. × 48000.)

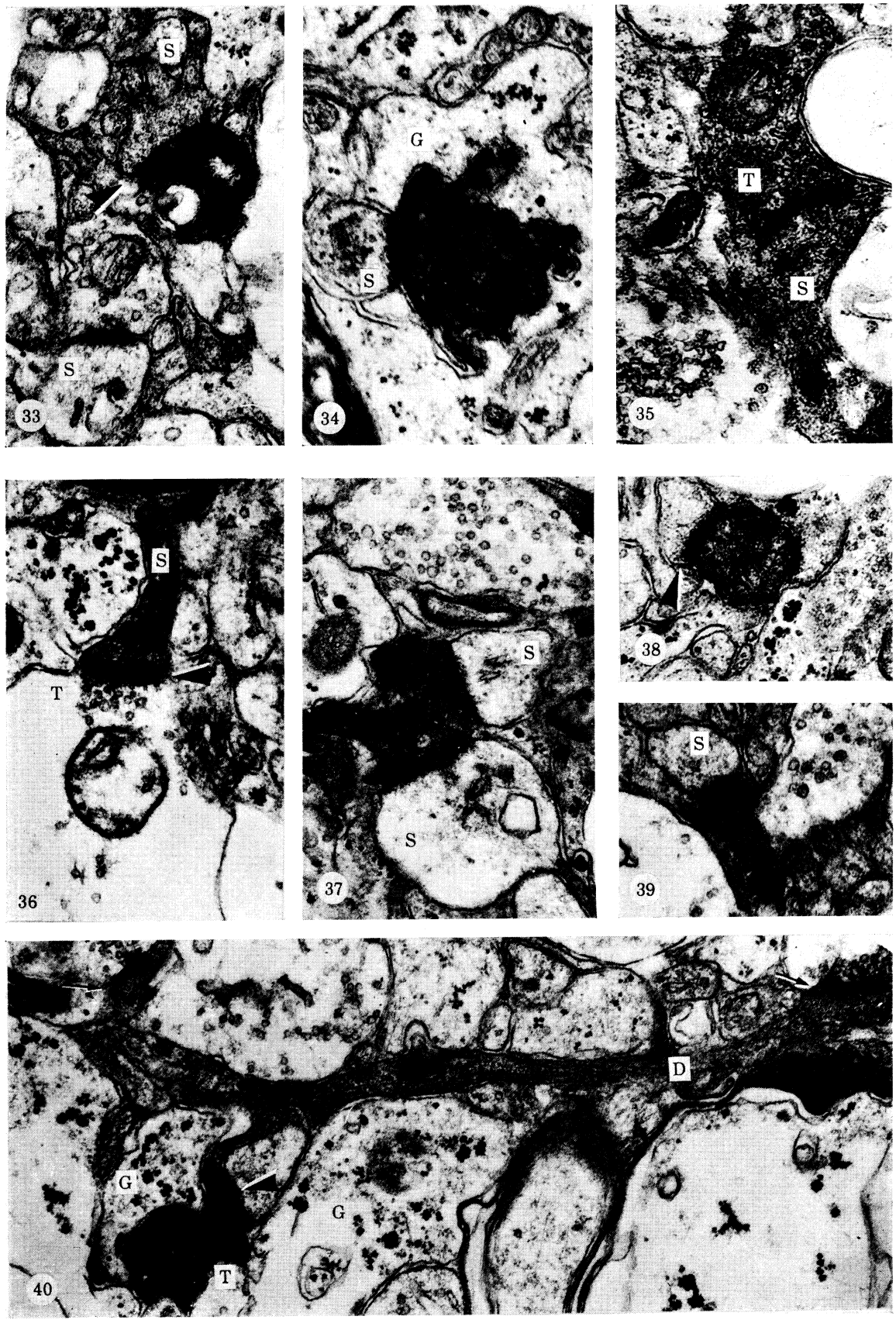
FIGURE 36. A dark spine (S) in which the spine apparatus can still be seen, making synaptic contact (arrowhead) with a disrupted nerve terminal (T) in layer III. (Magn. × 48000.)

FIGURE 37. A degenerating nerve terminal in layer III making asymmetrical contact with each of the two spines (S). (Magn. × 48000.)

FIGURE 38. A degenerating terminal in layer V making an asymmetrical synapse (arrowhead) with a small spine. (Magn. × 48000.)

FIGURE 39. A degenerating terminal in layer III making an asymmetrical synapse with a small spine (S). (Magn. × 48000.)

FIGURE 40. A small spine in layer III receiving an asymmetrical synapse (arrowhead) from a degenerating terminal (T), seen here at a late stage of degeneration and surrounded by glial processes (G). A dark dendrite (D) is seen nearby; this also receives an asymmetrical synapse (arrow). (Magn. × 42000.)



FIGURES 33–40. For description see opposite.

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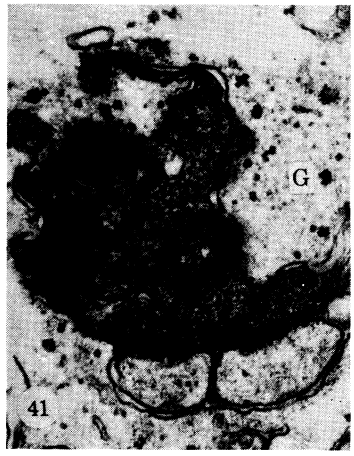

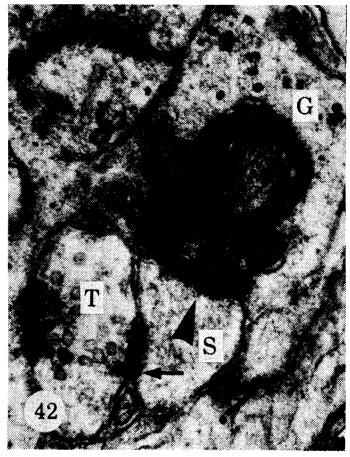

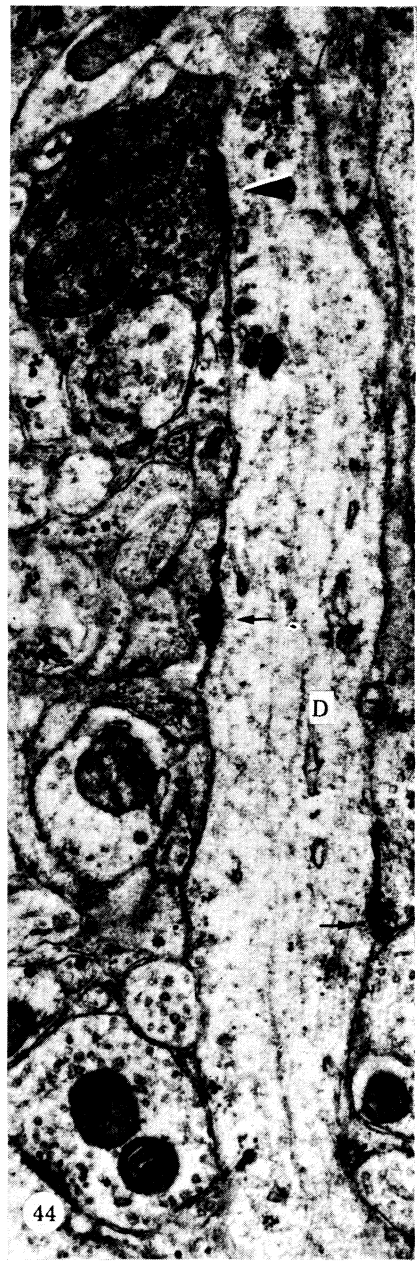

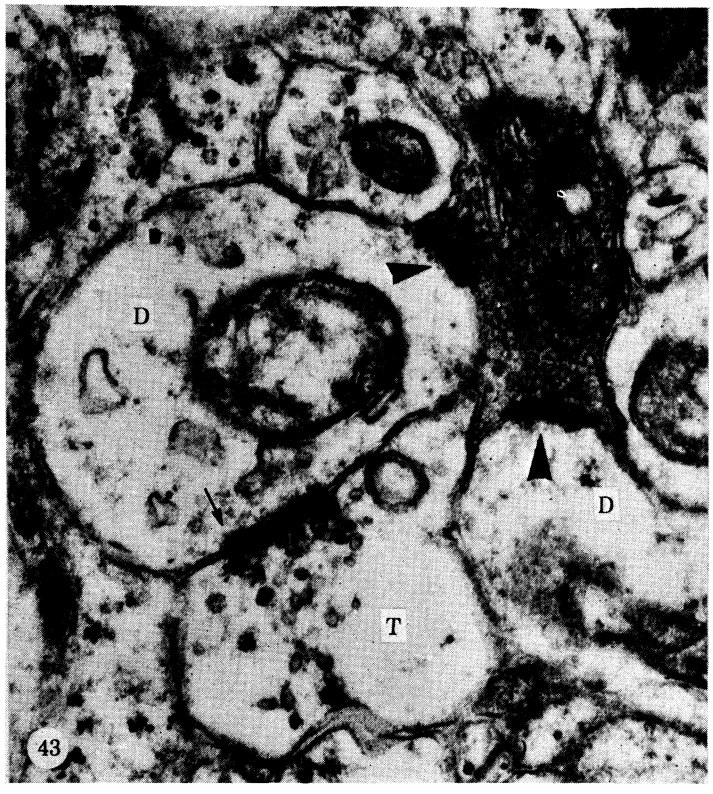

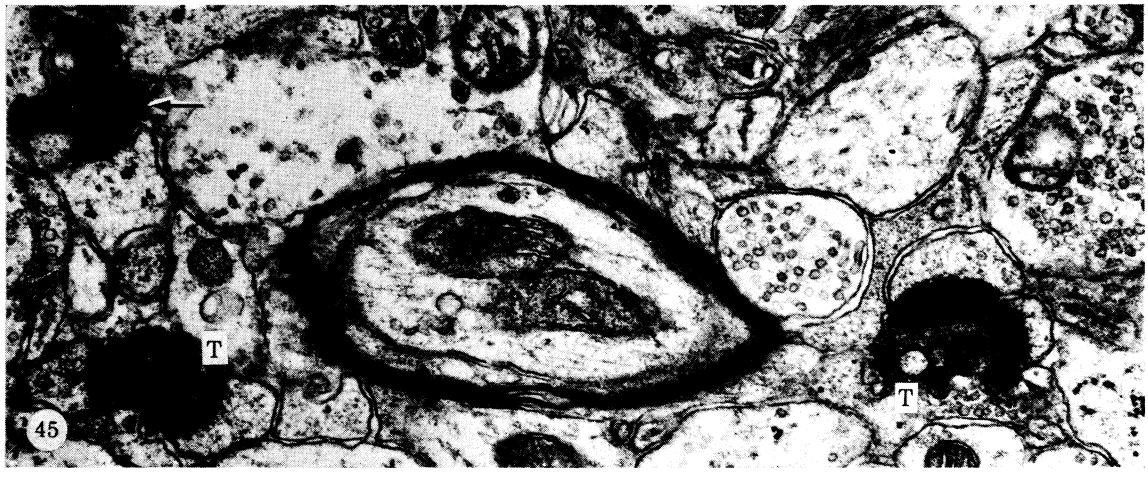

FIGURES 41–45. For description see opposite.

longitudinal section. These features of the dendrites strongly suggest that they originate from stellate cells. In one example (figure 48, plate 11) a stellate dendrite appears to receive two asymmetrical degenerating terminals. No degenerating terminals with asymmetrical membrane thickenings have been found to make synaptic contact with either a large or medium-sized dendrite which could be definitely identified as belonging to a pyramidal cell. Degenerating terminals of this type have, however, been found to form synapses on small dendritic profiles, but it is not possible to identify their cell of origin, and it is in relation to these dendrites and to small spines that there has been the greatest difficulty of identification. A few examples have been found of degenerating terminals making asymmetrical synaptic contact upon stellate cell somata upon which there are other, normal, asymmetrical axon terminals (figures 46 and 47, plate 11). No degenerating asymmetrical terminals were seen to form synapses on the somata of pyramidal cells.

Degeneration of symmetrical terminals

It is more difficult to be confident that an axon terminal has a symmetrical type of synapse than that it has an asymmetrical one, and for this reason degenerating terminals were only identified as having a symmetrical membrane thickening if the synaptic contact zone was cut perpendicularly and showed an absence of dense material adjacent to the postsynaptic membrane (cf. Gray 1959; Colonnier 1968). Although terminals which were identified as symmetrical formed only a small proportion of the total, they were found to form synapses upon all the constituent parts of a neuron, including the soma and initial axon segment; the great majority, however, were found to make contact with dendrites. Degenerating symmetrical terminals were found infrequently upon dendritic spines; in single sections they were either the only synapse upon the spine or were associated with another normal terminal making an asymmetrical synapse (figure 49, plate 12); no examples were found of a degenerating symmetrical terminal making synaptic contact with two spines or with a spine upon which there was a degenerating asymmetrical terminal.

Degenerating symmetrical terminals were found to make axodendritic synapses with both pyramidal and non-pyramidal-type dendrites, including, in contrast to the degenerating asymmetrical terminals, large proximal portions of pyramidal dendrites, identified by their

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Description of plate 10

Figure 41. A degenerating terminal in layer III, with asymmetrical synapses on to two adjacent small spines. The terminal is partly engulfed by a glial process (G). (Magn. × 48000.)

Figure 42. A degenerating terminal in layer III making asymmetrical contact (arrowhead) with a small spine (S) which also receives an asymmetrical contact (arrow) from a normal terminal (T). The degenerating terminal is again partly surrounded by glia (G). (Magn. × 48000.)

Figure 43. An axon terminal at a relatively early stage of degeneration, making asymmetrical contact (arrowheads) with two dendrites (D), one of which receives a further asymmetrical synapse (arrow) from another axon terminal (T). The latter may also be at an early stage of degeneration, as described by Westrum (1973). (Magn. × 55000.)

Figure 44. A degenerating axon terminal, at a rather early stage of degeneration, making asymmetrical contact with two structures in layer V, one of which (arrowhead) is a long straight dendrite (D), which also receives two normal synapses (arrows). The other postsynaptic profile is probably a small dendrite. (Magn. × 26000.)

Figure 45. Two degenerating terminals (T) close to each other in layer III. Each terminal makes asymmetrical synaptic contacts with dendritic spines. A degenerating pre-terminal fragment (arrow) is seen nearby. (Magn. × 35000.)

straight outlines and few synapses (see figures 53 and 54, plate 13; other examples of large dendrites receiving degenerating symmetrical terminals are shown in figure 58, plate 14 and figure 62, plate 16). Of the medium-sized dendrites, some were also pyramidal, while others were identified as being of stellate origin by the presence of other asymmetrical synapses (up to three) in close proximity to the degenerating terminal; one of the latter dendrites, within 1 mm of the lesion, was dark (figure 52, plate 12). Many examples were seen of one degenerating terminal making symmetrical synaptic contacts with two dendritic profiles of large or medium size (figure 57, plate 14), and in several cases at least one dendrite could be identified as that of a pyramidal cell. Degenerating terminals were also found making symmetrical synapses upon small dendrites (figure 50, plate 12) and the site of the synapse was often close to the origin of a spine, and sometimes immediately opposite (figure 51, plate 12). In one instance a degenerating terminal with symmetrical membrane thickenings was found upon a basal dendrite close to the cell soma in layer V, which has been tentatively identified as a Meynert cell (figure 59, plate 15) because of its large size and the appearance of the nucleus and cytoplasm. This type of degenerating terminal also makes axosomatic synapses, and in the five examples found the cells concerned have been pyramidal in two cases (figure 60, plate 16), of the large stellate type in two cases and the small stellate type in the remaining case (figure 56, plate 13).

In one experiment a degenerating terminal was found, at 250 μm from the lesion, to form a synapse upon the axon initial segment of a pyramidal cell in layer II (figures 63–65, plate 17). This terminal and initial segment were studied in twelve serial sections and other normal symmetrical endings were found making synaptic contact with the initial segment, but the degenerating terminal did not form a synapse with any other profile.

Degenerating fine non-myelinated fibres have been seen making symmetrical boutons *en passant*, and in the example shown in figure 55, plate 13, one axodendritic and one axospinous contact can be distinguished.

Quantitative comparisons

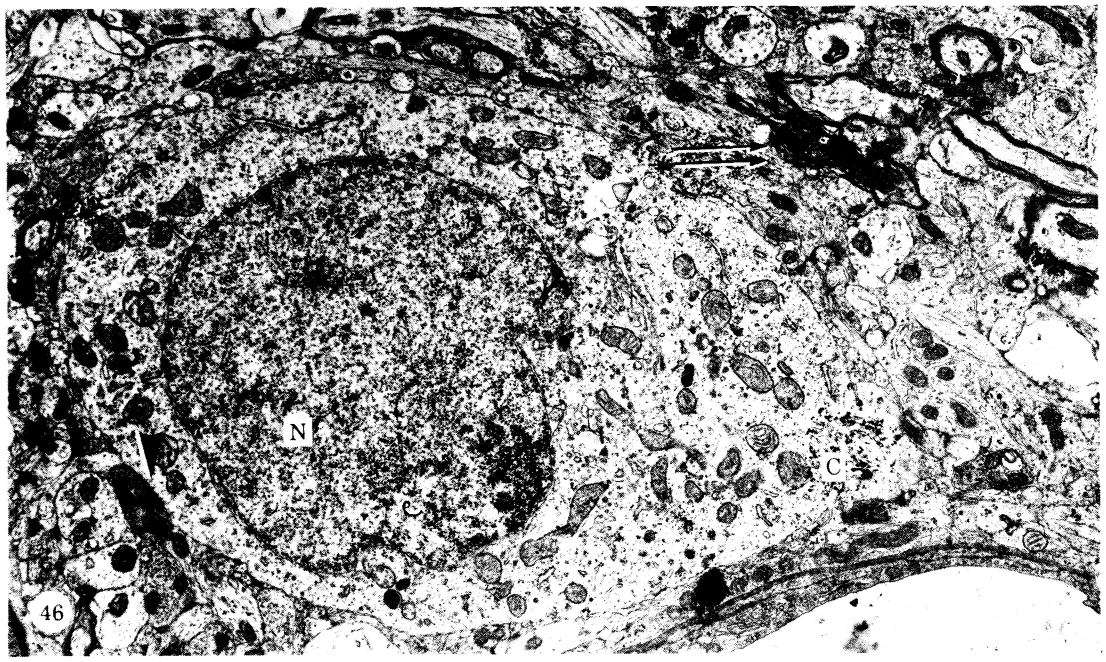
In addition to the examination of numerous sections, taken from several blocks at different survival periods, for the qualitative study of the type of axon terminal and postsynaptic structure and for a survey of the density of degeneration, more detailed information was obtained in two ways: first, the whole depth of the cortex was examined, in either one or two perpendicular sections, at precisely known distances from the lesion, as measured from the thick sections; secondly, three maps were made of the whole depth of the cortex, from the edge of the lesion to a distance of 3 mm away. The region to be surveyed was mapped as several areas, each about 1.5 mm by 0.75 mm, arranged so that there were no appreciable gaps between areas.

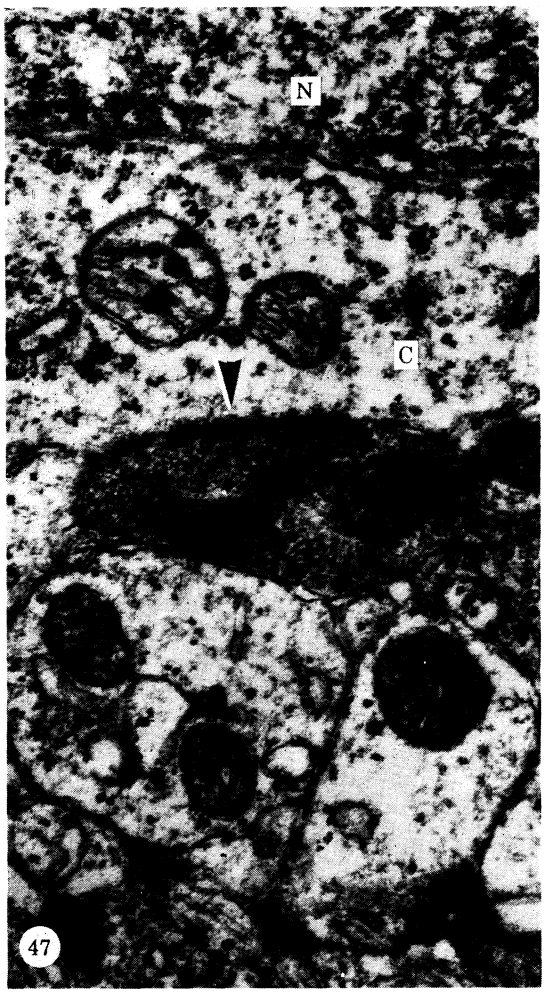
Description of plate 11

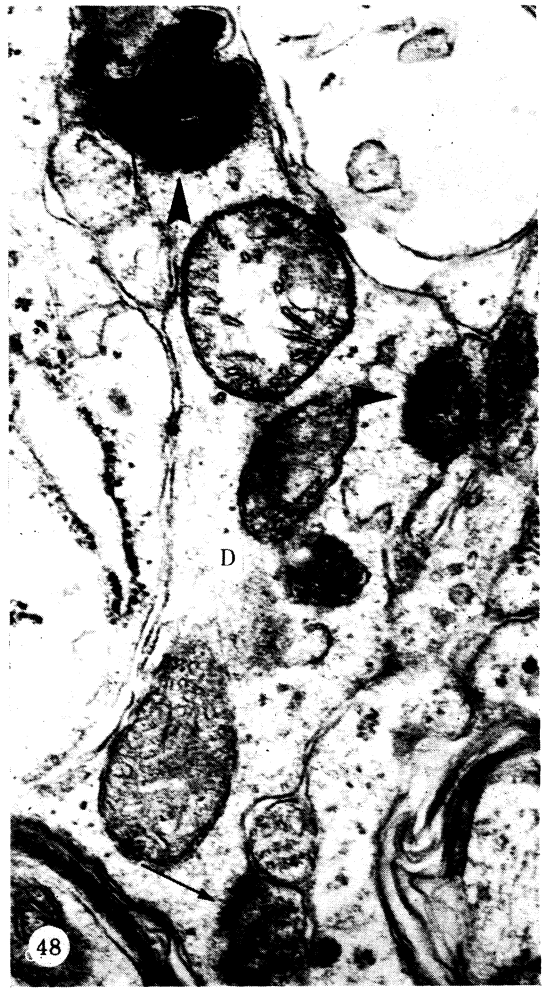
Figure 46. A stellate cell at the junction of layers II and III of the cortex, upon which a degenerating axon terminal is seen making an asymmetrical contact (arrowhead). A degenerating myelinated axon (paired arrows) is seen nearby. (Magn. × 10000.)

Figure 47. The degenerating axon terminal (arrowhead) of the previous figure, with an asymmetrical synapse, at higher magnification. (Magn. × 46000.)

Figure 48. A dendrite (D) in layer III on to which two degenerating axon terminals make asymmetrical synapses (arrowheads). A further synaptic contact is present on the dendrite (arrow). (Magn. × 44000.)







FIGURES 46–48. For description see opposite.

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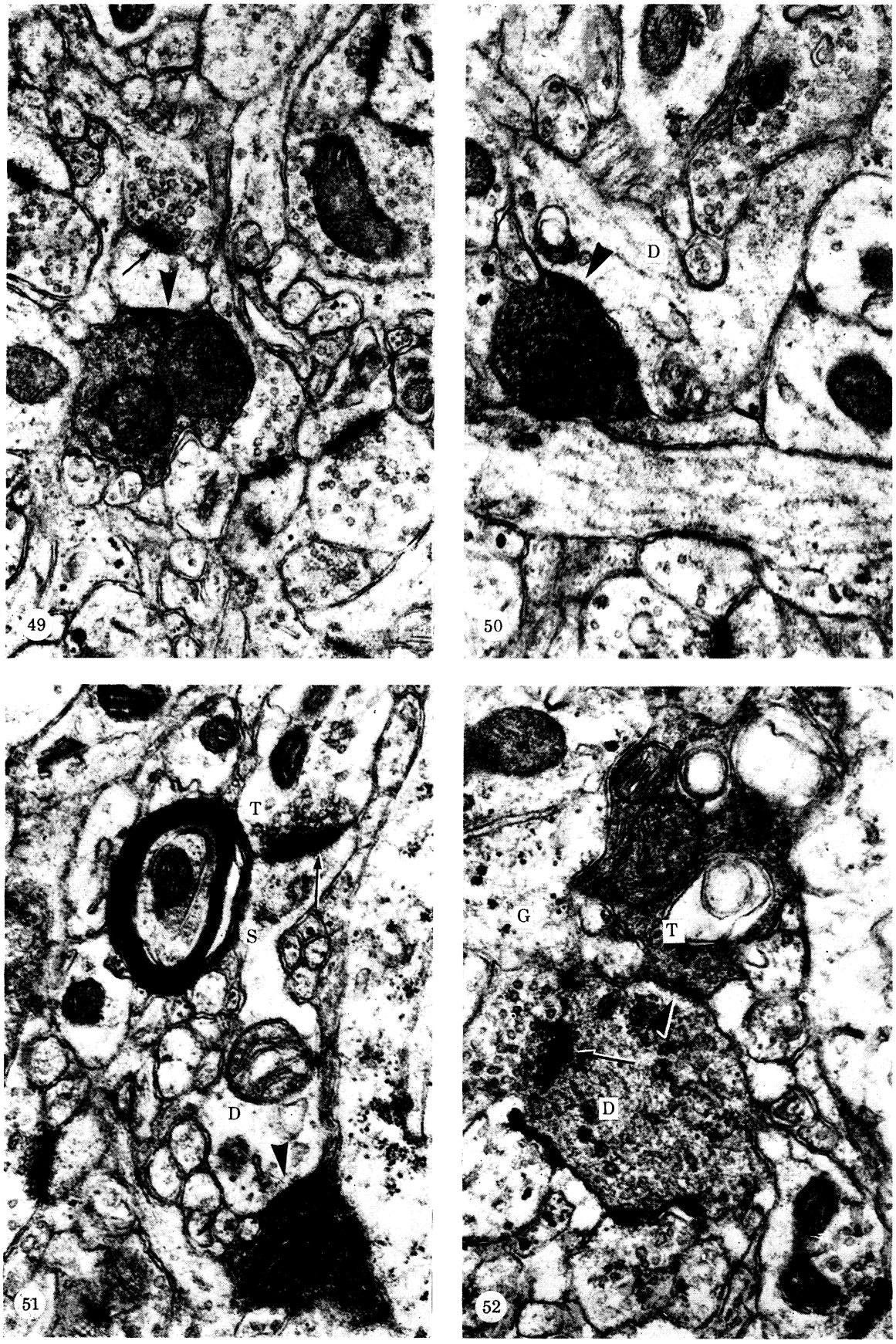

FIGURES 49–52. For description see opposite.

The block of tissue was trimmed to each area in succession and at each stage the size of the area and its position relative to the whole block face were recorded. When each area had been studied with the electron microscope, it was mapped out on graph paper and the individual maps were fitted together to form a representation of the whole region occupied by the block. The distance of 3 mm was chosen for the systematic mapping because the light microscopic study showed that little spread occurred beyond this distance and that it was essentially restricted to layer IIIc, and also because electron microscopic study of thin sections beyond this distance showed only an occasional degenerating terminal or fibre. The depth of a degenerating terminal was correlated with the cortical laminae on the basis of the electron microscopic features of the individual laminae, together with a careful comparison of the micrometer measurements made during the study of the thin sections with measurements of the 'thick' sections of the same block. While most of the laminae have features which allow them to be identified with reasonable confidence, and some have margins which are reasonably sharp, others merge insensibly into each other.

Figure 25 is one of the three systematic maps made of the full depth of the cortex for a distance of 3 mm from the lesion; there are only slight differences between it and the other two maps made in a similar way. It is also representative of the findings made both in the qualitative surveys and in individual sections at known distances from the lesion. It can be seen clearly that the greatest density of degeneration in all layers is within the first 1 mm or so; it then suddenly diminishes in amount and there is a more gradual decrease for the remainder of the distance. The histogram of the number of degenerating terminals at 0.5 mm intervals (figure 26), taken from the data of all three maps, also shows clearly the sharp fall-off at about 1 mm, and suggests further points about the distribution of degenerating symmetrical terminals; though few in number, these terminals show an appreciably more gradual diminution with distance than the asymmetrical terminals, so that they form an increasing proportion of the total at positions progressively further from the lesion; these combined data also indicate that axons with these two types of terminal extend overall for the same distance from the lesion. Table 1 gives the proportions of asymmetrical and symmetrical terminals at different distances from the lesion, as recorded in these mapping studies.

Within the first millimetre the distribution of the degeneration is more or less uniform throughout the depth of the cortex, with the notable exception that there are very few degenerating terminals in layers I and IV. Beyond this distance there is little discernible difference between the different laminae, except that, possibly, layers IIIa and b show a relatively greater diminution in density than the other layers. Both types of axon terminal have been seen in all

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Description of plate 12

Figure 49. A degenerating terminal in layer III making a symmetrical synaptic contact (arrowhead) upon a small spine, which also receives a normal, asymmetrical terminal (arrow). (Magn. × 42000.)

Figure 50. A degenerating terminal in layer IV making a symmetrical synapse (arrowhead) with a small dendrite (D). (Magn. × 42000.)

Figure 51. A degenerating terminal in layer V making a symmetrical synapse (arrowhead) upon a dendrite (D). This synapse is opposite to the origin of a spine (S), which can be seen receiving an asymmetrical synapse (arrow) from a terminal (T). (Magn. × 42000.)

Figure 52. A dark dendrite (D) in layer IV close to the lesion receiving a symmetrical synapse (arrowhead) from a degenerating axon terminal (T); the dendrite also receives a synapse (arrow) from a normal terminal. Glial processes (G) were common in this area. (Magn. × 42000.)

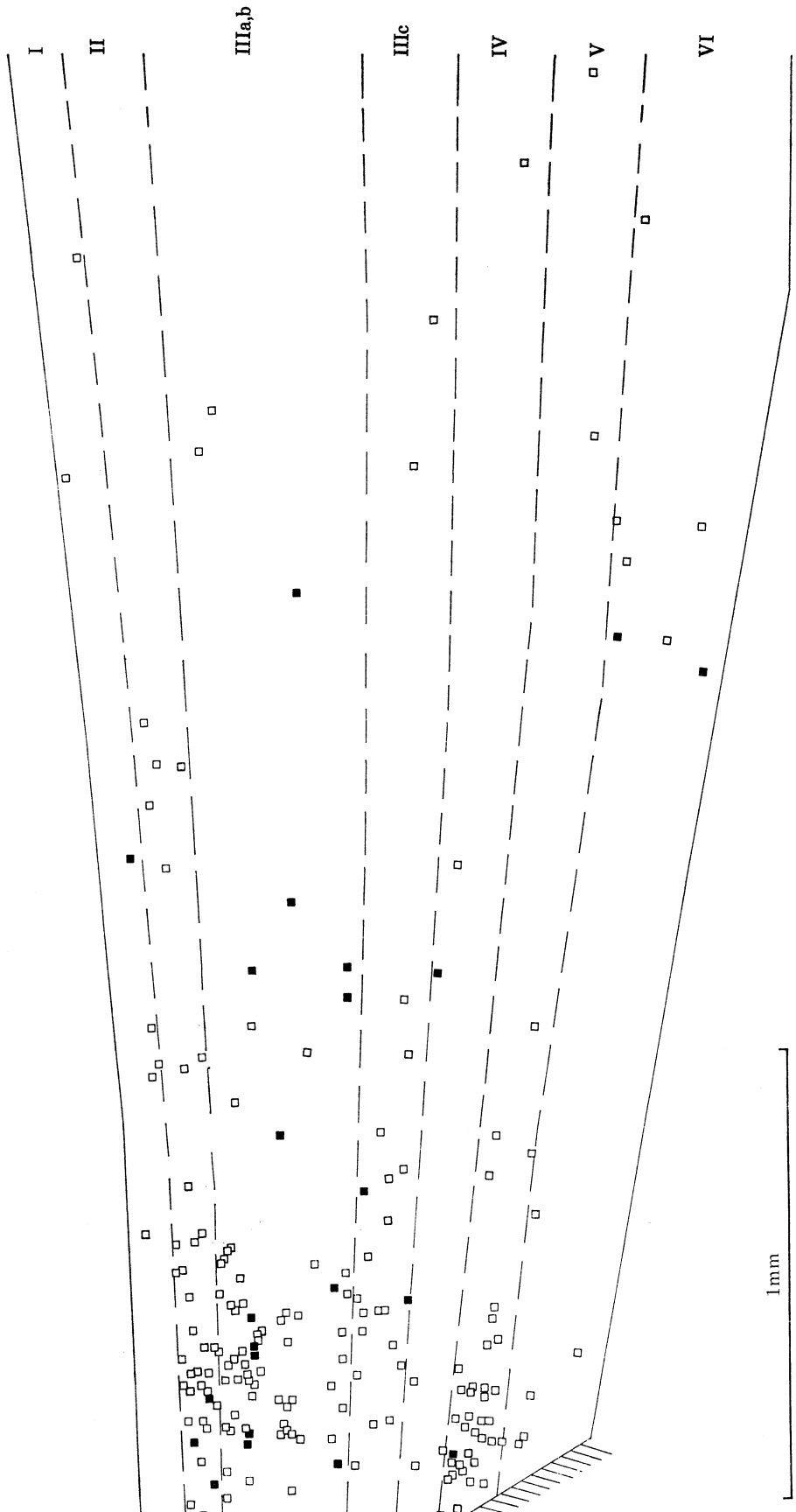


FIGURE 25. An example of a systematic map of vertical sections of the whole depth of the cortex, showing the distribution of degenerating terminals in the different laminae at different distances from the lesion (indicated by the hatching at the left-hand edge of the figure). □, asymmetrical terminals; ■, symmetrical terminals. Laminae of the cortex are indicated by Roman numerals.

laminae, and this is confirmed by the combined data from all of the quantitative studies, which will be discussed in more detail below. Even with the qualification that the extent of the tissue studied was determined by information obtained in the concurrent light microscopy studies, it is striking how well the findings made with the light and electron microscopic techniques agree; in particular the virtual absence of terminal degeneration in layer IV beyond the first few hundred micrometres may be noted.

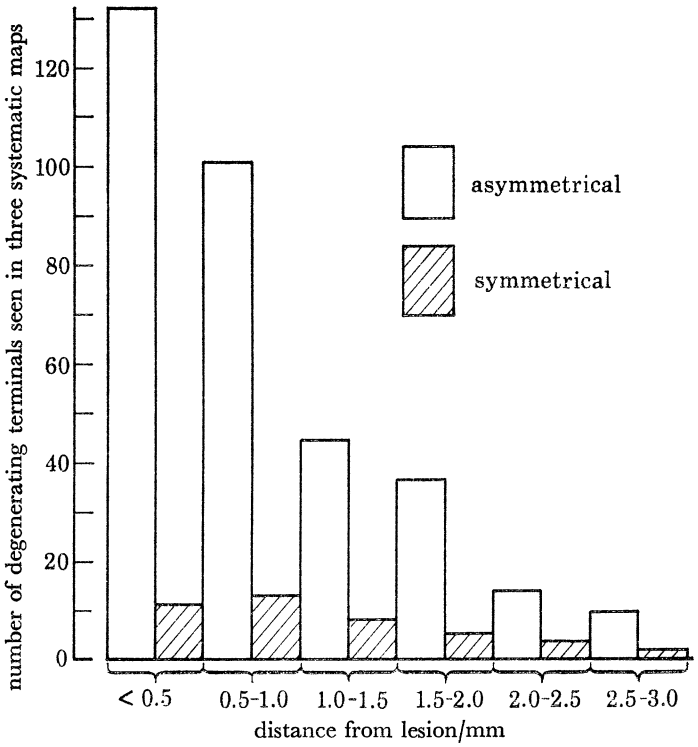


FIGURE 26. A histogram showing the total numbers of degenerating terminals seen in three systematic mapping studies of the cortex alongside a small lesion. White columns represent asymmetrical terminals and shaded columns represent symmetrical ones. Each column represents the total number of degenerating terminals, of the appropriate type, which were found in a 0.5 mm wide area of cortex at a known distance from the lesion.

TABLE 1. THE TOTAL NUMBERS OF ASYMMETRICAL AND SYMMETRICAL DEGENERATING TERMINALS AT DIFFERENT DISTANCES FROM THE LESION

(This information was obtained from three systematic maps of the cortex and is represented on the histogram of figure 26. Each figure in the percentage columns gives the proportion of the total number of terminals of a certain type which was present at a given distance from the lesion.)

distance from lesion/mm	no. (%) of asymmetrical terminals	no. (%) of symmetrical terminals
< 0.5	132 (38.9%)	11 (26.2%)
0.5–1.0	101 (29.8%)	13 (31.0%)
1.0–1.5	45 (13.3%)	8 (19.1%)
1.5–2.0	37 (10.9%)	5 (11.9%)
2.0–2.5	14 (4.1%)	3 (7.1%)
2.5–3.0	10 (3.0%)	2 (4.7%)
total	339 (100.0%)	42 (100.0%)

Table 2 includes all of the degenerating terminals found in the three mapping studies *and* in those sections taken at known distances from the lesion. This shows, first, that degenerating terminals with asymmetrical membrane thickenings form over 90 % (91.4 %) of the total, and secondly that the density of degenerating terminals is greatest in layers III a + b and V. In these layers the proportions of asymmetrical and symmetrical terminals are approximately the same as the proportions overall, whereas in layers I and II the proportion of symmetrical terminals is rather low (5.6 % and 2.7 % respectively), while in layer VI it is high (18 %). However, because of the known difficulty of drawing precise boundaries between adjoining laminae, and also because of the relatively high proportion of terminals about which it was difficult to be certain of the type of synaptic membrane thickening, too much emphasis should not be placed upon slight differences in proportions in the different laminae. It is generally agreed that in thin sections it is difficult to distinguish between layers V and VI, and it would probably be more reasonable to pool the results for these two layers, when the symmetrical terminal would form 14 % of the total. Despite this qualification, the relative number of symmetrical terminals in layers I and II does appear to be low, and this is in accord with the proportions of these types of terminal in normal material.

TABLE 2. A TOTAL OF 769 DEGENERATING TERMINALS FOUND IN QUANTITATIVE STUDIES (THREE MAPS AND SECTIONS AT KNOWN DISTANCES FROM LESION) CLASSIFIED ACCORDING TO NATURE OF POSTSYNAPTIC THICKENING

lamina	no. (%) of terminals with asymmetrical thickening	no. (%) of terminals with symmetrical thickening	no. of terminals with unidentifiable thickening
total	574 (91.4 %)	54 (8.6 %)	141
I	17 (94.4 %)	1 (5.6 %)	4
II	74 (97.3 %)	2 (2.7 %)	6
IIIa + b	226 (91.9 %)	20 (8.1 %)	64
IIIc	59 (92.2 %)	5 (7.8 %)	22
IV	45 (90 %)	5 (10 %)	9
V	117 (90 %)	13 (10 %)	27
VI	36 (82 %)	8 (18 %)	9

An analysis of the postsynaptic profiles which are related to the degenerating terminals (table 3) shows that two-thirds make contact with dendritic spines, approximately one-third with dendrites and less than 1 % with cell somata and initial segments. Of the identified degenerating terminals upon dendritic spines, 98 % (table 4) were asymmetrical, while of those upon dendrites, 75 % were asymmetrical.

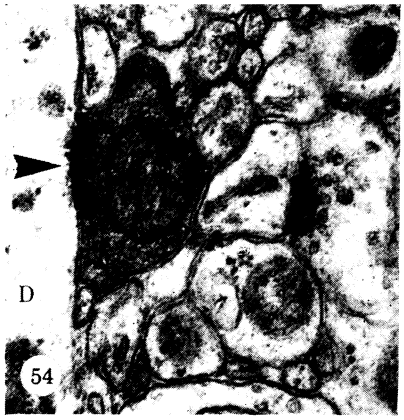
DESCRIPTION OF PLATE 13

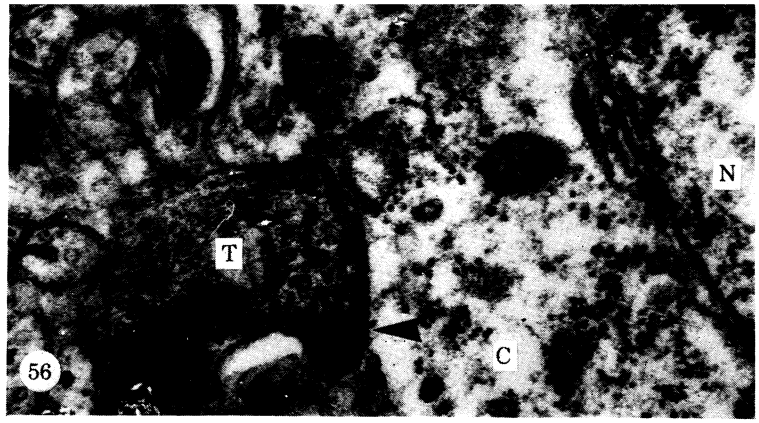
FIGURE 53. A large dendrite (D) in layer III receiving a symmetrical synapse (arrowhead) from a degenerating axon terminal. The dendrite is considered to be of a pyramidal cell because of its size, regular outline and the few synapses upon its surface. (Magn. × 35000.)

FIGURE 54. The degenerating terminal in figure 53 at a higher magnification. (Magn. × 48000.)

FIGURE 55. A degenerating axon in layer III making multiple symmetrical contacts (arrowheads), including one upon a dendritic spine (S) and one upon a large dendritic (D). (Magn. × 28000.)

FIGURE 56. A degenerating terminal (T) making a symmetrical synapse upon a cell soma (C) in layer III which is probably of the small stellate type. N, nucleus. (Magn. × 55000.)





FIGURES 53–56. For description see opposite.

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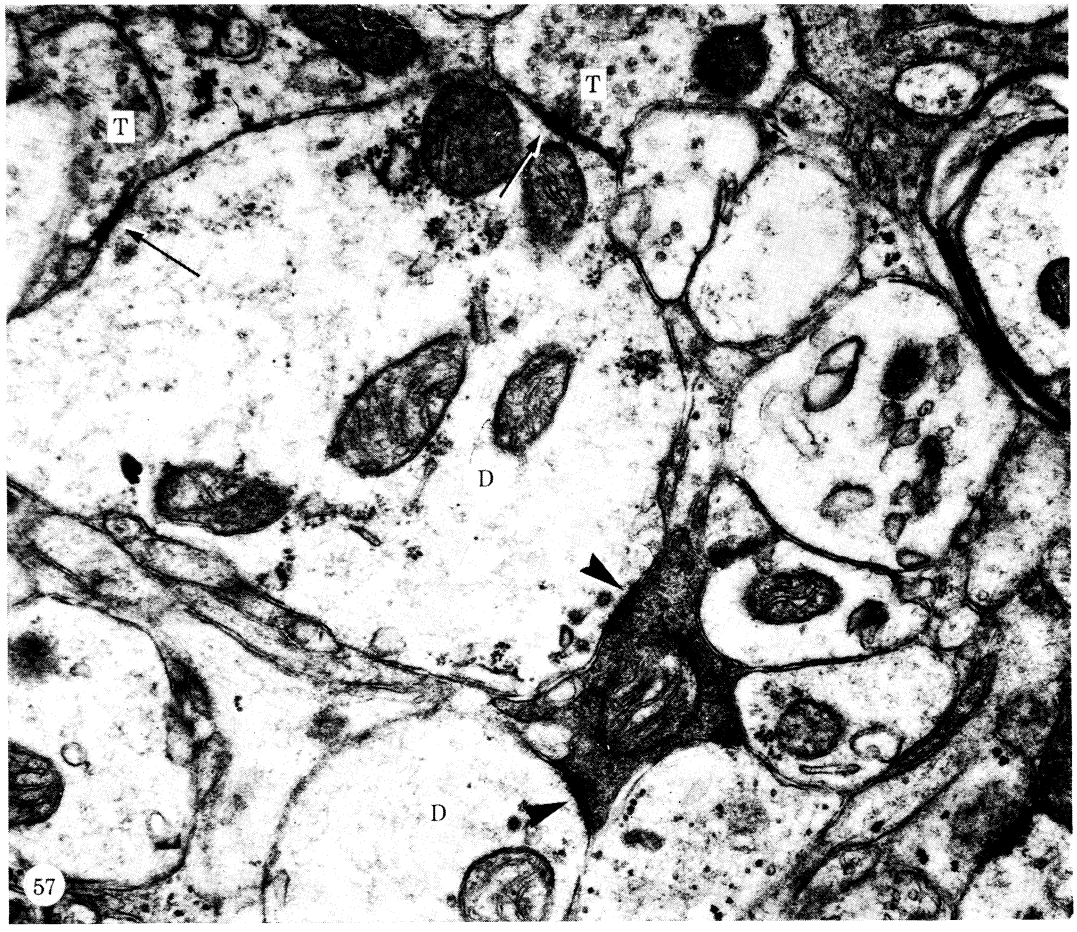

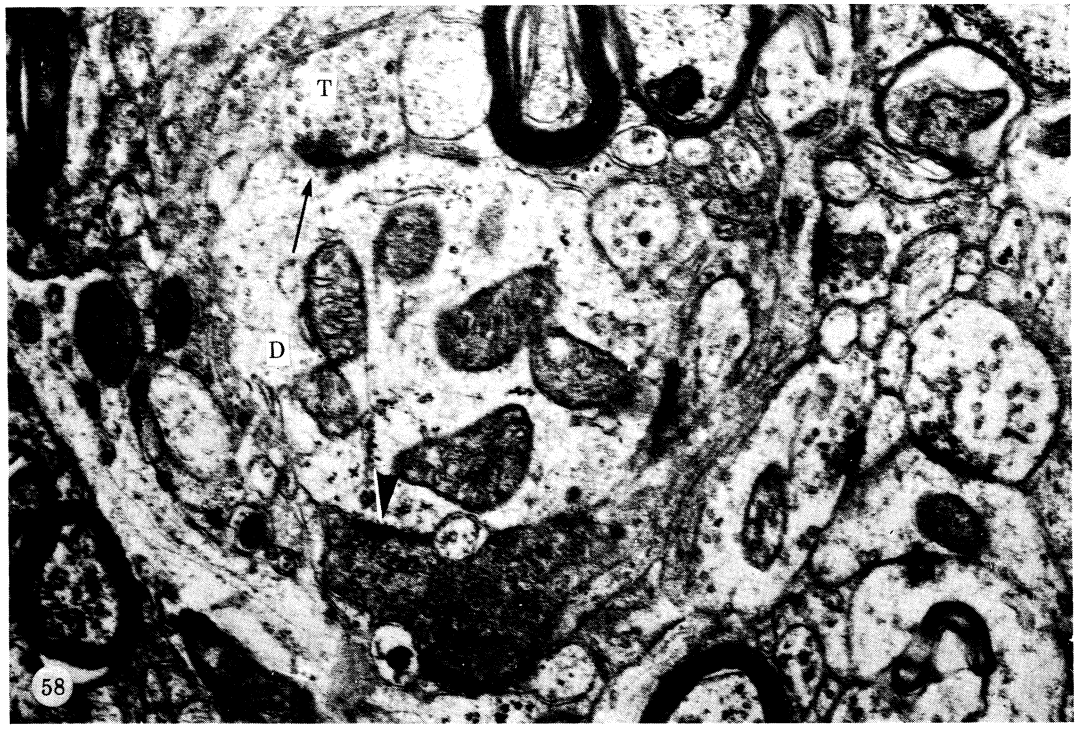

FIGURES 57 AND 58. For description see opposite.

A further analysis of the degenerating terminals which have been classified as asymmetrical or symmetrical shows (table 3) a striking difference between the two types, as 75% of the former synapse upon spines and 24% on dendrites, whereas 78% of symmetrical terminals are upon dendrites and only 13% on spines. Although both types of terminals contact cell somata, the numbers observed are too small to permit any comparison.

TABLE 3. THE NATURE OF THE POSTSYNAPTIC PROFILE WITH WHICH THE TWO MAIN TYPES (ASYMMETRICAL AND SYMMETRICAL) OF DEGENERATING TERMINAL MAKE CONTACT

	spines	dendrites	cell somata	unidentified profiles
total	307 (66.7%)	149 (32.4%)	3 (< 1%)	319
asymmetrical	276 (75%)	88 (24%)	1 (< 1%)	219
symmetrical	5 (13%)	29 (78%)	2 (~ 5%)	17

(In addition, one degenerating terminal with a symmetrical thickening was found to make contact with the initial segment of the axon of a small pyramidal cell.)

TABLE 4. THE MODE OF TERMINATION (ASYMMETRICAL OR SYMMETRICAL MEMBRANE THICKENING) OF DEGENERATING TERMINALS ON TO THE DIFFERENT TYPES OF POSTSYNAPTIC PROFILES

profile	asymmetrical terminals	symmetrical terminals	membrane thickening unidentifiable
spine	276 (98%)	5 (2%)	26
dendrite	88 (75%)	29 (25%)	32
cell soma	1	2	—

Although most of the results which have been described have been obtained from the study of material on the side of a lesion through the depth of the cortex, three other varieties of material have been examined, but less systematically. In the first of these, material in the angle between two slit lesions placed at right angles to each other shows a higher density of degeneration than is found in material taken from a single lesion, but, although no quantitative studies were made, there did not appear to be any obvious differences in the proportions of the types of terminals affected, the density in the different laminae or the proportions of postsynaptic profiles. Secondly, in a few blocks which included the lesion, the latter was found to extend down only to about the level of layer IV, and therefore sections were taken from the cortex deep to the lesion. In these sections the density of degeneration was less than after a lesion throughout the whole depth of the cortex, but again degeneration of both types of axon terminals was found. Finally, in one experiment in which a lesion had been placed in the peristriate cortex of the prelunate gyrus for a study of the association cortical connections into area 17, an unusually large number of degenerating terminals with symmetrical membrane thickenings were found. They were commonest in layer III, though occasional examples could be found in all other layers below layer I, and were found to form synapses predominantly on large

DESCRIPTION OF PLATE 14

FIGURE 57. A degenerating terminal in layer III making symmetrical synapses (arrowheads) with two dendrites (D), the larger of which receives other synapses (arrows) from normal axon terminals (T). (Magn. 35000.)

FIGURE 58. A degenerating terminal in layer IV making a symmetrical synapse (arrowhead) upon a large dendrite, which also receives a synapse (arrow) from a normal terminal (T). (Magn. x 32000.)

and medium-sized dendrites, with smaller numbers on dendritic spines and cell somata; all of these somata appeared to be pyramidal cells. In these sections there were also present 'dark' cell somata, which were mainly in layer III and could be identified as large stellate cells on the basis of the number and type of synapses on the cell soma; dark dendrites were also seen. These features were present on sections taken from several blocks at distances up to 5 mm from the 17/18 boundary. It should be emphasized that such a large proportion of symmetrical degenerating terminals have been found only in this one brain and that such terminals were not present in other experiments with comparable lesions of the peristriate cortex or with slit-like lesions of area 17 close to the 17/18 boundary. A careful examination of the thick sections of some of the blocks from this brain and of adjoining regions of area 17 showed small foci of gliosis and dark cells in the superficial layers of the cortex, which strongly suggests that the high proportion of degenerating symmetrical terminals was a consequence of incidental damage to the small blood vessels of the overlying pia mater. This interpretation agrees with that of Sloper (1973*b*) in relation to similar findings in the motor cortex in one experiment.

Commissural connections: light microscopy

In the monkey, several areas of clearly localized terminal degeneration could be seen in the sagittal sections; one of these is at the junction of areas 17 and 18, while others are in regions of the peristriate cortex which fit closely in position and extent with those described by Zeki (1970) in horizontal sections. However, as the electron microscopic study has been concerned only with the region at the junction of areas 17 and 18, a detailed description will be given of degeneration in this region only.

The terminal and fibre degeneration is clearly restricted to a narrow region approximately 2 mm wide, the centre of which is formed by the junction of architectonic areas 17 and 18 (figure 66); the latter is marked by a group of half a dozen or so conspicuous, large pyramidal cells situated exactly at the junction of layers III and IV (figures 67 and 68, plate 18; figures 69 and 70, plate 19) (cf. von Bonin & Bailey 1947). In area 18 degeneration is found throughout all layers of the cortex; in the layers superficial to layer V it is mainly granular, terminal degeneration, while in layers V and VI there are in addition a number of degenerating fibres, some of which undoubtedly run obliquely, though the majority are arranged perpendicular to the cortical surface. The density of the fine terminal degeneration in layer IV is slightly greater than that in the layers superficial and deep to it. As one traces the degeneration towards area 17 a definite change occurs, in that the degeneration in layer IV suddenly diminishes and disappears completely immediately beyond the large cells. The degeneration in the layers superficial and deep to layer IV continues, however, the maximum extent being seen in the most superficial and deep parts of the cortex. The distribution of the degeneration, which has a surprisingly sharp edge, leaves a clear zone in the peripheral part of area 17 which is

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DESCRIPTION OF PLATE 15

FIGURE 59. A large cell in layer V, which may be a Meynert cell on account of its size, the appearance of its nucleus (N) which shows the typical pallor of a pyramidal cell nucleus, with absence of chromatin clumps under the nuclear membrane, and because of its cytoplasm (C) which contains numerous mitochondria. A basal dendrite of this cell (D) receives a symmetrical synapse (arrowhead) from a degenerating axon terminal (T). (Magn. × 8400.)

Inset. The degenerating terminal and its synapse at higher magnification. D, dendrite. (Magn. × 16800.)

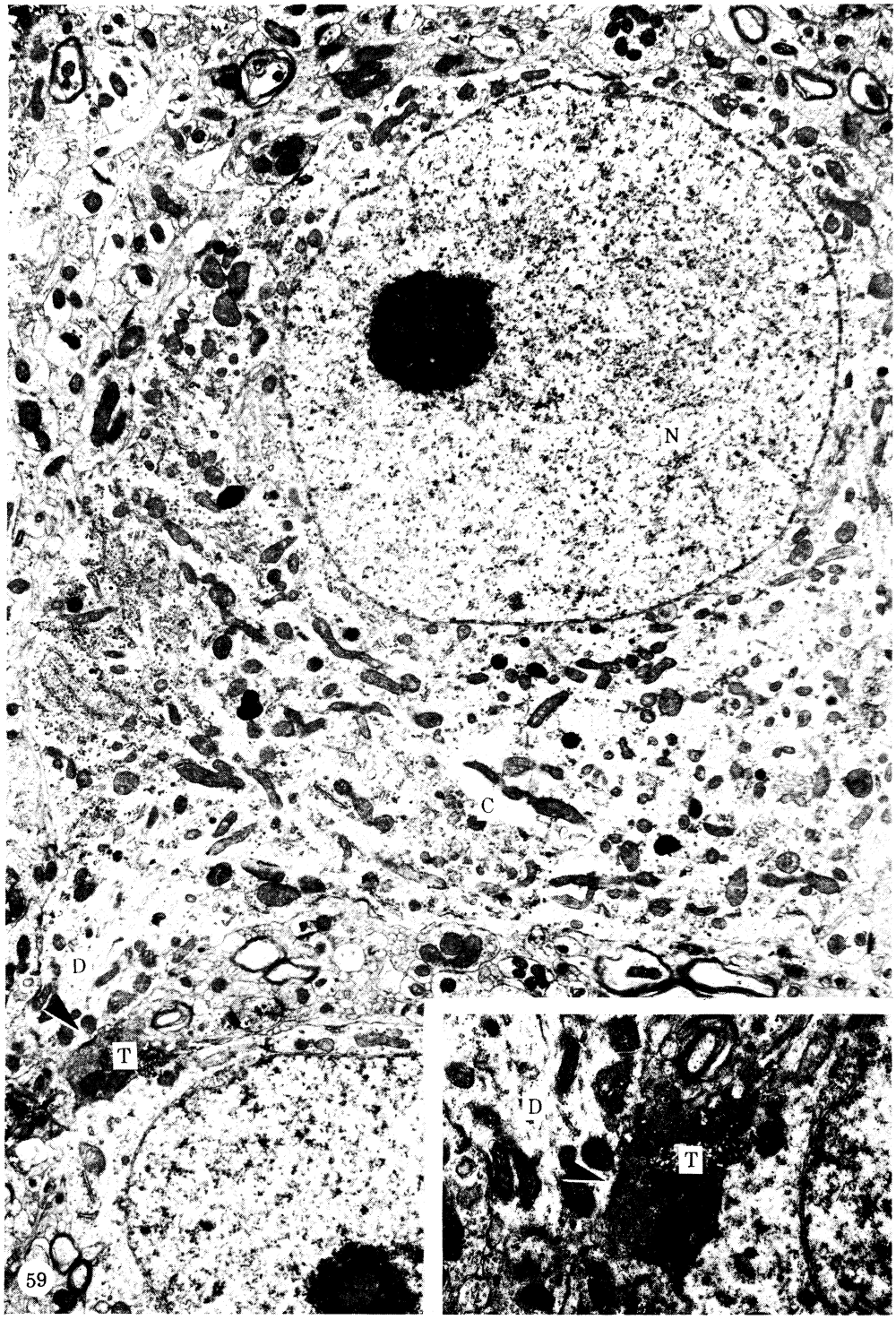

FIGURE 59. For description see opposite.

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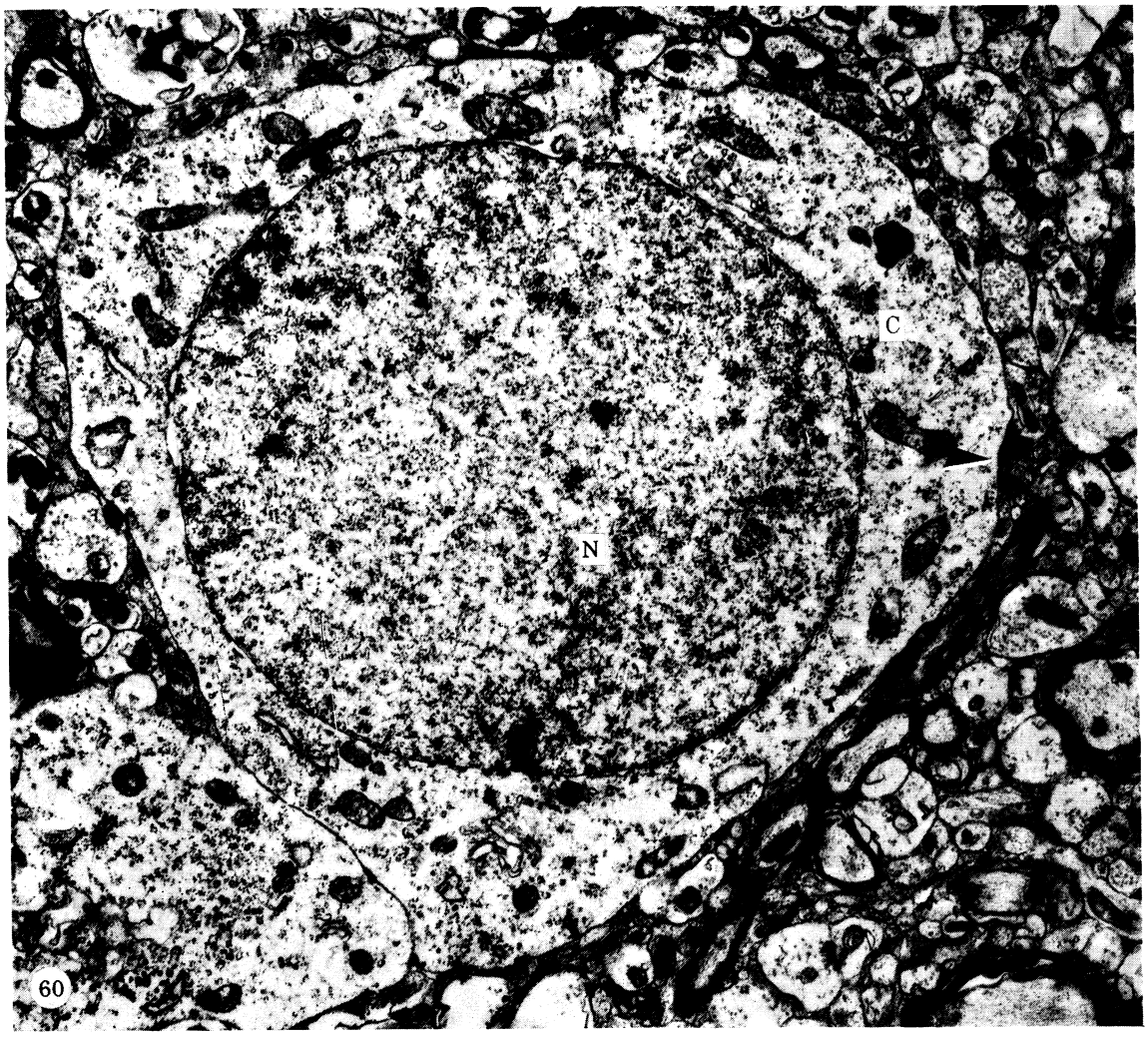
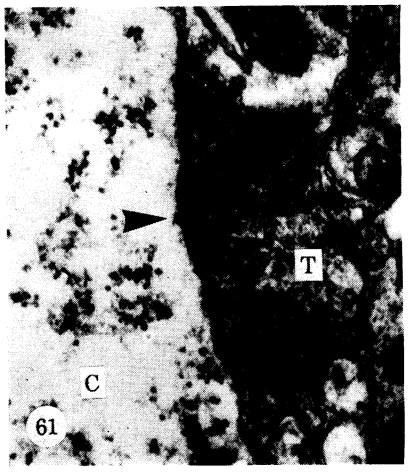
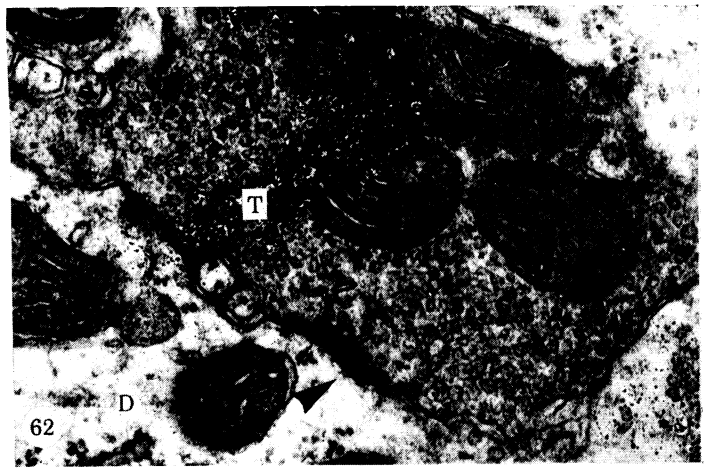






FIGURES 60–62. For description see opposite.

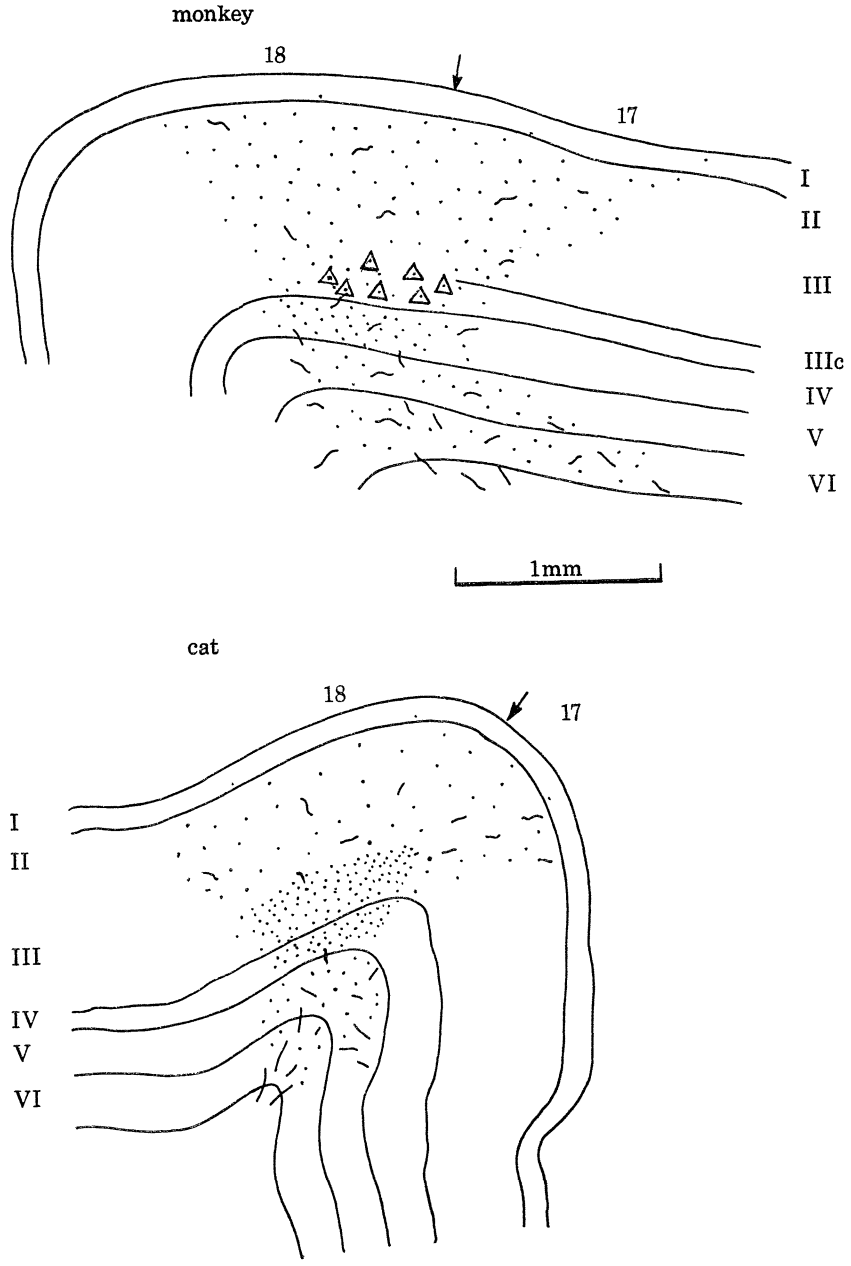


FIGURE 66. A schematic representation of the light microscopic appearance of a parasagittal section through the occipital lobe of the monkey's brain (above), and of a coronal section through the visual cortex of the cat (below), showing the pattern of fibre and terminal degeneration at the boundary of areas 17 and 18 after a lesion of the corresponding region of the opposite side. In these figures fibre degeneration is represented by short lines, terminal degeneration by stippling and the layers of the cortex are indicated by Roman numerals. The figures show how degeneration in the middle layers, especially layer IV, ceases abruptly at the 17/18 boundary, while that in the superficial and deep layers continues into area 17 but becomes progressively confined to the extreme superficial and deep zones. At the 17/18 boundary in the monkey there are a few conspicuous large cells in the deep part of layer III (represented here by triangles).

DESCRIPTION OF PLATE 16

FIGURE 60. A pyramidal cell in layer V, showing the typical appearance of a pale nucleus (N) with diffuse chromatin and pale cytoplasm (C), with relatively few organelles. The cell receives a symmetrical synapse (arrowhead) from a degenerating axon terminal. (Magn. × 8500.)

FIGURE 61. The degenerating terminal (T) and the axo-somatic synapse shown in Fig. 60 at higher magnification. (Magn. × 52000.)

FIGURE 62. A degenerating terminal (T) in layer V making a symmetrical synapse (arrowhead) with a large dendrite (D). (Magn. × 52000.)

wedge-shaped with its apex at the large cells situated at the 17/18 boundary; in particular, the spread of degeneration towards area 17 in the superficial layers is very striking. An exactly similar distribution of commissural degeneration has been described recently at the striate/peristriate boundary in the Virginia opossum (Benevento & Ebner 1971). These features have been presented in some detail as they are important for the interpretation of the electron microscopic findings both of ourselves and of earlier workers.

The distribution of commissural fibre and terminal degeneration in terms of the architectonic subdivisions of the visual cortex of the cat has already been described (Wilson 1967; Garey, Jones & Powell 1968; Heath & Jones 1971), and the present description will be concerned with the boundary of areas 17 and 18 only, which is also the subject of the accompanying electron microscopic study. The degeneration is mainly in area 18 but extends for a short distance into area 17 (figure 66). There is fibre and terminal degeneration throughout the depth of the cortex, but it is less dense in layers I and II and the superficial part of layer III. In the deep half of layer III and the superficial part of layer IV there is a prominent band of dense, fine granular degeneration; the density of the granules diminishes in the deep part of IV, and in layers V and VI there are many degenerating fibres, with a moderate amount of terminal degeneration scattered throughout. At about the boundary of areas 17 and 18 the dense degeneration in layers III and IV stops abruptly, and medial to this in area 17 the degeneration is largely restricted to layers V and VI, with a very much smaller amount in the superficial part of layer III. It is well known that it is difficult to delimit precisely the boundary between areas 17 and 18 in the cat, and because of the curvature of the cortex and the change in thickness in the laminae in this region it is also difficult to be certain of the precise limits of the individual laminae. For these reasons the allocation of the band of dense degeneration must be considered provisional; nevertheless, it is striking how closely this pattern resembles that already described in the monkey, in that degeneration in layer IV stops abruptly at the boundary of areas 17 and 18.

Commissural connections: electron microscopy

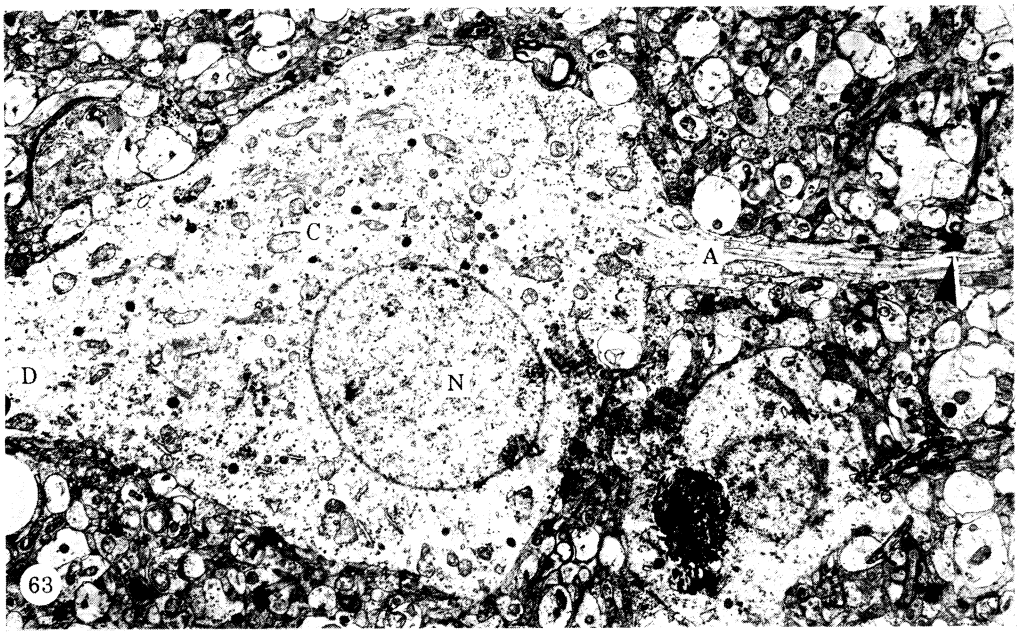
Degenerating terminals seen in this material showed various stages of dark degeneration; no examples were seen of terminals showing a filamentous type of reaction. The appearance of these stages of degeneration was essentially the same as that described after lesions within area 17; the terminals showed progressive darkening, followed by distortion and disruption of vesicles, shrinkage and crenation of the terminal outline and engulfment by reactive glial processes. Only those terminals were accepted for further consideration which could clearly be seen to be in one of these phases of degeneration and which were definitely associated with a synaptic contact showing distinct membrane specializations.

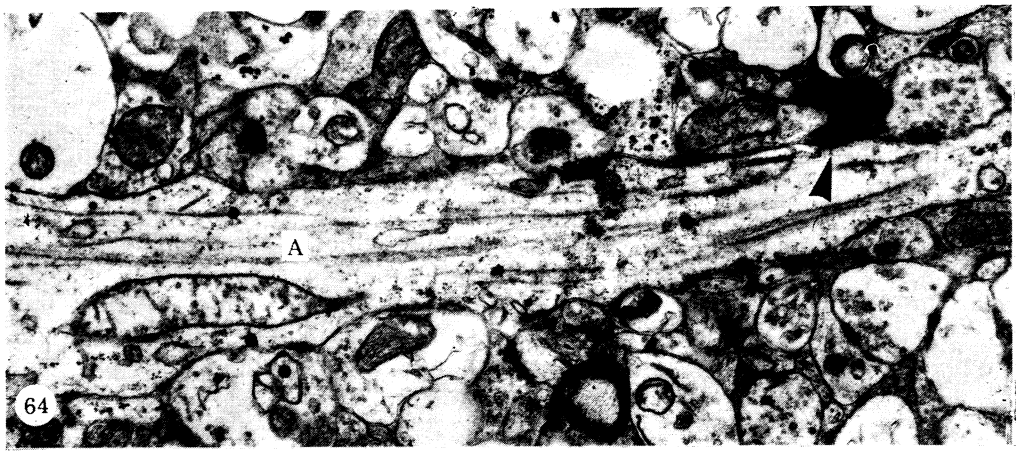
DESCRIPTION OF PLATE 17

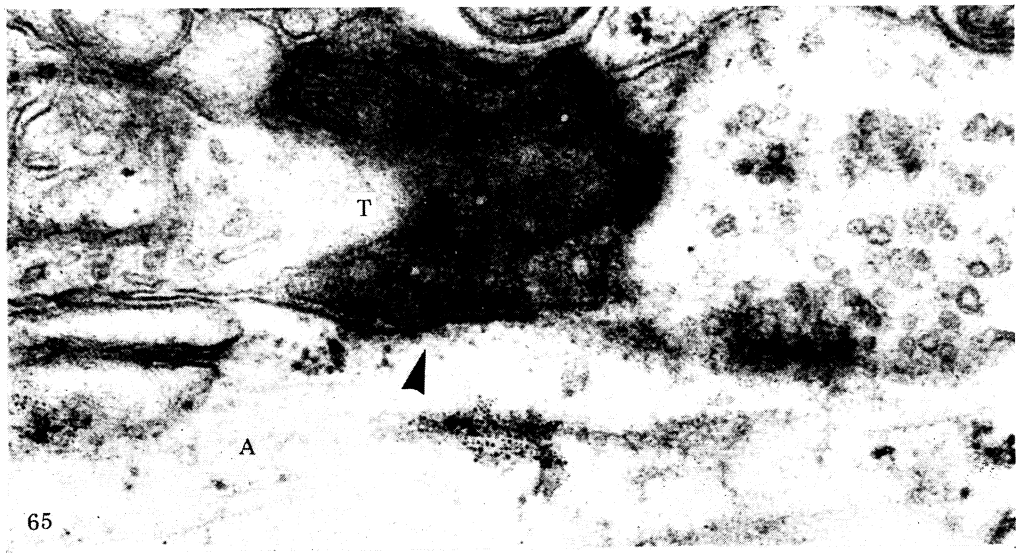
FIGURE 63. A small pyramidal cell in layer II with its apical dendrite (D) at the left of the figure. The axon initial segment (A) can be seen at the right of the figure; it receives a synapse (arrowhead) from a degenerating terminal. N, nucleus; C, cytoplasm. (Magn. × 3500.)

FIGURE 64. The axon initial segment (A) of the cell in figure 63, with the synapse made by the degenerating axon terminal (arrowhead). (Magn. × 14000.)

FIGURE 65. The same degenerating axon terminal and axo-axonic synapse shown in the previous two figures. The axon terminal (T) and initial segment (A) make synaptic contact (arrowhead) with one another, the synapse having symmetrical membrane thickenings. (Magn. × 70000.)







FIGURES 63–65. For description see opposite.

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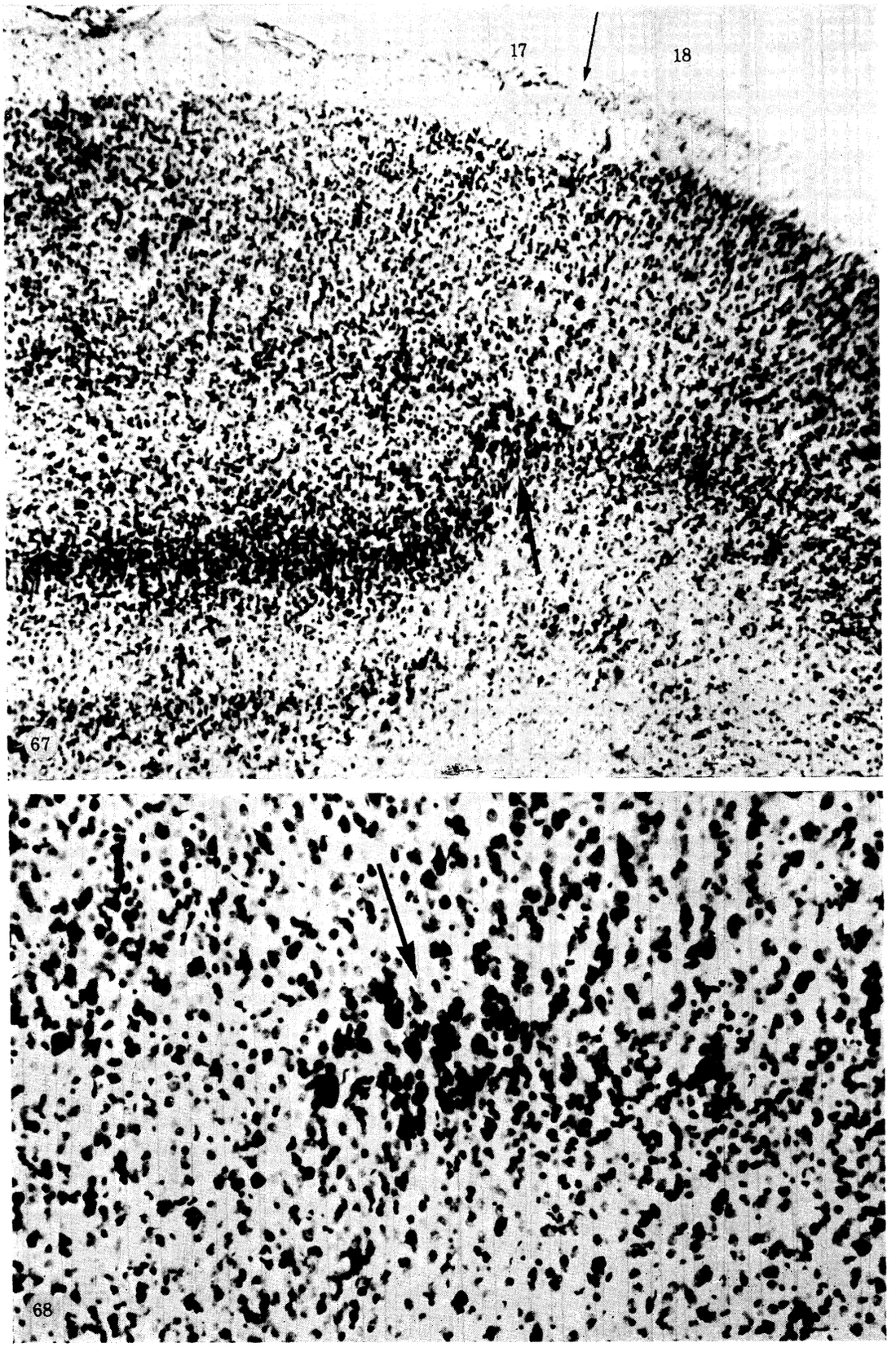


FIGURES 67 AND 68. For description see opposite.

All of the degenerating terminals seen in this study had asymmetrical membrane thickenings, which is in agreement with those of workers on the commissural connections in other cortical areas. Most of the degenerating terminals in both the cat (76 %) and the monkey (72 %) synapsed on dendritic spines (table 5). A few examples have been seen, in both species, of degenerating terminals making contact with more than one spine (figure 73, plate 20) and of a single degenerating terminal upon a spine and an adjoining dendrite (figures 74 and 75, plate 20). Some of the spines which receive commissural afferents receive other synapses as well, and a spine receiving a degenerating callosal terminal together with a normal, symmetrical terminal is shown in figure 72, plate 20. Unfortunately it has not proved possible to identify the type of cell to which these spines belong. The remaining callosal terminals make contact with dendritic shafts and where it has been possible to identify them these have been found to be of the varicose type, considered to belong to stellate cells; they bore a large number of synapses, many of which were of the asymmetrical type (figure 71, plate 20). In the deeper layers of the cortex a certain number of degenerating myelinated fibres were seen; most of these were vertically oriented and of fine to medium calibre (1–2 μm). The number of such fibres decreased progressively as one approached the more superficial layers.

TABLE 5. NUMBERS OF DEGENERATING AXON TERMINALS ON TO DENDRITIC SPINES AND DENDRITIC SHAFTS AS SEEN AT THE AREA 17/18 BOUNDARY ON ONE SIDE AFTER A LESION OF THE CORRESPONDING REGION ON THE OTHER SIDE

cat		monkey	
spines	99 (76 %)	spines	31 (72 %)
dendrites	32 (24 %)	dendrites	12 (28 %)
unclassified	71	unclassified	28

Although blocks for electron microscopic study were taken only from the sites at which degeneration was seen in sections of an immediately adjoining slice of tissue, including area 17 and the peristriate cortex, the distribution of the degeneration on maps of the thin sections showed definite variation from block to block, particularly in regard to degeneration in the middle layers (for example, the maps of figures 80 and 81). A possible explanation for this variability was found on a detailed re-examination of the Nauta-stained sections, when it was observed that the distribution of the degeneration in the different laminae changed suddenly at the 17/18 boundary. The degeneration in the deep part of layer III and layer IV suddenly diminishes within a few hundred micrometres as one moves towards area 17, and because the whole band of degeneration is only a few millimetres wide, it is more or less inevitable that a variation of only a few hundred micrometres in the precise position of the blocks for electron microscopy would result in changes in the amount of degeneration in the middle layers of the cortex. Blocks of tissue, approximately 4 mm wide and 0.5 mm or so thick, were therefore taken from a representative monkey brain so that the 17/18 boundary was in the middle of each block.

DESCRIPTION OF PLATE 18

FIGURE 67. The cortex at the boundary of areas 17 and 18 of the monkey, to show the large cells in the deep part of layer III (arrow). Thionin stain. (Magn. × 90.)

FIGURE 68. The deep part of layer III and layer IV of the preceding figure, at a higher magnification. The large cells are indicated by the arrow. Thionin stain. (Magn. × 220.)

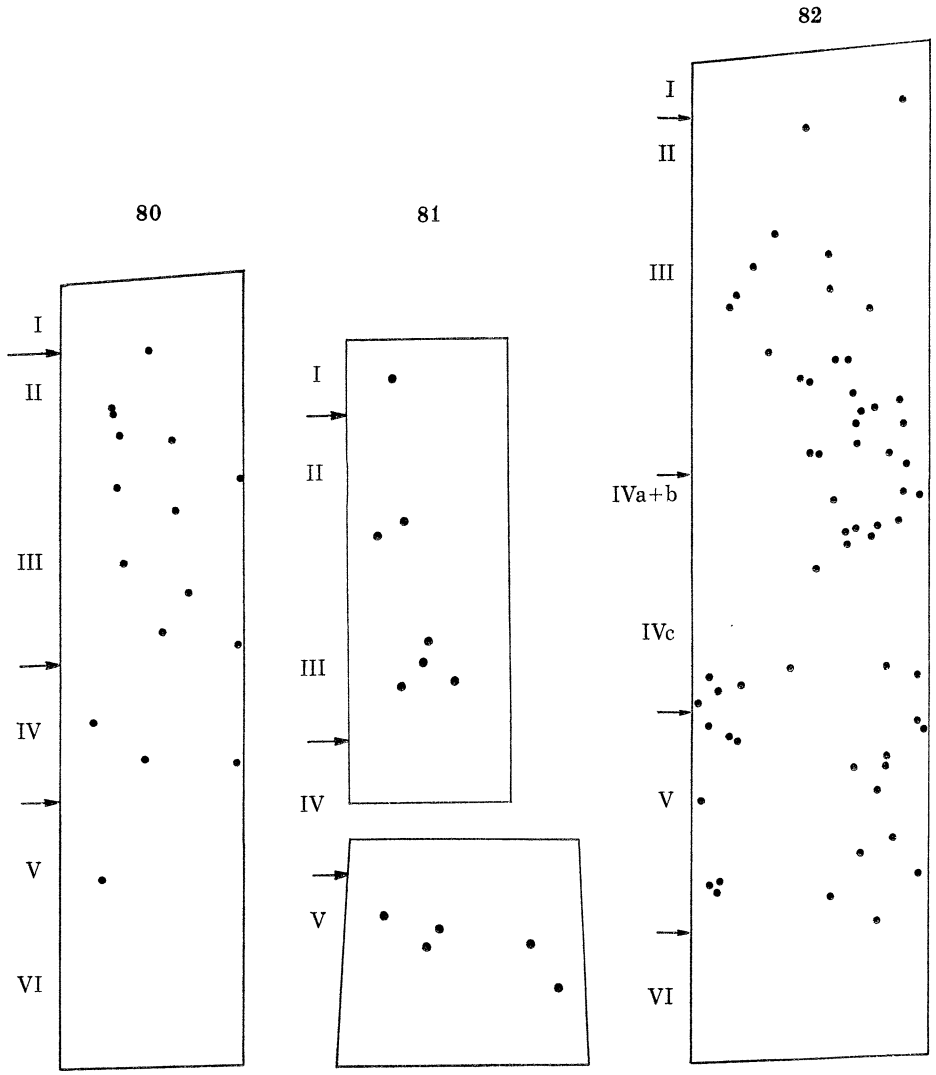


FIGURE 80. A map of a vertical section taken from the boundary of areas 17 and 18 in the monkey, made with the electron microscope, showing the distribution of degenerating terminals (black dots) seen after a lesion of the visual cortex of the opposite side. In this map the degeneration is relatively light and is distributed fairly evenly through the layers of the cortex (indicated by roman numerals).

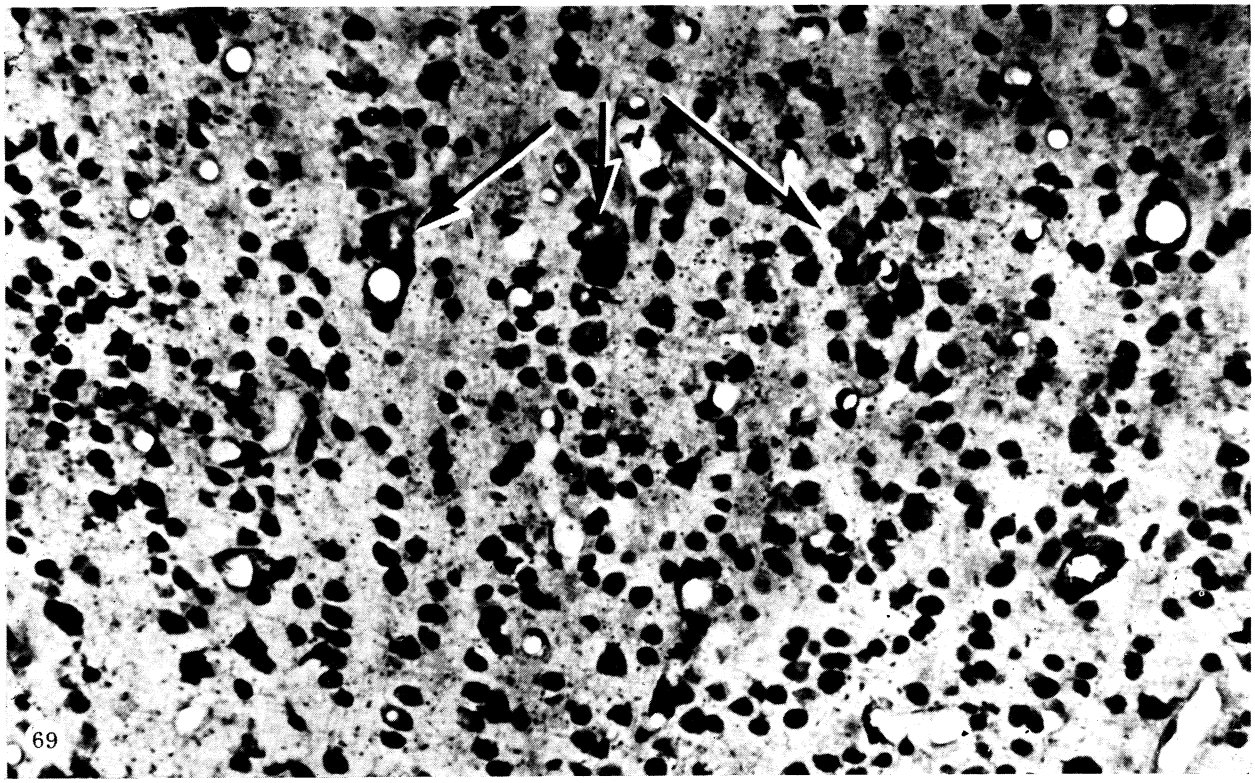
FIGURE 81. A map similar in type to that of figure 80, but taken from a different block of the same animal. The degeneration is again relatively light, but the distribution is more irregular with no degenerating terminals in layer IV.

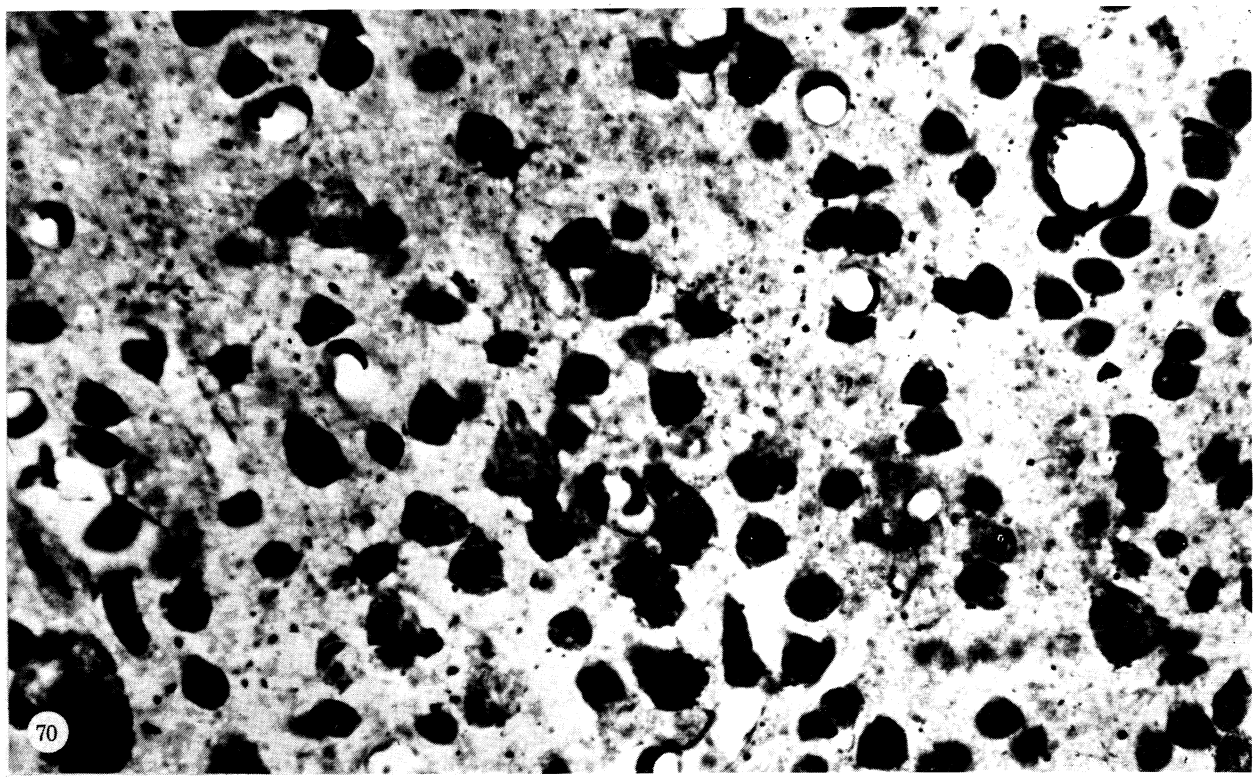
FIGURE 82. A map of a vertical section of the cat's area 17, made with the electron microscope, showing the distribution of degenerating terminals seen after a lesion of the adjoining area 18; degenerating terminals are indicated by dots. The distribution of the degeneration is reasonably even throughout the middle layers of the cortex, but layers I and II and layer VI show very few terminals.

DESCRIPTION OF PLATE 19

FIGURE 69. The deep part of layer III and layer IV at the boundary of areas 17 and 18 in a Fink–Heimer stained section of the cortex of the monkey, to show the fine degeneration of commissural fibres in the region of the large cells in layer III. The large cells are indicated by arrows. (Magn. × 300.)

FIGURE 70. The part of the preceding figure with large cells, at higher magnification. (Magn. × 550.)





FIGURES 69 AND 70. For description see opposite.

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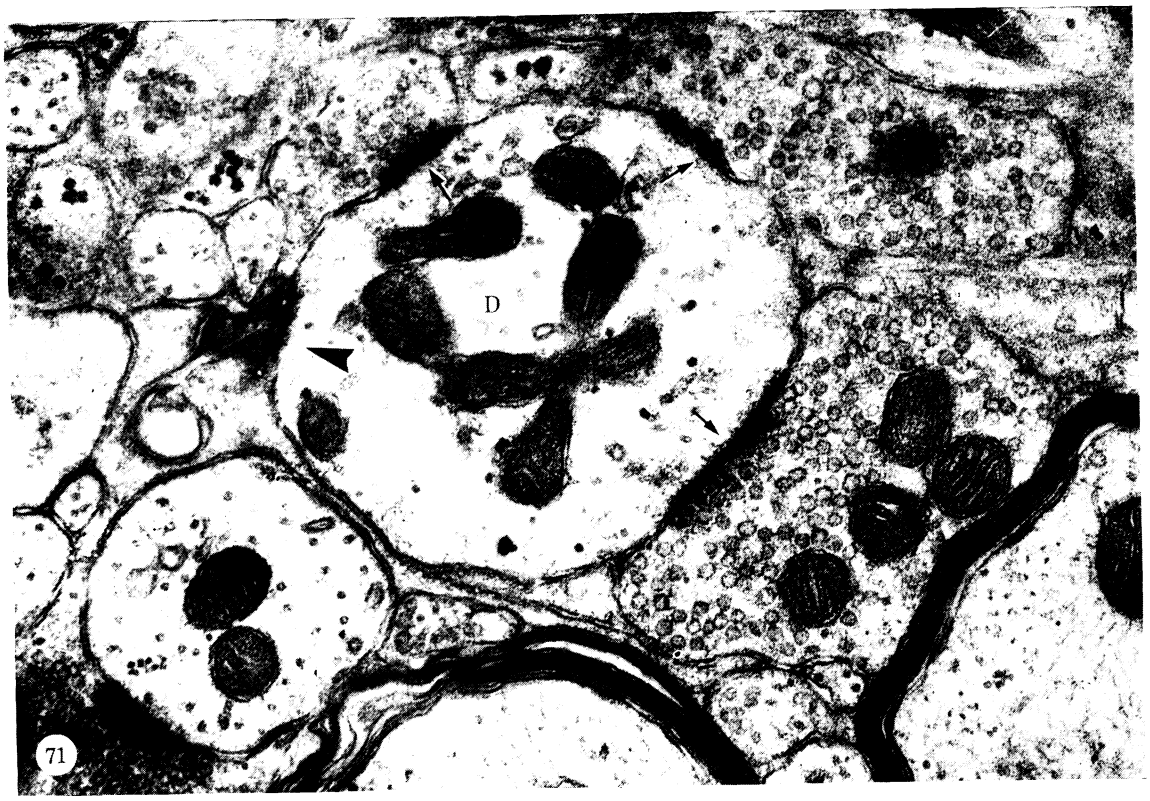

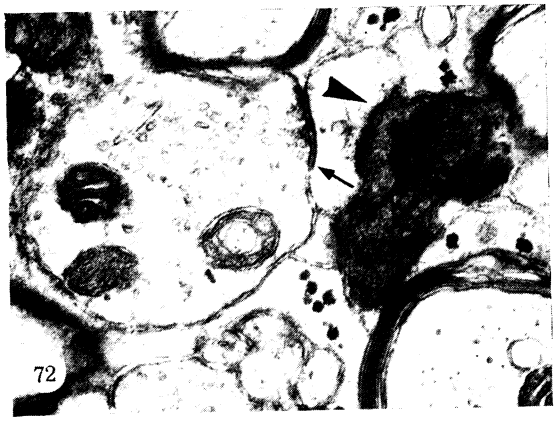

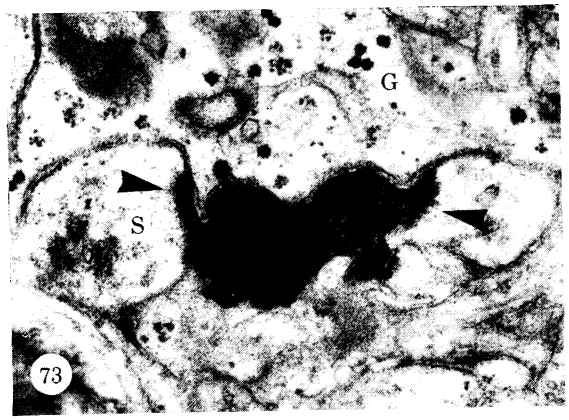

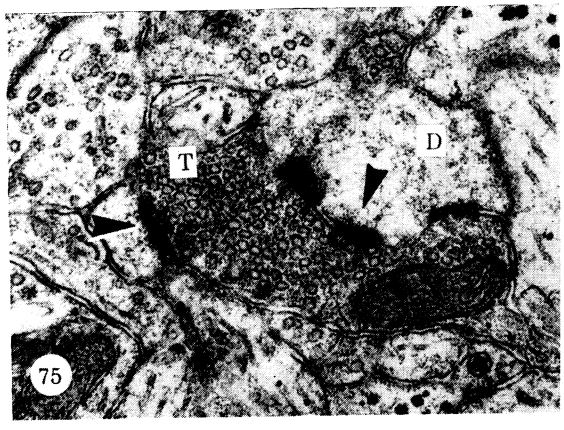

FIGURES 71–75. For description see opposite.

In the 'thick' sections of these, the large cells at the 17/18 boundary were identified. Thin sections were taken from the area 18 side, and on qualitative survey of these sections degeneration was found throughout the layers of the cortex, including layer IV. Sections taken from the area 17 side of such blocks showed very little degeneration in layer IV. It is considered therefore that the earlier variations are explicable on the basis of the differences in laminar distribution on either side of the 17/18 boundary together with the difficulty in determining the precise site of the ultrathin sections. Similar variability in the distribution of degeneration on electron microscope sections was seen in the cat.

Association connections

The present results are based on observations made in the three cat brains which had needle lesions in area 18 on the lateral gyrus without involvement of underlying white matter or of adjoining cortical areas. The terminal and fibre degeneration seen with the light microscope was heavy in area 18 but decreased quite suddenly at the boundary with area 17. In the latter, marked degeneration of fine fibres in layer I extended down almost to the level of the suprasplenial sulcus; in addition, degenerating fibres could be seen entering layer VI from the white matter, passing obliquely downwards and medially to ramify mainly in layers V and VI. Distributed throughout these layers and extending up into layer III was a little fine granular degeneration. This degeneration in the deeper layers was restricted to the lateral part of area 17 and, in contrast to that in layer I, did not extend down to the level of the suprasplenial sulcus.

With the electron microscope degenerating axon terminals were again seen to be undergoing various stages of dark degeneration. Degenerating terminals are found in appreciable numbers only in the lateral part of area 17 near the boundary with area 18. They are present in all layers of the cortex, but seem to be more numerous in the middle layers and rather less so in the superficial layers and in layer VI; a representative map showing this distribution of degeneration is given in figure 82. All of the degenerating terminals seen had asymmetrical membrane thickenings. Most (62 %) made synaptic contact with dendritic spines (table 6), and one spine was seen in continuity with its parent dendrite (figure 77, plate 21). A few examples were seen of a degenerating bouton making contact with two spines (figure 78, plate 21) or a spine

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DESCRIPTION OF PLATE 20

FIGURE 71. A large dendrite (D) in layer III of the visual cortex of the cat which receives an asymmetrical synapse from an axon terminal which is degenerating (arrowhead) following a lesion of the visual cortex of the opposite side. The dendrite receives three other synapses (arrows) from normal axon terminals, one of which is asymmetrical. The dendrite is presumed to be one of a stellate cell. (Magn. × 52000.)

FIGURE 72. A degenerating commissural terminal in layer III of the visual cortex of the cat forming an asymmetrical synapse upon a small spine (arrowhead); the spine also receives a normal, symmetrical terminal (arrow). (Magn. × 44000.)

FIGURE 73. A degenerating commissural terminal in layer V of the cat's visual cortex making asymmetrical synaptic contacts (arrowheads) upon two spines, one of which (S) has a spine apparatus. Reactive glial processes with glycogen (G) can be seen nearby. (Magn. × 42000.)

FIGURE 74. An axon terminal at a relatively early stage of degeneration in layer VI of the visual cortex of the monkey after a lesion of the opposite visual cortex. The terminal makes asymmetrical synaptic contacts (arrowheads) with a dendrite (D) and a small spine. (Magn. × 44000.)

FIGURE 75. An axon terminal (T) in layer II of the cat's visual cortex, at an early stage of degeneration after a lesion of the opposite visual cortex. The terminal makes asymmetrical synapses (arrowheads) upon a small spine and a small dendrite (D). (Magn. × 44000.)

which received another normal asymmetrical terminal. Occasionally a degenerating terminal formed synapses upon both a spine and a nearby dendrite (figure 76, plate 21). The remaining 38% of degenerating terminals were upon the shafts of dendrites, and those which could be identified were of the stellate type (figure 79, plate 21).

TABLE 6. NUMBERS OF DEGENERATING AXON TERMINALS ON TO DENDRITIC SPINES AND DENDRITIC SHAFTS AS SEEN IN AREA 17 AFTER A LESION IN THE IPSILATERAL AREA 18 (CAT)

spines	74 (62%)
dendrites	46 (38%)
unclassified	54

DISCUSSION

Perhaps the most striking feature of the horizontal intrinsic connections of area 17 is their restricted extent, as in both light and electron microscopic studies of experimental material the degeneration does not extend beyond 5–6 mm. Although the degeneration extends over such a short distance, both the widths of the cortex in which the distinctly different patterns of fibre and terminal degeneration can readily be discerned, and the differential involvement of the laminae, were remarkably constant in experiments with lesions in various sites, in different brains and in sections cut in different planes. The constancy of these findings indicates that the intrinsic cortical connections passing outwards from any part of the cortex have a regular organization, in terms of distance and laminae, and the lengths of these connections are in good agreement with the dimensions of certain small zones of the cortex, defined in recent studies by Hubel & Wiesel (1974*a*, *b*), as regards both visual field representation and some of the different types of functional columns. These observations also confirm the findings of Le Gros Clark (1941) in studies of area 17 of the monkey with the Marchi method; after small lesions of a few millimetres in size he found that association fibres never extended for more than 4–5 mm from the lesion.

A notable and invariable feature of the degeneration of intrinsic connections within area 17 was its asymmetry in extent on the two sides of the lesion. This was found irrespective of whether the sections were cut coronally or sagittally and the degeneration in all layers, except layer IV, was found to extend about twice as far on one side of the lesion as on the other. It was not possible to correlate this observation with any known feature of the structure or organization of

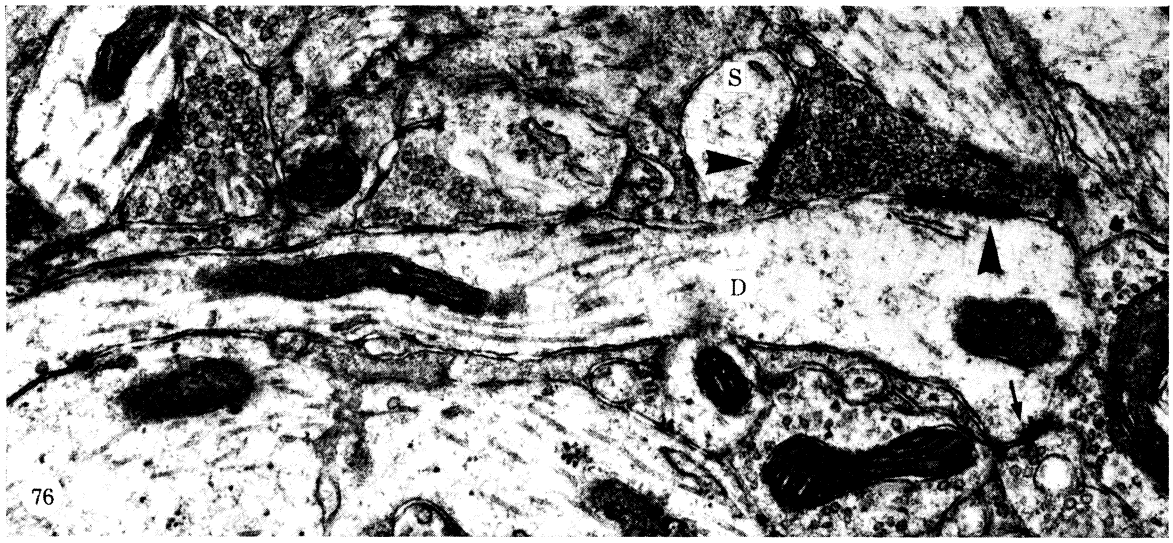
DESCRIPTION OF PLATE 21

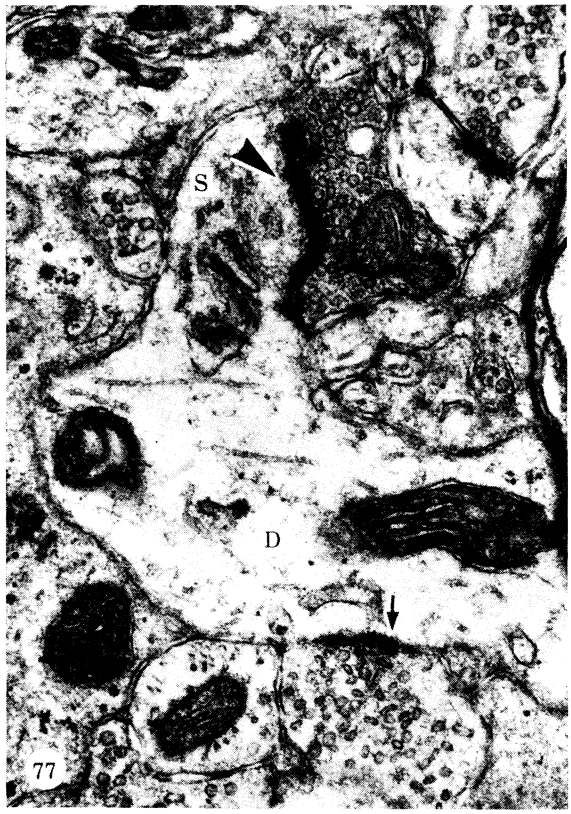
FIGURE 76. A degenerating terminal in layer IV of area 17 of the cat after a lesion of the adjoining part of area 18 of the same side. The terminal makes asymmetrical synapses (arrowheads) with a spine (S) and a dendrite (D); the latter also receives a synapse from a normal terminal (arrow). (Magn. × 42000.)

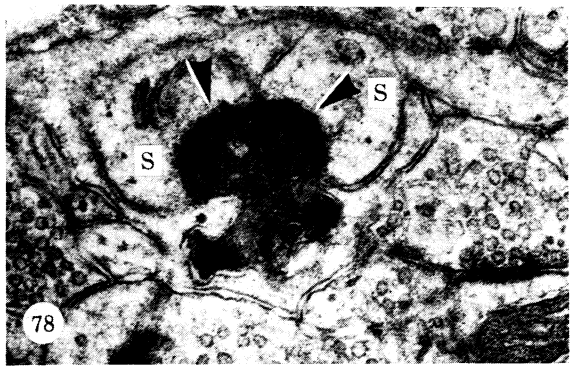
FIGURE 77. A degenerating terminal in layer III of area 17 of the cat following a lesion of area 18 of the same side. The terminal makes an asymmetrical synapse (arrowhead) upon a spine (S), which contains a spine apparatus and can be seen arising by a short pedicle from its parent dendrite (D); the latter receives a normal, symmetrical synapse (arrow). (Magn. × 48000.)

FIGURE 78. A degenerating terminal in layer III of the cat's visual cortex (area 17) after a lesion in area 18. Asymmetrical synapses (arrowheads) are made with two small spines (S), one of which contains a spine apparatus. (Magn. × 52000.)

FIGURE 79. A dendrite (D) in layer IV of area 17 of the cat after a lesion in area 18. One of the axon terminals which makes an asymmetrical synapse (arrowhead) with the dendrite is at an early stage of degeneration. The dendrite receives several other synapses (arrows) and is probably one of a stellate cell. (Magn. × 52000.)







FIGURES 76–79. For description see opposite.

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the connections of the cortex, and the only suggestion that can be made is that in some way it is associated with the arrangement of the geniculo-cortical terminals in bands crossing the whole cortex (LeVay, Hubel & Wiesel 1975) and with the intracortical mechanisms related to orientation/direction sensitivity of cortical cells (Creutzfeldt, Kuhnt & Benevento 1974).

The type and density of degeneration differed appreciably at varying distances from the damage. In a width of 200 μm on each side of the lesion there was very dense fine granular degeneration in every layer, and in a particular lamina this was the same after lesions which passed through the whole depth of the cortex or after damage confined to a single lamina. It can be seen from several of the figures illustrating degeneration in individual experiments that the *total* width of the lesion together with that of fine degeneration on *both* sides is between 500 and 1000 μm, and usually about 600 μm. This dense degeneration diminishes suddenly and gives its edge a sharp margin which demarcates it in most layers from the next zone of moderate degeneration. In layer IV, however, the degeneration ends at this distance and the absence of fragmentation beyond this point stands out prominently between the degeneration in layer IIIc superficially and layer V on its deep aspect.

Beyond the zone of dense degeneration there is a moderate degree of degeneration which extends in all layers, except the stria and layer IV, for 1.5–2 mm on one side and for 0.5–1 mm on the other. In layers II and IIIa and b this degeneration is almost entirely granular with very few fibres, and it again stops quite suddenly so that its outer edges can be clearly delimited. Its total width in all layers, except the stria, on both sides of the lesion is between 2–3 mm. Certain points about the type and extent of this degeneration in different layers may be noted. It was surprising to find that the degeneration in layer I did not extend for more than 1–2 mm on either side of the lesion as in previous studies on other areas of the cortex (Szentágothai 1973; Jones & Powell 1973) such degenerating fibres were seen to extend for about 5 mm irrespective of whether they crossed the architectonic boundary in doing so. Repeated series of sections in several experiments were stained in order to ensure that the short distances found were not due to imperfect impregnation, but its significance can probably be found in a correlation with the functional observations on area 17 (Hubel & Wiesel 1974*a*, *b*). In layers V and VI, in contrast to layers II and IIIa and b, there were a number of degenerating fibres among the terminal granules. The absence of many degenerating fibres in the more superficial layers is almost certainly a reflection of their short length and fine diameter.

If the damage is restricted to layers I and II of the cortex there is no degeneration deep to the superficial part of layer III and none in the stria. When layers IIIa and b are damaged the extent and quantity of degeneration in the stria in layer IIIc is essentially the same as in the other layers except that more fibres are present. When the lesion extends more deeply and involves the stria itself or deeper layers, the density of the fibre degeneration increases markedly and the fragmentation extends further than that in the layers superficial and deep to it. This fibre degeneration is again asymmetric and reaches 3.5–4 mm in one direction and 1.5–2 mm in the other. Degenerating fibres leave the stria to enter layer IIIb and the superficial part of layer IV, and consequently there is a difference in connections between the superficial and deep parts of layer IV. The absence of severe and extensive degeneration of horizontal fibres in the stria after damage to layers superficial to it suggests that these fibres arise from cells within and below it rather than from those above. This view is supported by an experiment in which a microelectrode lesion which involved layer IIIc alone gave rise to extensive degeneration in the stria. It also appears that degeneration in the stria after a lesion of layers I, II and III,

including IIIc, is virtually as dense as after lesions of the full depth of the cortex, suggesting that fibres reaching the stria from below travel almost exactly vertically. A small microelectrode lesion in layer IV resulted in considerable degeneration in the stria and degenerating fibres appeared to spread obliquely upwards and outwards from the focus of damage; a high proportion of fibres in the stria, and particularly the longer ones, therefore probably arise from cells in layer IV (or V and VI). This conclusion agrees with the interpretation of other experimental work that the stria is made up mainly of fibres arising within the cortex (Poliak 1932; Le Gros Clark & Sunderland 1939). The degeneration of fibres and terminals in layer V, including horizontally disposed fragments in the inner band of Baillarger, after lesions restricted to layers I–III, is evidence of a projection from these supragranular layers to layer V. The degeneration in layer V after lesions in layers I–IIIc, however, is less than after a lesion of the whole depth of the cortex or after lesions of layers I–V, which suggests that many of the intrinsic connections of layer V arise within layers IV, V and VI. The experiments have provided little information about the vertical connections between the layers. After small focal lesions in layers I and II, few if any fibres descend beyond the upper part of layer III. From layers IIIa and b a small number of horizontal connections pass into the stria and others descend vertically to layer V where they join the inner band of Baillarger in this layer and few pass through layer VI to the white matter. The majority of efferent fibres entering the white matter would therefore seem to arise from layers V and VI, which is in agreement with previous observations (Le Gros Clark 1942; Spatz, Tigges & Tigges 1970; Holländer 1974). In regard to ascending intrinsic connections, the evidence that the majority of fibres in the stria ascend from layer IV (or deeper layers) has already been discussed, and the only other observations on ascending fibres are those suggesting a reciprocal projection from layer V to layers IIIa and b. The degenerating fibres were always restricted to a narrow vertical column lying above or below the lesion, and this was particularly striking in layer IV when the vertically disposed fibre fragmentation was always within the narrow zone of fine degeneration. Except in the cortex close to the boundary of areas 17 and 18 no bands of degeneration were seen in layer IV beyond 200 μm or so from the side of a lesion through the depth of the cortex, which suggests that the incoming thalamo-cortical fibres ascend vertically after entering the cortex. This observation is at variance with the description (Hubel & Wiesel 1972) of degenerating fibres 'criss-crossing' in layers V and VI after lesions of the lateral geniculate nucleus and with their inference that 'It was as if a fiber only decided on its destination after entering the cortex, and took a diagonal course in the deeper layers in order to get to an appropriate band or interband in layer IV.'

The findings in the present study of only slight to moderate degeneration in layer V after small lesions in layers I, II and III is different from the massive degeneration seen in layer V after the larger lesions of these layers in the experiments of Spatz *et al.* (1970) and Nauta, Butler & Jane (1973) and with similar findings using the autoradiographic technique (Martinez-Millán & Holländer 1975). In the material of all these workers, however, a greater horizontal extent of the superficial layers was involved than in our focal lesions, so the most probable explanation for the difference in the severity of the degeneration is that the origin of the fibres to any point in layer V is rather diffuse. This interpretation suggests a considerable degree of convergence of the superficial layers upon cells in layer V, which is not surprising in view of the fact that the majority of the efferent fibres arise from the deeper layers. It would be of interest to determine whether the horizontal extent of the origin of descending fibres to any point in layer V is of the order of magnitude of the moderate degeneration in layer III (2–3 mm).

The observations with the electron microscope are in good agreement with the light microscope findings, particularly with regard to the rather restricted extent of the degeneration and the variations in density and extent of degeneration between the different laminae. The terminals which degenerate after an intrinsic lesion of the cortex form only a small proportion of the total number of terminals present, which may seem surprising. It is, however, the product of a number of factors: if it is assumed that a given cell in the cortex can receive horizontal connections from any cell within a radius of 3 mm of it in any direction, then it is clear that a slit lesion will destroy a *maximum* of only 50 % of the connections to that cell, since connections from cells on the side away from the lesion will be preserved. If to this is added the consideration that a given cell receives vertical connections as well as horizontal ones, and that degenerating terminals could only be positively identified if certain morphological criteria were met (so that a number of degenerating terminals would be missed by this study) the apparently low yield of degenerating terminals after intrinsic lesions can readily be explained.

The majority (approximately 90%) of all terminals had asymmetrical membrane thickenings. Most of these asymmetrical intrinsic terminals (75 %) made contact with dendritic spines, and the higher proportion in layers I and II probably results from the fact that the peripheral parts of pyramidal cell dendrites, which are numerous in these layers, bear a larger proportion of dendritic spines than the more proximal parts (Valverde 1967; Jones & Powell 1969*a*; Peters & Kaiserman-Abramof 1970), and it is known that the overwhelming majority of synapses on spines are asymmetrical (Jones & Powell 1969*a*). A significant proportion (24 %) of asymmetrical intrinsic terminals form synapses upon dendrites, whereas only 14 % of thalamocortical terminals do so (Garey & Powell 1971). Those dendrites which received asymmetrical terminals were stellate in certain cases and no examples were seen on identifiable pyramidal cell dendrites, though they could certainly make contact with the peripheral parts of such dendrites. A few examples were observed of asymmetrical terminals making contact with the cell somata of stellate cells, but none was found on pyramidal cells.

Intrinsic terminals with symmetrical membrane thickenings form only about 10 % of the total. Their distribution with respect to the constituent parts of neurons is complementary to that of asymmetrical terminals as 78 % are on dendrites and only 13 % on spines. They make contact with both pyramidal and nonpyramidal-type dendrites. On a few occasions a symmetrical intrinsic terminal has been seen to form a synapse opposite the origin of a dendritic spine. Symmetrical terminals also make contact with the somata of cells, pyramidal and stellate, and one has been seen on the basal dendrite of a Meynert cell in layer V. One example has been seen of a degenerating symmetrical terminal making contact with the initial axon segment of a small pyramidal cell in layer II, which confirms earlier suggestions (Jones & Powell 1969*c*) that synapses on initial segments are made by axons which are intrinsic in origin. The fact that more examples were not found may suggest that such terminals arise from axons which run for a very short distance, so that most of their terminals would lie within the region 200 μm wide alongside the lesion; the one example found was only some 250 μm from the lesion.

One interesting feature of the degeneration seen with the electron microscope was that the asymmetrical terminals, though greatly in the majority, were numerous only within the first millimetre from the lesion, falling off in density thereafter, while the symmetrical terminals, though never so dense as the asymmetrical, were much more evenly spread throughout the 3 mm or so from the lesion which they occupied.

Our understanding of the functional organization of the sensory areas of the neocortex has

advanced considerably in recent years and it has been possible to correlate some of the physiological observations with certain anatomical features. There is little anatomical evidence, however, concerning the arrangement of cortical cells into functional columns and the apparently high degree of specificity of the connections between them. This problem presents a particular challenge in the case of area 17 of the visual cortex in the monkey, where the functional aspects have been elucidated in most detail by the extensive studies of Hubel & Wiesel (1968, 1974*a*, *b*). The present investigation was started soon after the preliminary report that the fibres from the layers of the lateral geniculate nucleus related to one or other eye terminate in a mosiac arrangement in layer IV (Hubel & Wiesel 1969), in which the cells had been shown to be simple and monocular (Hubel & Wiesel 1968). As the majority of the cells in the layers superficial and deep to layer IV are binocular and complex or hypercomplex, it was thought of interest to attempt the study of the intrinsic connections which arise in layer IV and which may connect these different functional types of neurons. The experiments have not given much information about the connections between layer IV and the layers superficial and deep to it, but it has been encouraging to find that certain of the findings are in close accord with the measurements of the different functional columns of the same area of the Macaque monkey in recently published studies (Hubel & Wiesel 1974*a*, *b*). Before discussing the correlations of the findings in these independent investigations it should be emphasized that our observations on the origin and distribution of intrinsic fibre connections is mainly in terms of the *laminae* of the cortex, and they provide little direct evidence about the nature of the cells from which the fibres arise or upon which they end; in addition, we have little information on the vertical connections of the cortex. It may also be noted that all our measurements of the extent of the degeneration have been made on frozen sections of aldehyde-fixed material with no correction for shrinkage which probably amounts to 10–20 %.

Two major types of functional columns have been identified in the visual cortex, 'ocular dominance' and 'orientation' columns. The ocular dominance columns are 200–500 μm in width as shown by regularly alternating bands of degeneration and clear areas in layer IV after a lesion of one layer of the lateral geniculate nucleus (Hubel & Wiesel 1969, 1972), by the autoradiographic demonstration in the cortex after injection of labelled amino-acids and fucose into one eye (Wiesel *et al.* 1974), and by oblique or tangential microelectrode penetrations (Hubel & Wiesel 1974*a*, *b*). They are distributed over the cortex in parallel sheets or slabs (LeVay *et al.* 1975). In layer IV the cells are monocular and those in the more superficial and deep layers, although binocularly influenced, are arranged so that those lying above or below a part of layer IV related to one eye also respond more favourably to that eye. There is a close similarity in the width of an adjoining pair of left and right ocular dominance columns, and that of the total width of orientation columns that encompass a complete cycle of orientations through 180°. These larger columns have been designated hypercolumns. It is significant therefore that the width of the fine dense granularity on either side of the lesion in our experiments is of the order of 200 μm, and that this is so irrespective of whether the whole depth of the cortex is damaged or if the damage is more restricted and in the form of a small focus in layers III and IV. The *total* width of the lesion and the fine degeneration on both sides is 500–1000 μm and often about 600 μm with a small focal lesion. A further point is that in layer IV, which is the major site of termination of the thalamic afferent fibres, the degeneration is clearly confined to this distance. It may be suggested therefore that the narrow band of dense degeneration on one side of the lesion represents the intrinsic connections present *within* a single ocular domi-

nance column and that the *total* width between the *outer* margins of degeneration on *both sides* of the lesion is that of the hypercolumn–ocular dominance or orientation. In other words, the cells *within* such a hypercolumn are closely interconnected horizontally and very much less closely with cells immediately adjoining them. It also means that adjoining monocular columns in layer IV are *not directly* connected by fibres passing *within* that layer. It is also significant that degenerating fibres which pass vertically, above or below a damaged point, were also found to be restricted to a narrow band of the same width situated directly above or below a lesion, and this was particularly striking in layer IV after lesions restricted to more superficial layers. This finding indicates that the cells in one of the hypercolumns are predominantly connected with those in the same column in different depths. The electron microscope observations contribute little to this correlation, as the proximity to the direct damage precluded detailed study, but it can be stated that in this region there was intense degeneration of nerve terminals. It has already been pointed out that the number of degenerating terminals even at 500–1000 μm away from the lesion formed only a very small proportion of the total number of synapses and the reasons have been given why this should be so. Consideration of this problem had suggested to us that the only way to obtain the degeneration of the majority of the terminals within a given region would be to isolate completely a cylinder of cortex by inserting a hollow needle of suitable internal diameter; should the diameter of such a cylinder be that of the width of a hypercolumn, that is up to 1 mm?

Hubel & Wiesel (1974*b*) have also found that 'A certain constant distance along the cortex, amounting to 2–3 mm, must be traversed in order to obtain a shift in field position comparable to the size of the fields plus their scatter', and had noted the similarity in these measurements to those given for the horizontal extent of the intrinsic connections in a preliminary publication of the present results (Fisken *et al.* 1973). The total horizontal extent of the moderate degree of fibre and terminal degeneration in all layers of the cortex, except in the stria and layer IV, is remarkably constant at between 2 and 3 mm, and it seems reasonable to conclude that this degeneration represents the connections within the region of the cortex which contains 'by a comfortable margin the machinery it needs to analyse the region of visual field that it subserves' (Hubel & Wiesel 1974*b*). Although the origin of all the horizontal fibres in layer I is not known with certainty, there is evidence that many arise from layers IV, V and VI (Szentágothai 1973) and others from the thalamus (Hubel & Wiesel 1969, 1972; Garey & Powell 1971). It is significant that the extent over which these fibres degenerate is also 2–3 mm, as this is about half of that in other cortical areas which have been studied (Szentágothai 1973; Jones & Powell 1973), and for long we were uncertain whether the shorter distance might be due to incomplete impregnation.

It was found in the physiological studies that the relationship of receptive field plus scatter to 2–3 mm of cortex was the same in different parts of area 17, despite variations in the size of the receptive field. With the qualifications which have already been mentioned about the extent of the visual cortex which has been studied in the present investigation, the same horizontal extent of degeneration has been found irrespective of the site of the lesion.

In their study of the dimensions of the ocular dominance and orientation columns, Hubel & Wiesel (1974*a*, *b*) penetrated the cortex obliquely or tangentially, and as such penetrations were deliberately made in an investigation of the somatic sensory cortex of the monkey (Powell & Mountcastle 1959) it is of interest to compare the findings in these two sensory areas. One of the unexpected and puzzling observations in the study of the somatic sensory area was that

as the electrode passed tangentially for long distances through the cortex of area 3 in the posterior wall of the central sulcus no changes in submodality properties were observed often for distances as great as 1–2 mm. In these blocks of cortex the receptive fields of the neurons did not move progressively and 'were confined well to the same peripheral region. Occasionally however the peripheral field shifted suddenly from the volar to the dorsal surface of the wrist.' It was concluded that 'the important observation is, we believe, that the peripheral location of the field of the successive neurons encountered is more or less constant, they do not gradually shift. This indicates that the electrode in such a traverse is passing across a considerable volume of tissue devoted to cutaneous receptors of a local part of the body.' In view of the recent observations and interpretations in the visual cortex of hypercolumns and of the dimensions of cortex capable of analyzing the visual field to which it is related, it would appear reasonable to suggest that the blocks of cortex 1–2 mm in width in area 3 of the somatic sensory area are very comparable regions for the analysis of the part of the surface of the body to which they are related, particularly as the site of the receptive fields in the skin of the constituent neurons was so close and overlapping. It would be of interest now to study the extent of the intrinsic connections in this sensory area.

Hubel & Wiesel (1972) have suggested that simple, monocular cells of layer IV project to complex, binocular cells in more superficial and deep layers of the cortex. This would involve some degree of an oblique lateral projection from cells in one monocular column to those in the adjoining column. It has already been mentioned that the present experiments provided little direct evidence bearing on this question, but of the several possible patterns of connections a few may be worth discussing. Some of the degenerating fibres which have been seen passing obliquely upwards into the stria from a lesion in layer IV may be serving this function as they could synapse upon the basal dendrites of cells in the more superficial layers which are binocular and complex. Another possibility is that cells in layer IV project directly to layer II and more superficial parts of layer III either as axons which terminate there or as collateral branches of fibres ascending to layer I. The fibre degeneration found in layers V and VI after damage of the deep part of layer III and of layer IV provides a basis for the binocularity of the cells in these deep layers. The observation that degenerating fibres which pass vertically up or down for any distance from a small lesion in the cortex were confined to a narrow band is in accord with the physiological finding that the cells lying vertically above or below a part of layer IV which is related to one eye also respond more favourably to that eye (Hubel & Wiesel 1968).

On the available evidence however it is quite possible for binocular cells to be contacted directly by geniculocortical afferent fibres – on to the apical dendrites and side branches of cells in layers V and VI as they pass through layers IV and the deep part of layer III, on to the basal dendrites of cells in layer III and on to the peripheral branches of apical dendrites in layer I. For activation by fibres from layers of the lateral geniculate nucleus related to both eyes the dendrites of these cells need to extend horizontally no more than 200 μm in the deep part of layer III and in layer IV in order to extend into two adjoining monocular columns, and the finding that most binocular cells are influenced predominantly by one eye would suggest that their major connections are within one monocular column.

The severe fibre degeneration in the stria of Gennari which results from damage of the stria itself or of layers IV, V and VI extends for about twice as far as the moderate degeneration in the other layers. This greater extent of the degeneration has no apparent functional correlation at present as the monocular columns in layer IV are only 300 μm wide and fibre connec-

tions between them would not require projections of up to 3.0–3.5 mm from any point. It is possible that such longer connections could serve some other integrative function, such as linking up distant columns with the same preference for stimulus orientation, for stimulus type (slit, edge or dark bar) or for degree of symmetry of response to stimulus movement. The greater length of the connection in the stria may also reflect the dimensions of a further hierarchical functional column or may provide the basis for interaction between adjoining slabs of cortex which are able to 'analyse the region of the visual field it subserves' (Hubel & Wiesel 1974*b*), the dimensions of the degeneration in the stria being approximately twice that of these slabs. Perhaps a clue is provided by the distribution of the terminal degeneration associated with these fibres, which is confined to the stria and to the immediately adjoining part of layer IIIb and the superficial part of IV, and the suggestion of its aggregation in patches of widths corresponding to the monocular columns. Many of the cells in these layers are simple and monocular, and the thalamic fibres which end in the superficial part of layer IV arise in the ventral magnocellular layers of the lateral geniculate nucleus and those which end in layer IIIb come from the small celled layers (Hubel & Wiesel 1972). Thus the laminar distribution of the terminal degeneration of the strial fibres together with the probable origin of some of them at least in layer IV make it possible that they are connecting cells which are activated respectively by fibres from the small and large celled laminae of the lateral geniculate nucleus, and the patchy distribution would indicate that they are linking simple monocular columns related to one or other eye. Thus the monocular columns in layers IIIb and IV (up to 10–12 over the total width of 5–6 mm) could be interconnected not by fibres passing within layer IV, the major site of termination of thalamic afferents, but through the stria which is largely devoid of thalamic terminals. This interpretation would be in accord with the marked development of the stria in primates, in which the large and small cells of the lateral geniculate nucleus have become segregated into quite separate and distinct layers, and also with the clear development of six layers in the geniculate. This tentative interpretation of the functional significance of the stria of Gennari raises another point about the projection of the large and small celled layers of the geniculate upon the cortex. The number of cells in the large-celled layers is much less than those in the small-celled layers. After a large lesion of the visual cortex in the monkey the large cells undergo retrograde degeneration more slowly and less severely than the small cells (Walker 1938). Following a small lesion of a few mm in extent in area 17 there is a narrow *wedge* of retrograde cellular degeneration in the lateral geniculate nucleus with the apex in layer I, indicating that fewer cells in the magnocellular layers are projecting to the damaged area than in the more dorsally situated small-celled layers. The most likely explanation of these three observations is that a fibre from a cell in the magnocellular layer terminates, through branching, in a larger area of cortex than one from a small cell. A cell or group of cells in the small-celled layers would project to fewer monocular columns in a smaller area of layer IV than would a cell or group of cells in the magnocellular layer. On this hypothesis it would be understandable for a monocular column whose afferent fibres were from small cells to be linked with a larger number of monocular columns related to large cells. The evidence presented by Hubel & Wiesel (1972) of the extent of the fibre degeneration in area 17 after small lesions of the different layers of the lateral geniculate nucleus does not apparently support this idea, as they did not find appreciably larger areas of degeneration after small lesions of the magnocellular layers as compared with ones of small celled layers. As the lesions were in different parts of the foveal representation in the geniculate, however, these findings cannot be

considered as evidence against the hypothesis and it would be of interest to compare the areas of degeneration after lesions of similar size in those parts of the large and small celled layers which are in register with respect to the foveal representation. It may be significant that the pattern of the bands of degeneration after lesions of the large and small celled layers were different in that those due to damage of the large cells were narrower, more irregular, less parallel and 'the tendency for interlacing and cross links was very marked, and was seen in both the areas of degeneration and in the spaces between'. Whether or not these interpretations of the main fibre component of the stria are correct, it would appear that the stria is a concentrated band of fibres which is closely related to the cells receiving the afferent fibres from the thalamus and that it may be considered as one of the first intracortical connections underlying the processing of information. There are clearly no fibre connections passing horizontally between monocular columns within layer IV itself. If the stria can be thought of as a horizontal intrinsic pathway closely related to the *input* of the cortex, it is reasonable to suggest that the inner band of Baillarger in layer V is similarly related to the major *output* from the cortex: it is situated in the deep layers from which most efferent fibres (particularly subcortical) arise (Le Gros Clark 1942; Spatz *et al.* 1970; Holländer 1974), and there is a dense projection into it from the supragranular layers (Spatz *et al.* 1970; Nauta *et al.* 1973; Martinez-Millán & Holländer 1975). If the suggestion made earlier about the origin of these fibres from the supragranular layers being diffuse is correct, this is in one way the reverse of the position in the stria, in that it would represent a *convergence* from the supragranular layers to layer V, whereas from a focal lesion in layer IV there is *divergence* over 5–6 mm of degeneration in the stria.

It is difficult at present to make useful functional correlations of the electron microscopic observations for a number of reasons: the suggestion that asymmetrical and symmetrical terminals may be respectively excitatory and inhibitory is not generally accepted as being sufficiently established to allow predictions of function in regions where the physiology is not known; the relative importance of the effect of synapses upon spines, dendrites, soma and initial segments is not clear, and finally neither the cell types of origin of the degenerating fibres, nor the cell types bearing the different postsynaptic profiles, could be identified. Whatever the functional significance ultimately proves to be, however, certain of the electron microscopic findings will have to be taken into account. Axon terminals with symmetrical synapses, although forming a small proportion, were regularly found to be degenerate in this material after intrinsic lesions of the cortex, and they have never been seen to degenerate after interruption of any afferent pathway to the cortex (see also Jones & Powell 1970). One such degenerating terminal was present upon an initial segment, and as far as we are aware this is the only description of degeneration at this site on a neuron. Although degeneration of the asymmetrical terminals was always more numerous at any distance from the lesion, the degenerating symmetrical terminals appeared to diminish more gradually than the asymmetrical, which fell off suddenly and rapidly after 1 mm. Like the distribution of degenerating terminals after section of the extrinsic fibre pathways to the cortex, the vast majority of the terminals formed synapses upon dendritic spines, but there was a clear complementarity in the profiles which received the asymmetrical and symmetrical terminals.

The present observations are mainly in terms of the laminae of the cortex and because there is more than one type of neuron, as impregnated with the Golgi method, in most layers, it is almost certain that several different types were destroyed by the lesions made in these experiments. For this reason it is not possible to make detailed correlations with descriptions of Golgi-

impregnated material (Cajal 1911; Valverde 1971; Szentágothai 1973; Lund 1973; Lund & Boothe 1975) but several of the observations made in such material are in accord with a number of the present experimental findings: axons of stellate cells in layer IV have been seen ascending into layer III, recurrent axon collaterals of pyramidal neurons in layers V and VI reach up to layers II and III, axons from layers III and IV pass to or through layer V and may give off branches which run horizontally in that layer, and fibres of up to 1500 μm in length have been found in the stria. What is needed now is more detailed studies with the combined use of methods for labelling cells on the one hand, together with the use of the electron microscope and of experimental material in which fibre pathways have been interrupted on the other.

Commissural fibre connections

With the light microscope the distribution of the commissural fibres in the cat and monkey was found to be restricted to narrow bands in accord with previous descriptions (see, for example, Garey *et al.* 1968; Zeki 1970). In the monkey degeneration at the boundary of areas 17 and 18 was clearly confined to the region of the group of conspicuous large pyramidal cells in layer III. There is experimental evidence for these cells being the origin of the commissural fibres (Glickstein & Whitteridge 1974; Wong-Riley 1974; Winfield, Gatter & Powell 1975) so it would appear that as in the somatic sensory area (Jones & Powell 1969*b*) such fibres end in regions which also give rise to them. Secondly, careful examination of the degeneration showed that in area 18 it was distributed throughout all layers of the cortex, but in area 17 fragmentation rapidly disappeared in lamina IV and became progressively more restricted to the more superficial and deeper aspects of the cortex. This difference in laminar distribution on either side of the boundary of areas 17 and 18 was confirmed with the electron microscope and it is of significance for two reasons. First, it is probably the explanation for previous discrepancies between the descriptions of degeneration of commissural fibres involving layer IV or not, as differences of less than a millimetre or so in the precise situation of the sections examined would result in layer IV being either affected or clear. Secondly, it also indicates that not only is area 17 as a whole free of commissural fibres, but that even in the narrow part of area 17 at the boundary region which receives commissural fibres lamina IV is devoid of these connections. With the electron microscope the commissural fibres were found to terminate with asymmetrical terminals and predominantly upon dendritic spines, as in the visual cortex of the rat (Lund & Lund 1970) and cat (Szentágothai 1973) and in other functional areas (Jones & Powell 1970; Sloper 1973 *b*).

Association fibre connections

In the cat the fibres from area 18 passing into area 17 were found to end only in the lateral part of area 17 and this is in agreement with earlier work (Garey *et al.* 1968) and again layer IV was essentially clear. These fibres also terminate, as did all the other afferent pathways, in terminals with asymmetric synapses and although the majority ended on spines a large proportion (30 %) ended on dendrites.

Perhaps the major point of these studies of the commissural and association pathways is that they show not only that most of area 17 is in receipt of *thalamic afferents only*, which on the available evidence makes it unique, but that layer IV is left *completely* free of all but geniculo-cortical connections. Except for approximately 200 μm on each side of a given point, in which numerous intrinsic connections end, this layer appears to receive further connections only from adjoining regions of up to a few millimetres through the stria and from layers more superficial and deep

vertically above or below it. Layer IV of area 17 thus appears to be left clear for afferent connections purely from the lateral geniculate nucleus and, in the monocular bands, from layers related to one eye – an anatomical finding which is in close accord with the physiological observations.

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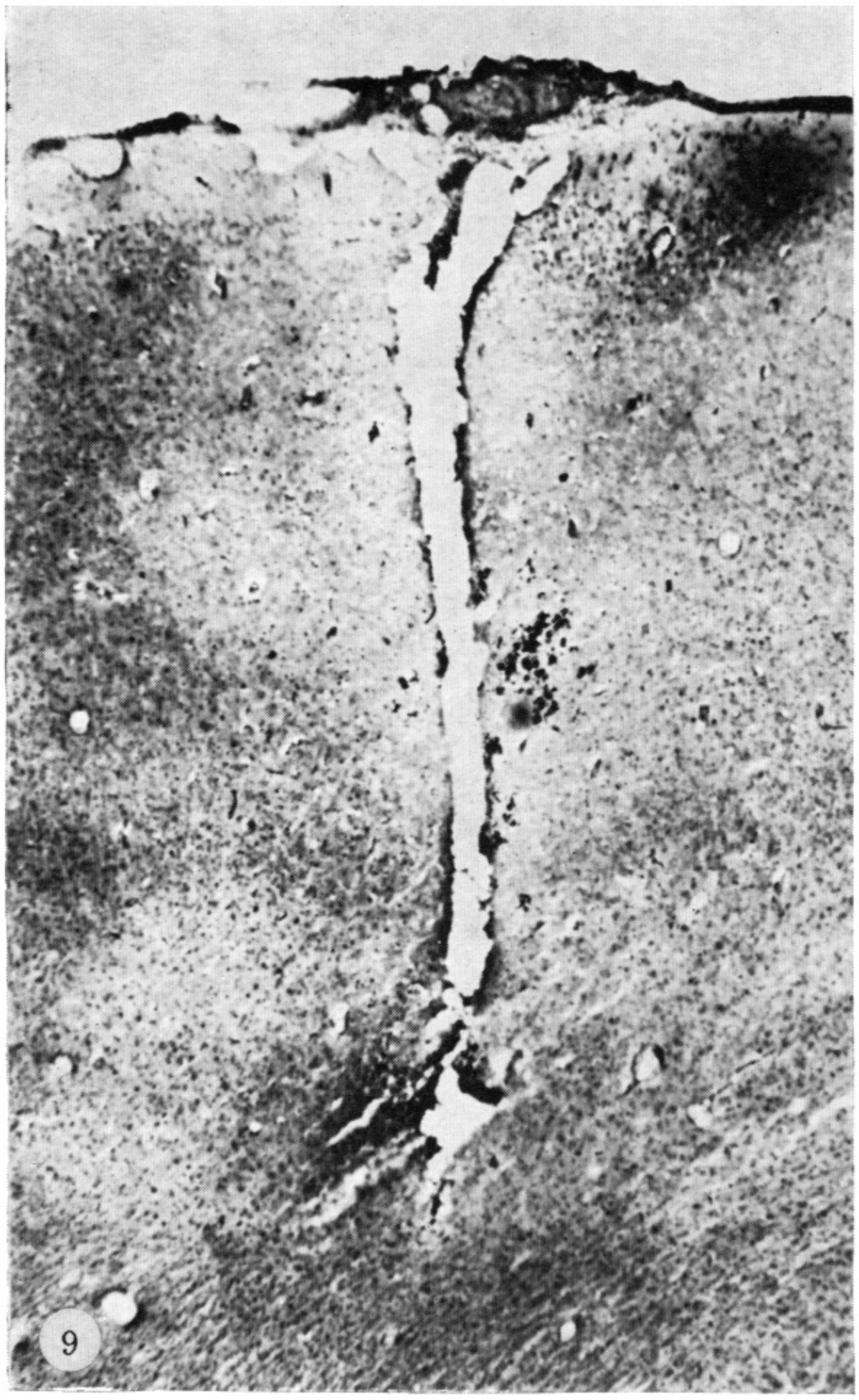
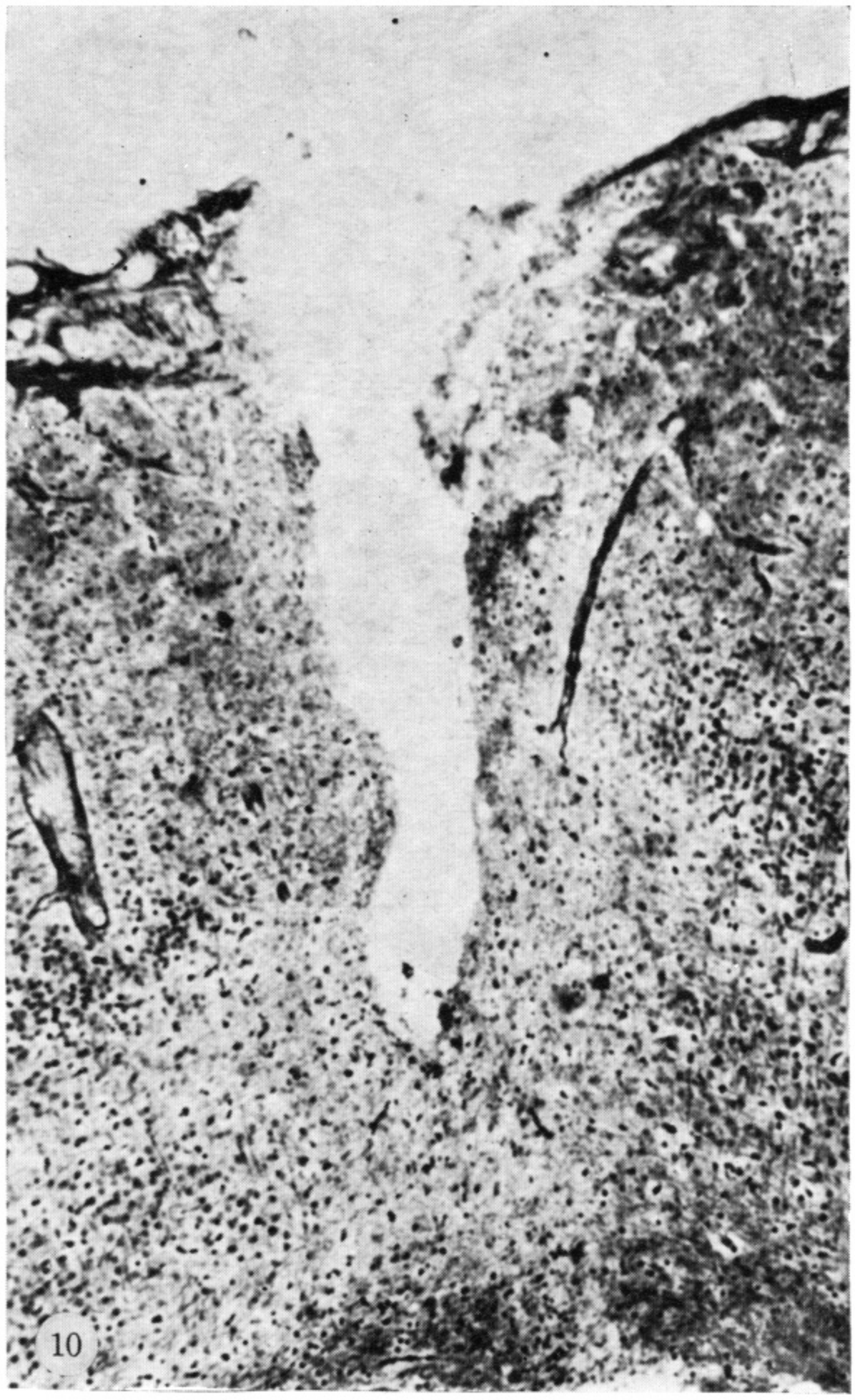
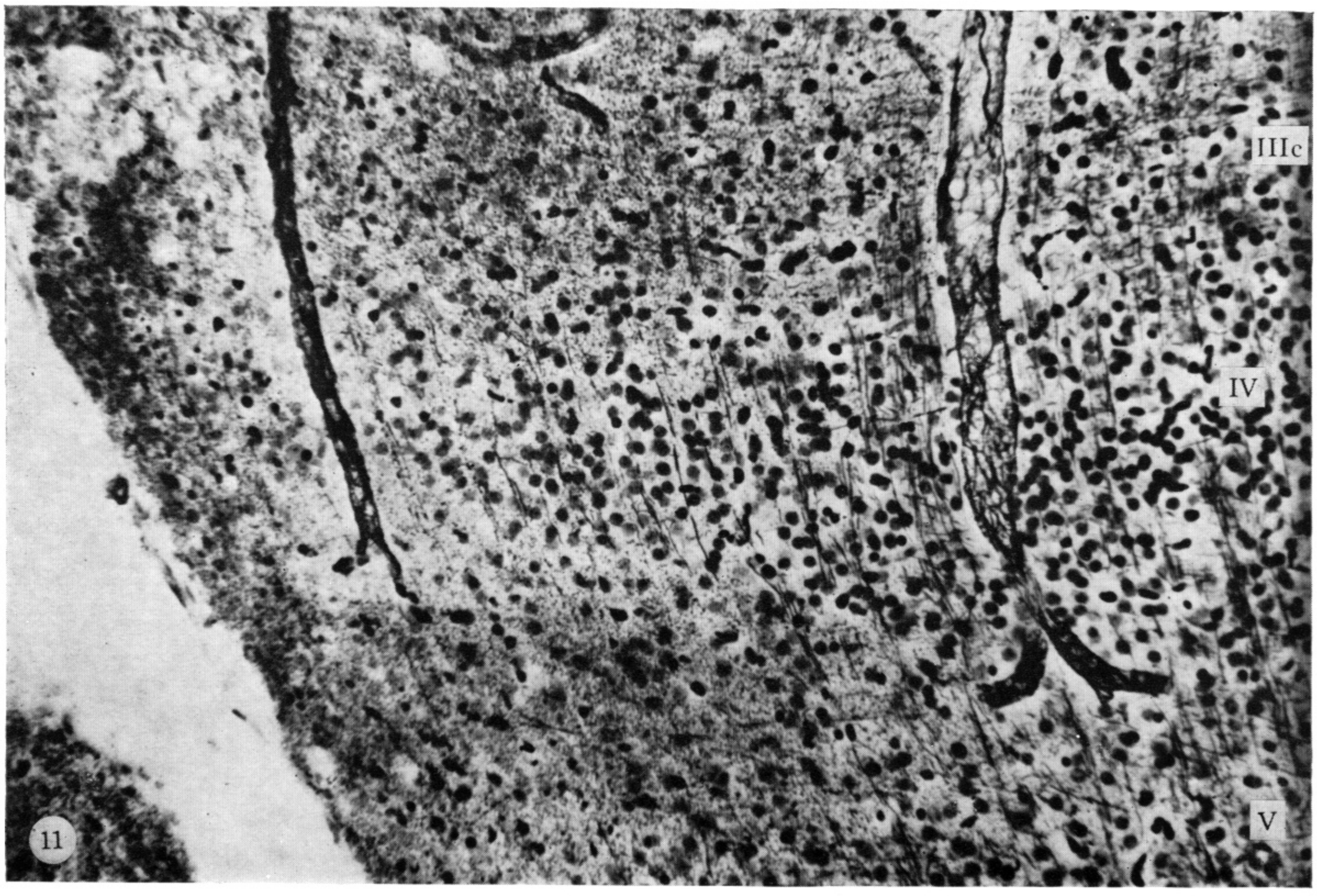
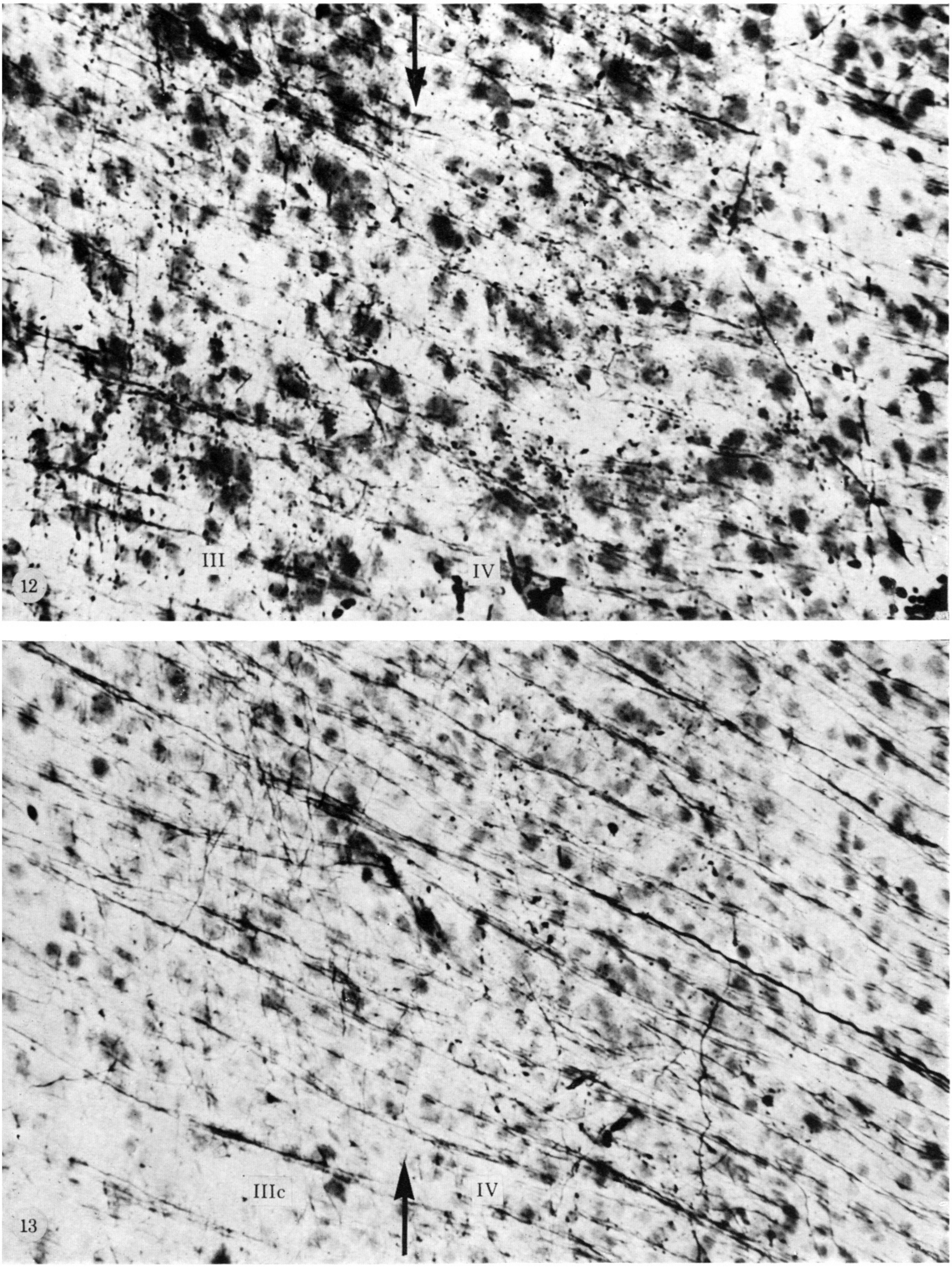


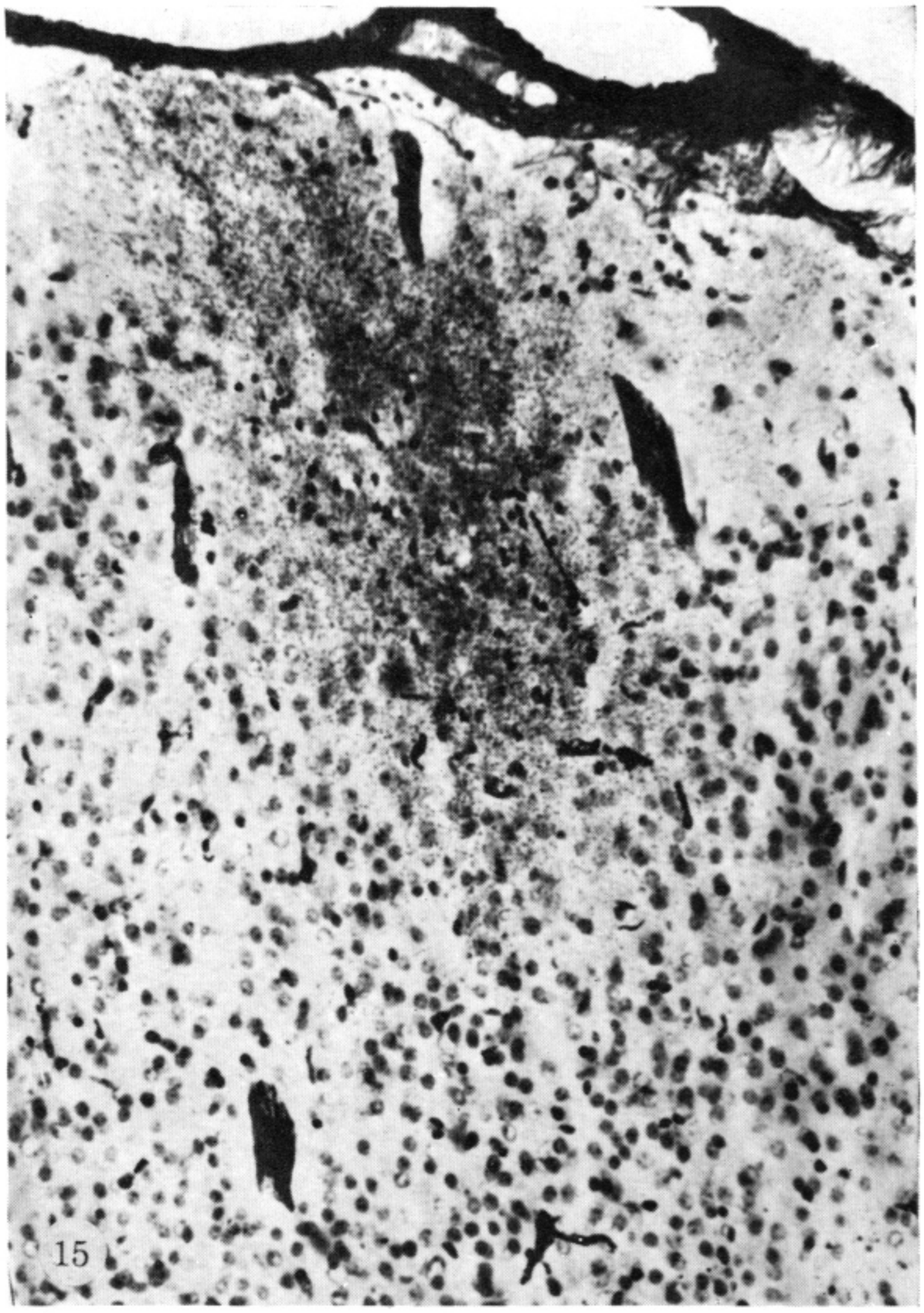


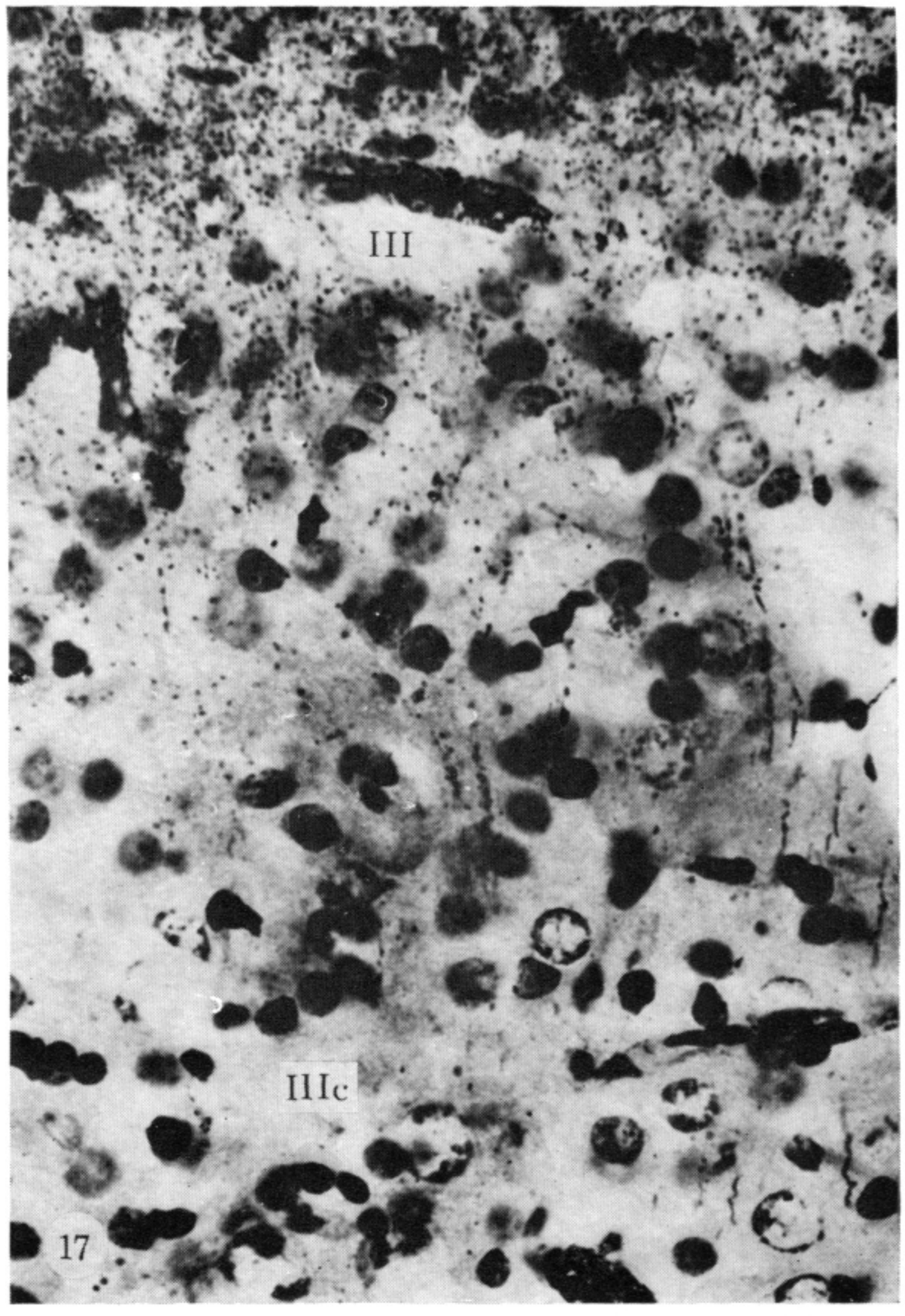


FIGURES 9–11. For description see opposite.

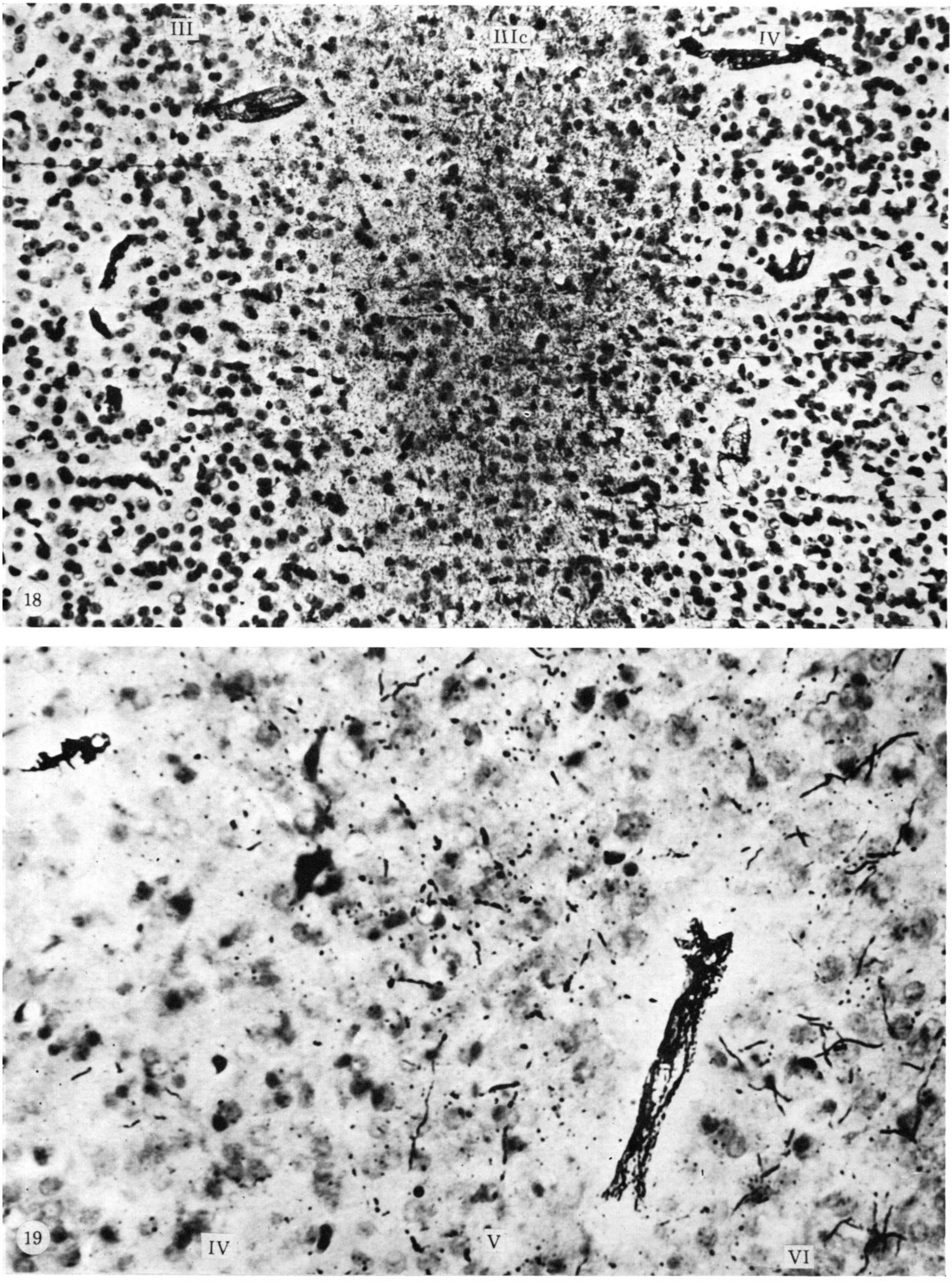


FIGURES 12 AND 13. For description see opposite.

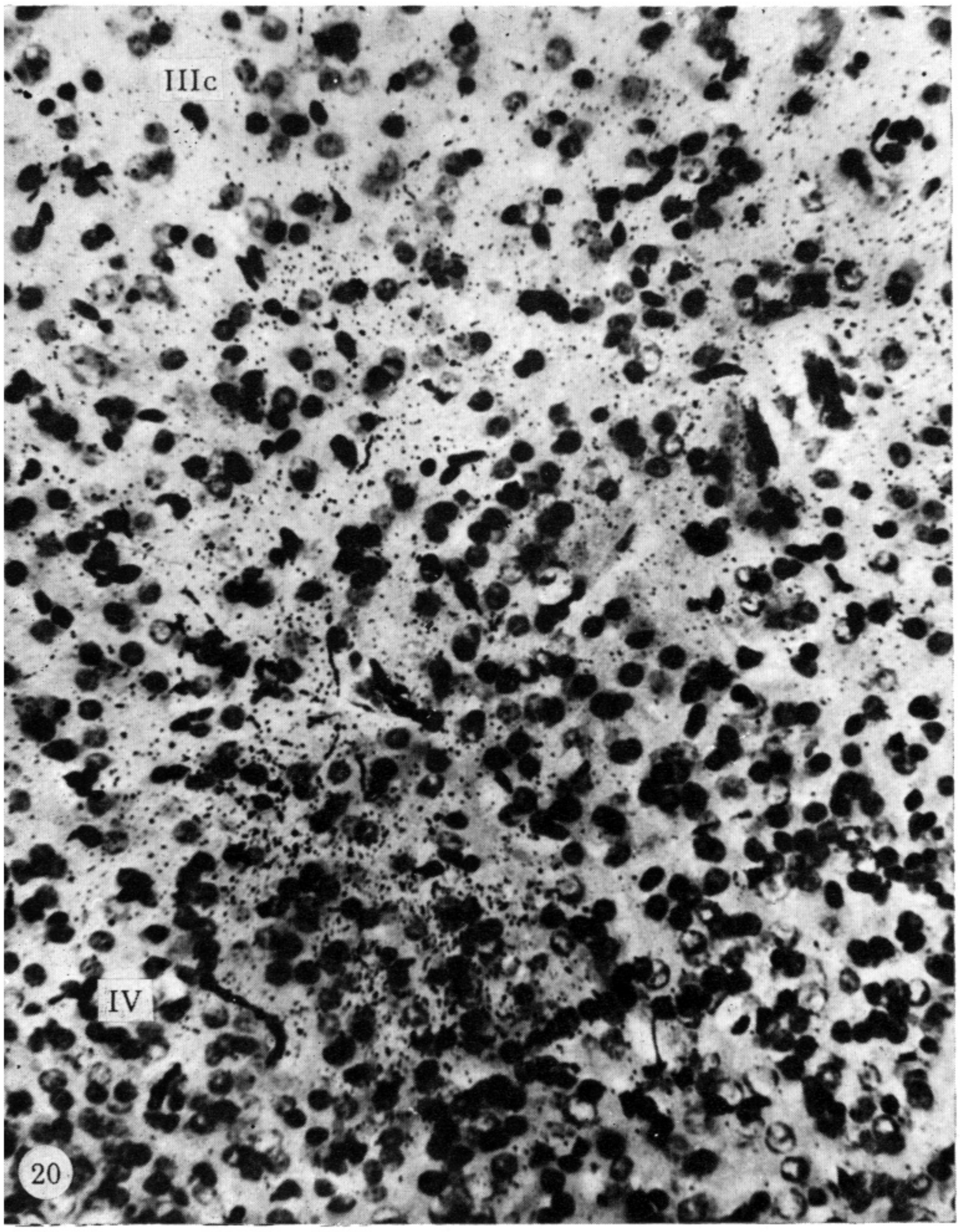


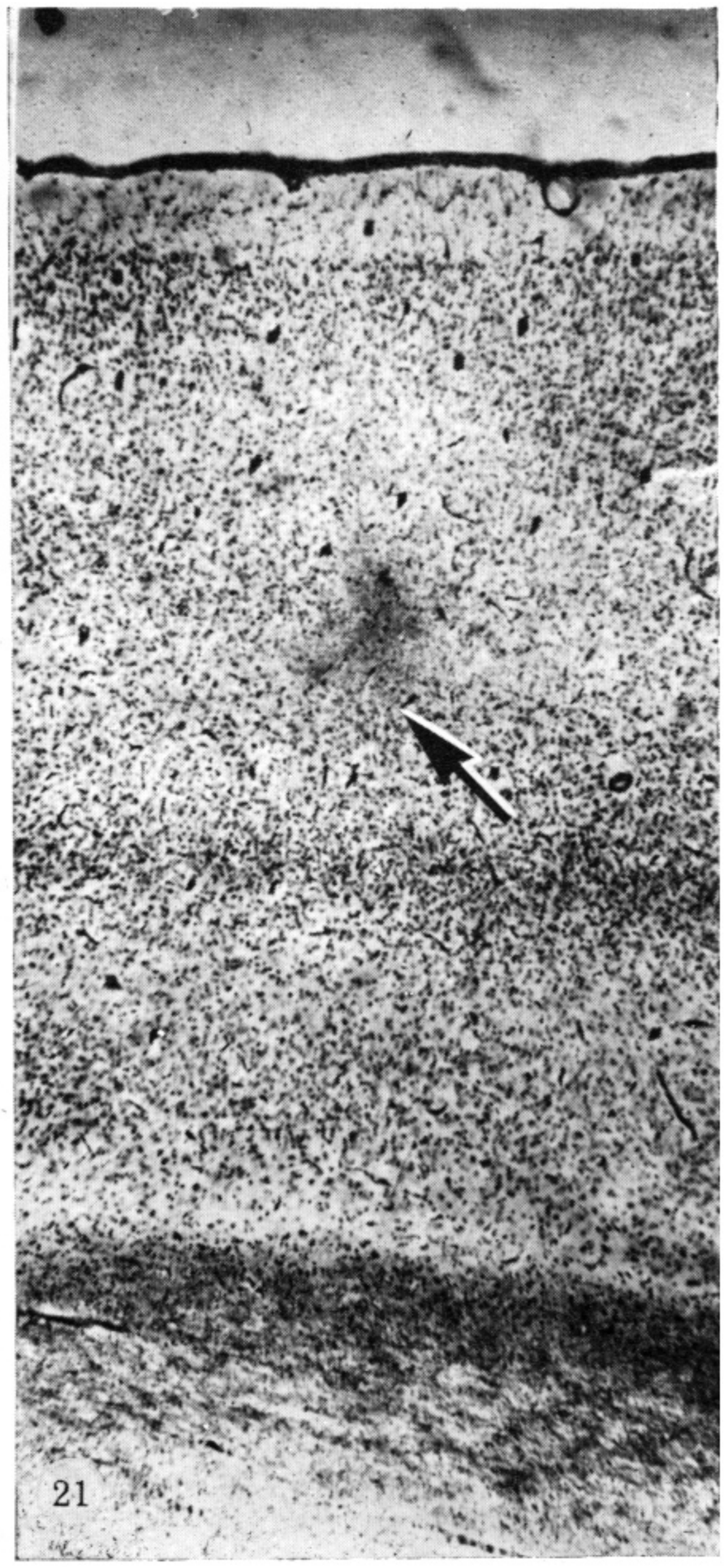


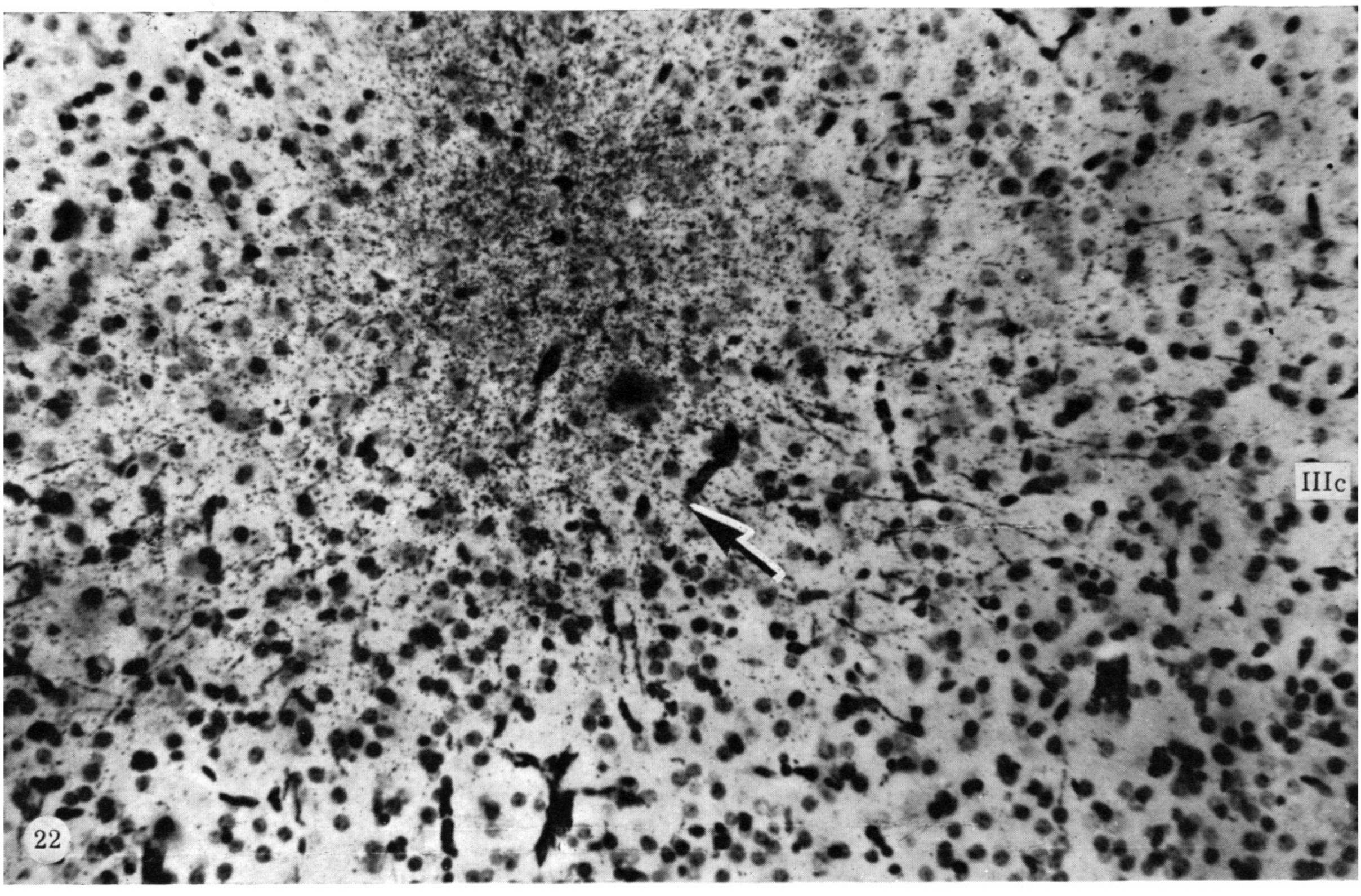
FIGURES 14–17. For description see opposite.



FIGURES 18 AND 19. For description see opposite.







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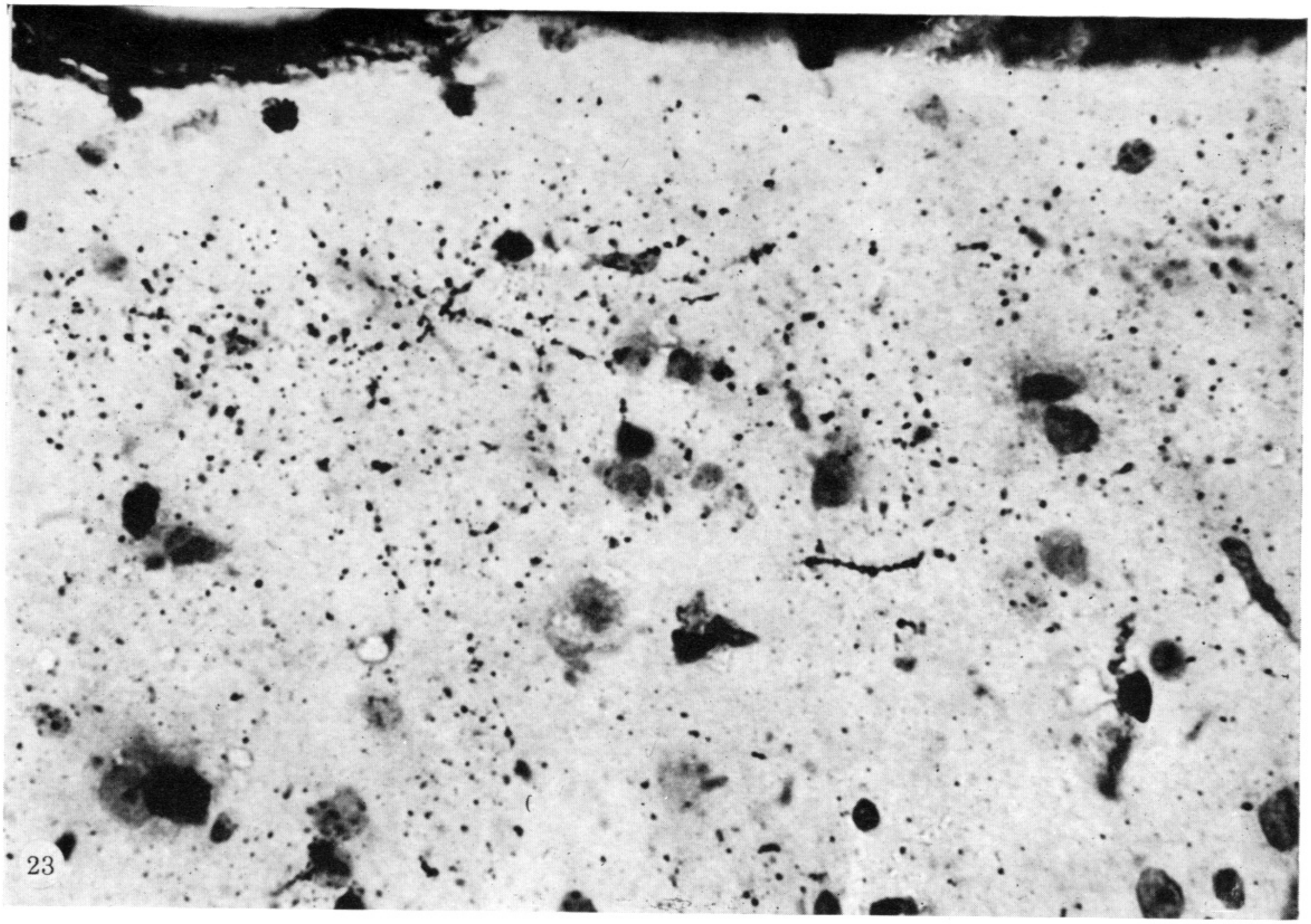
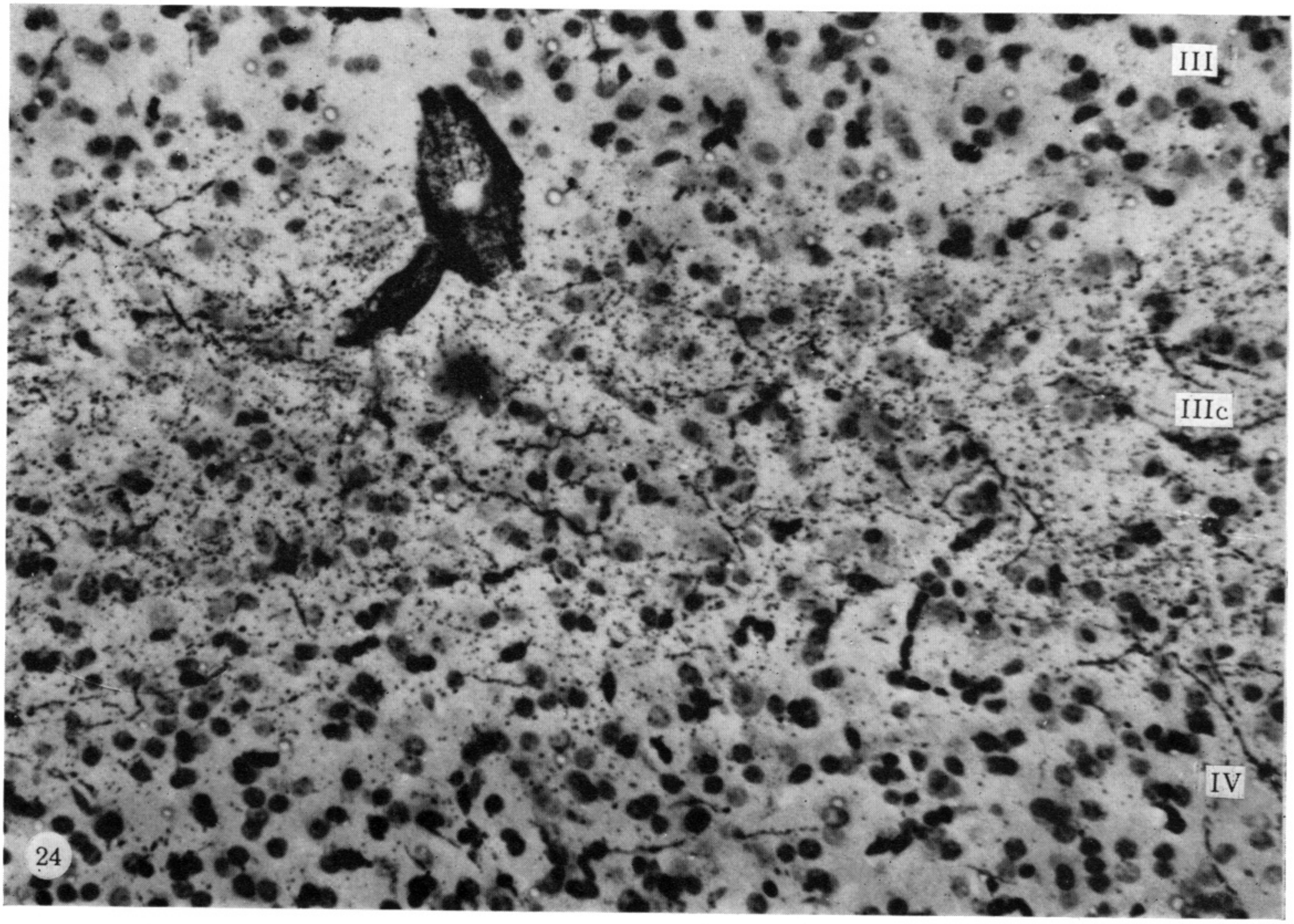
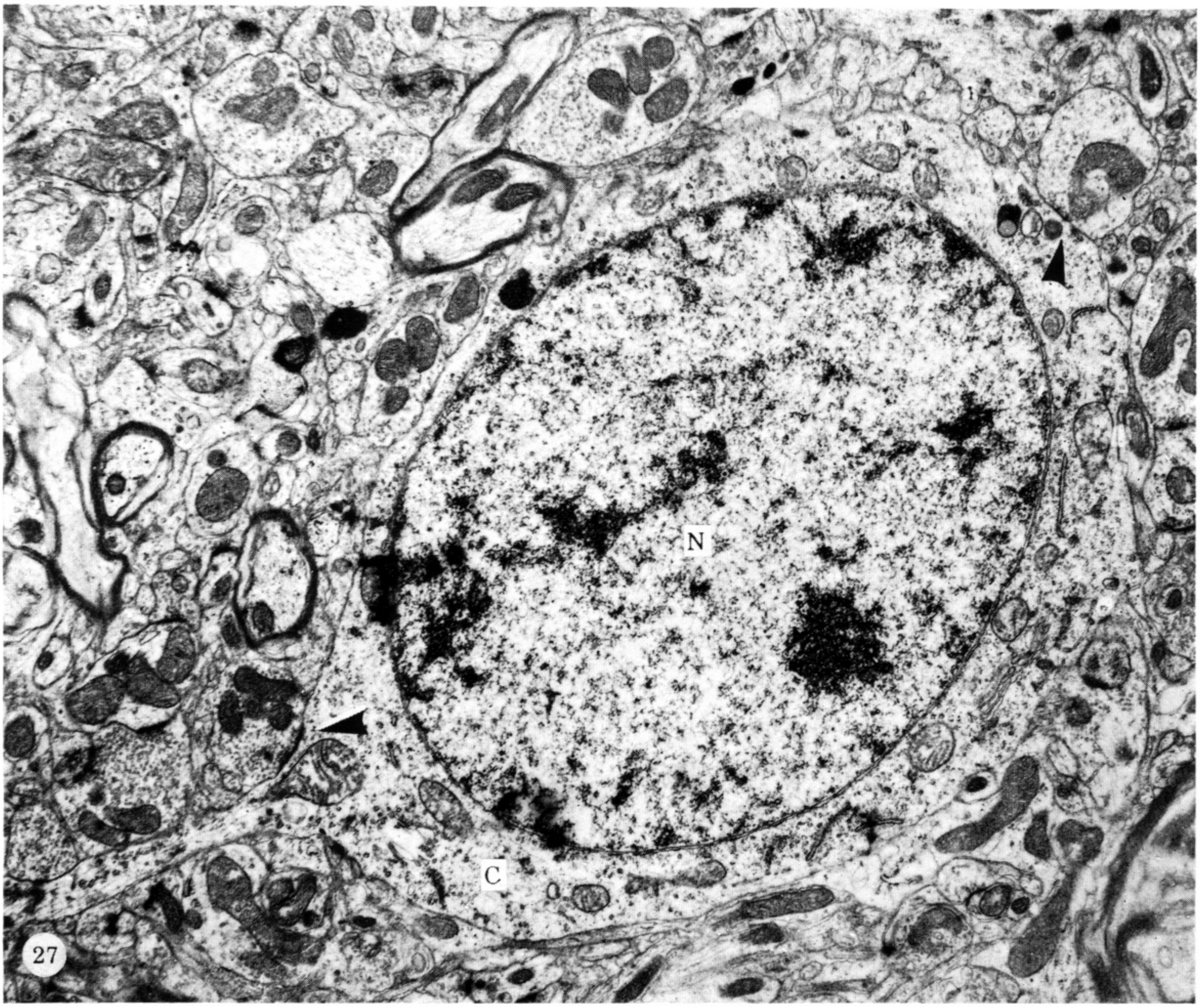
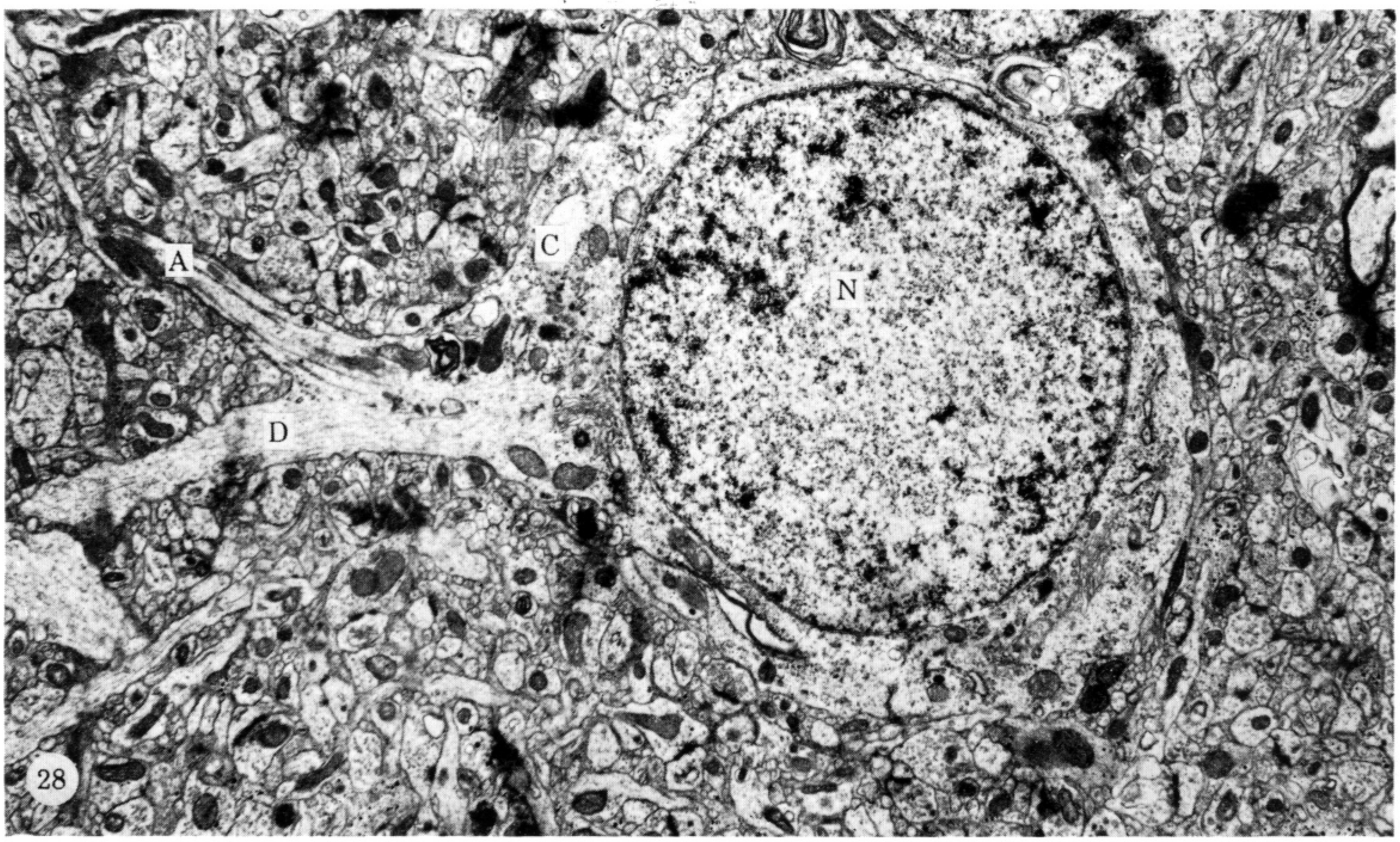


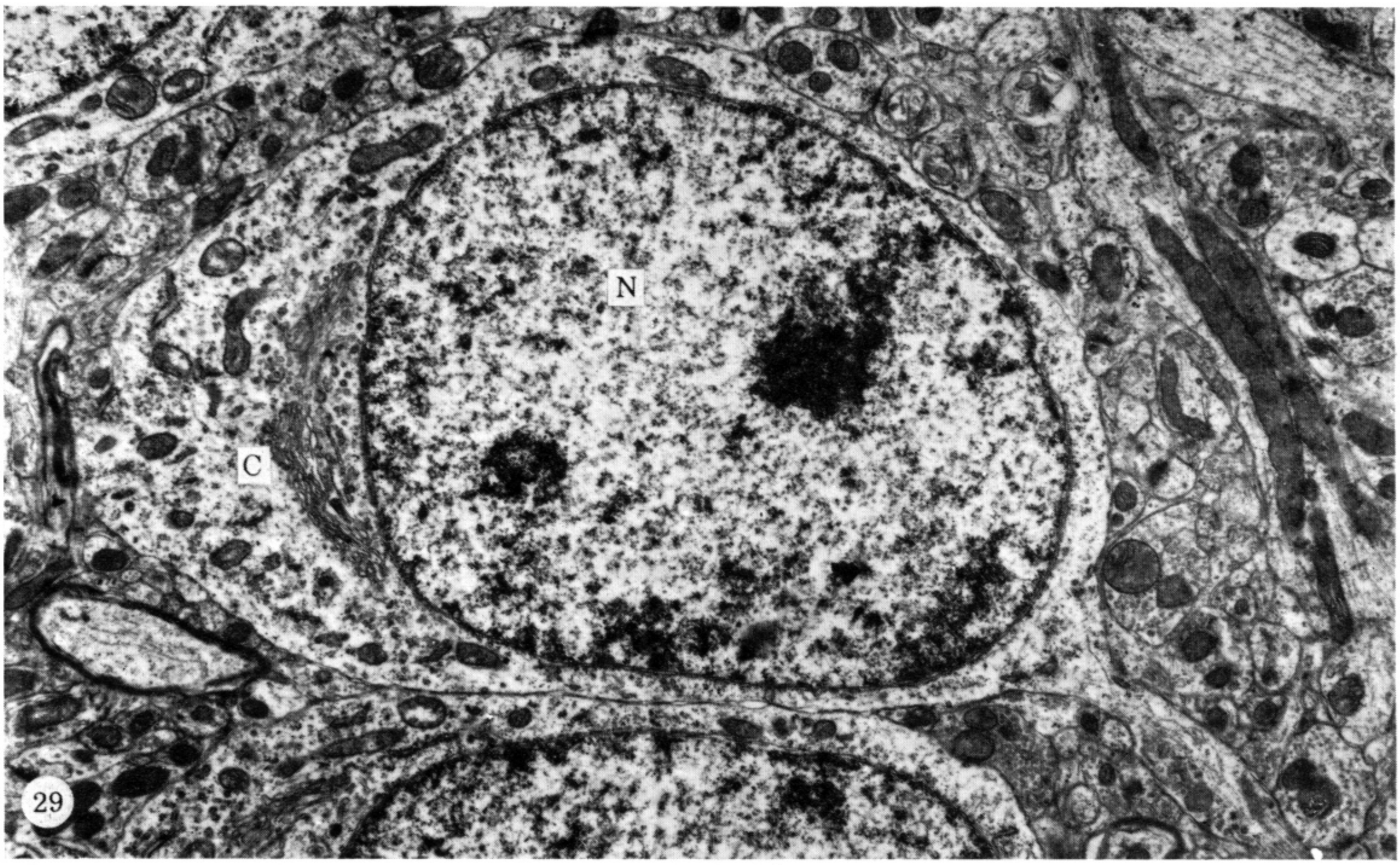


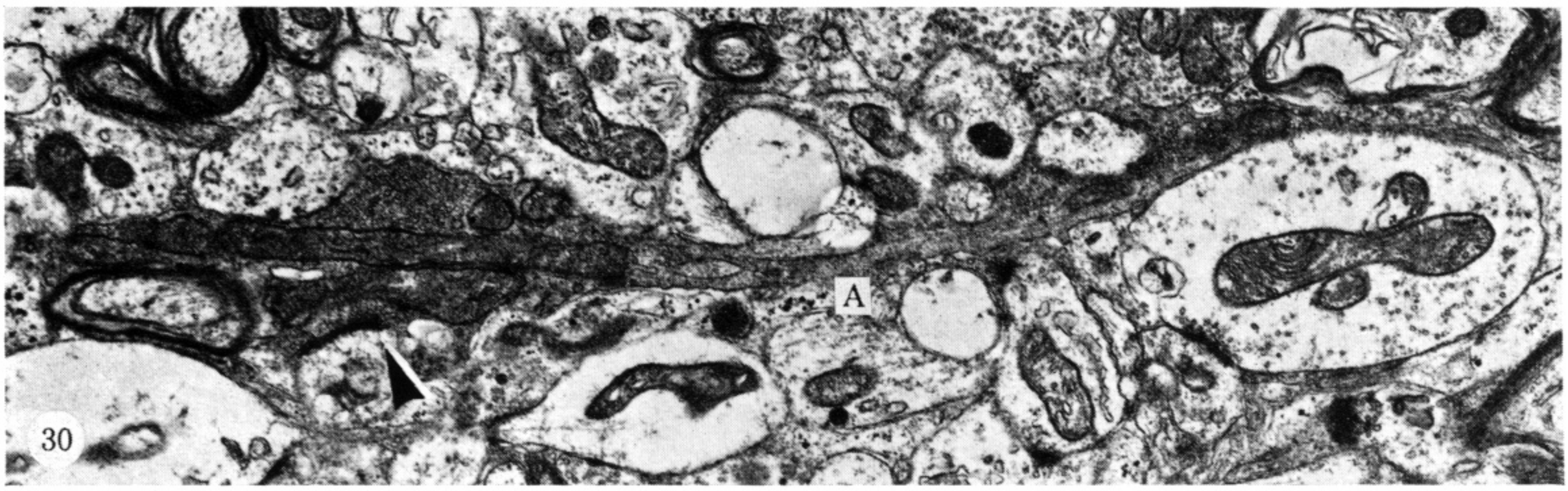
FIGURES 23 AND 24. For description see opposite.

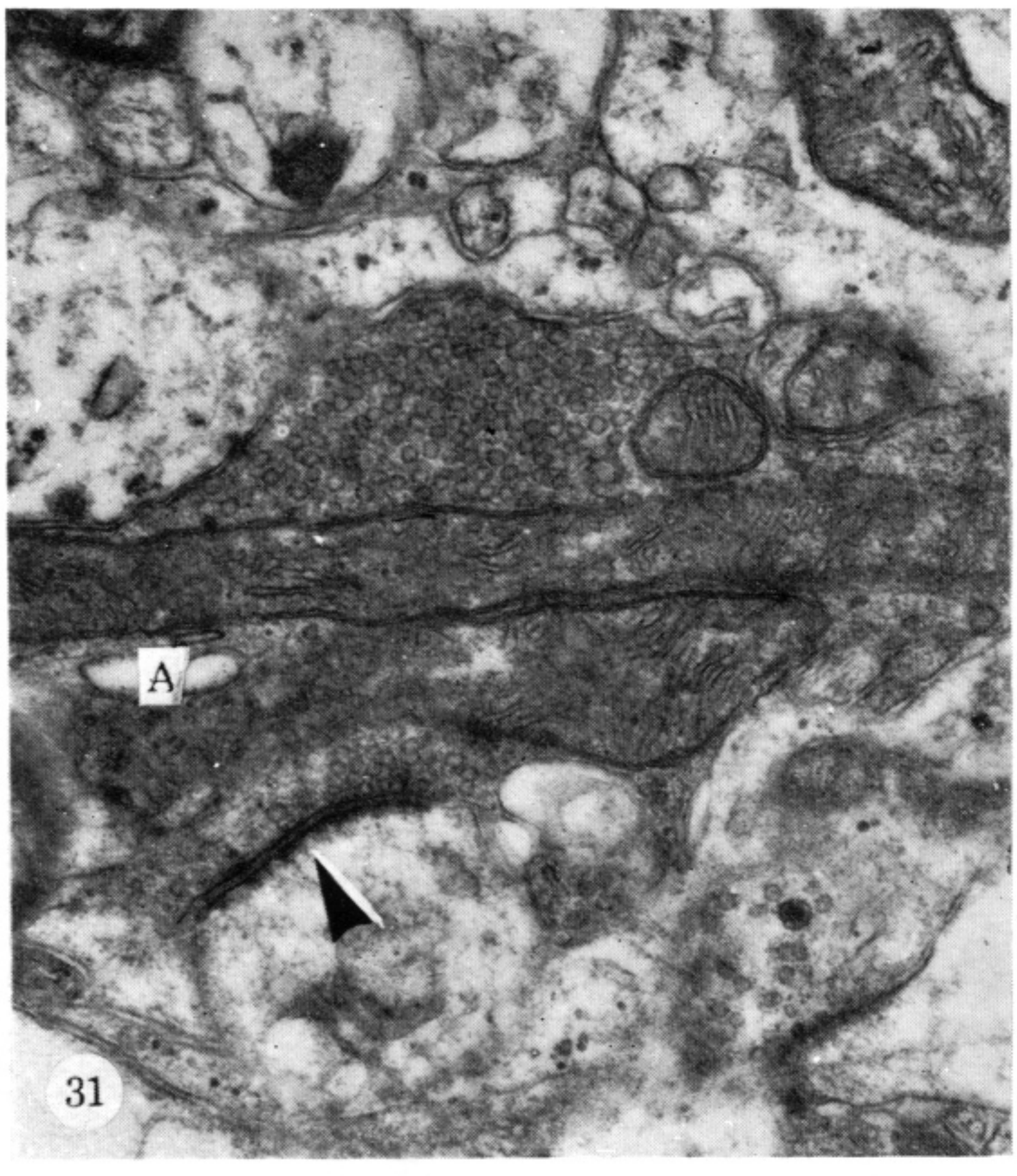


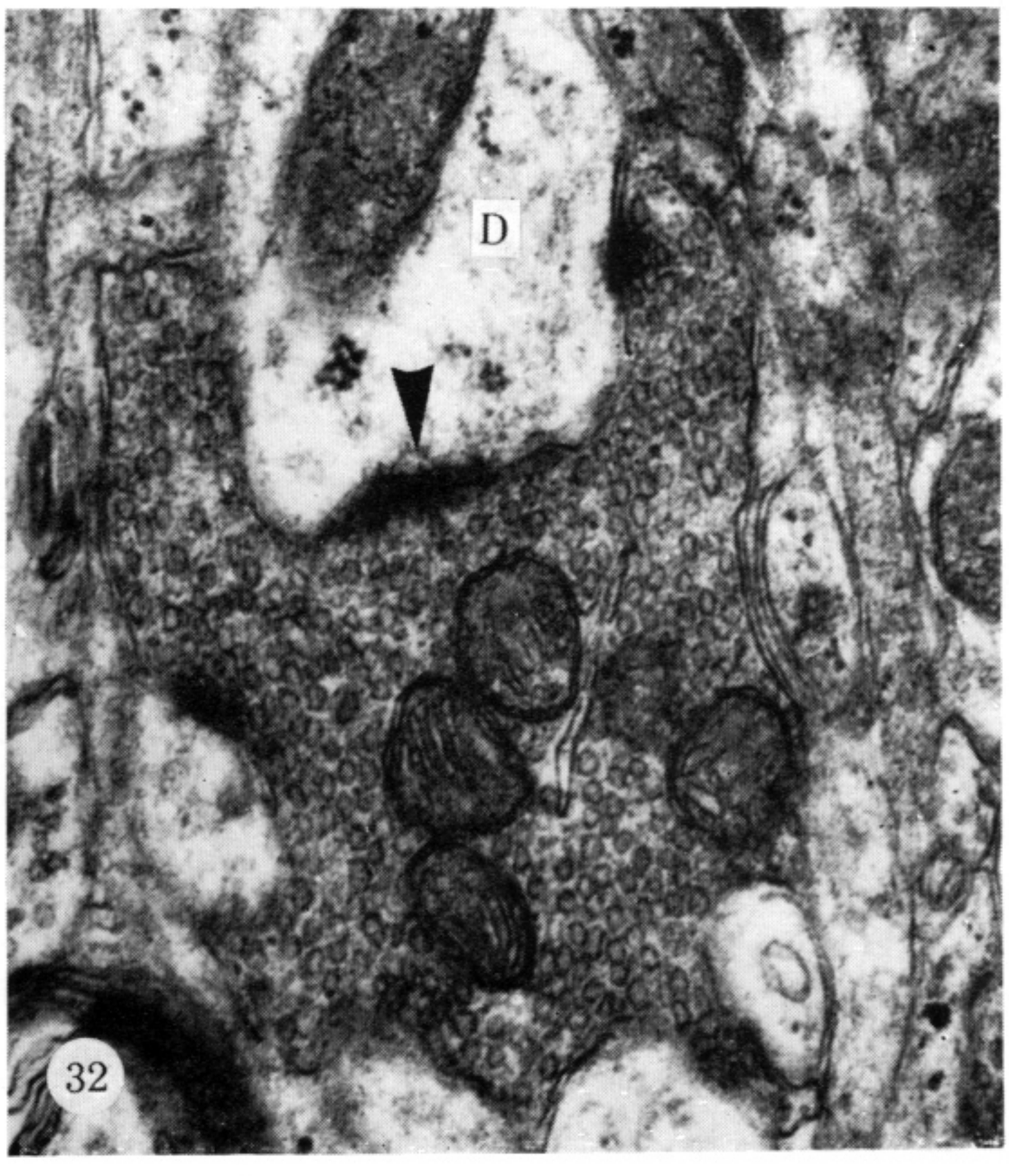


FIGURES 27 AND 28. For description see opposite.









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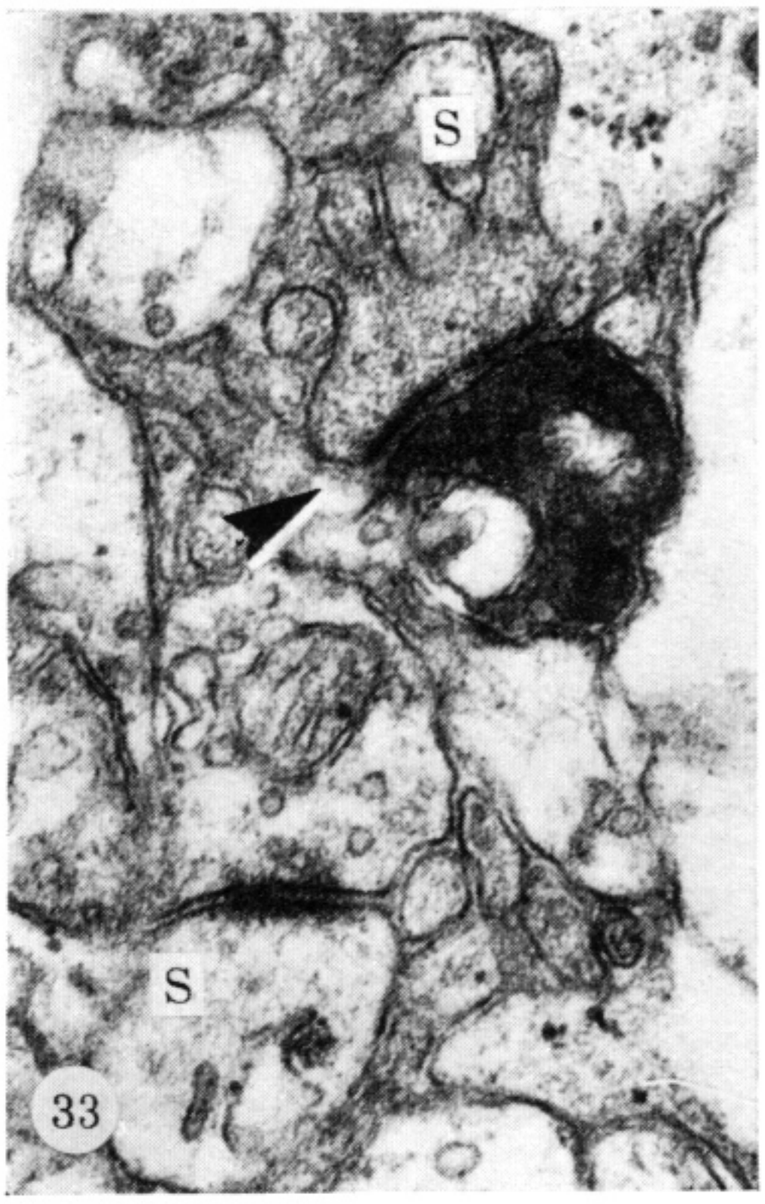
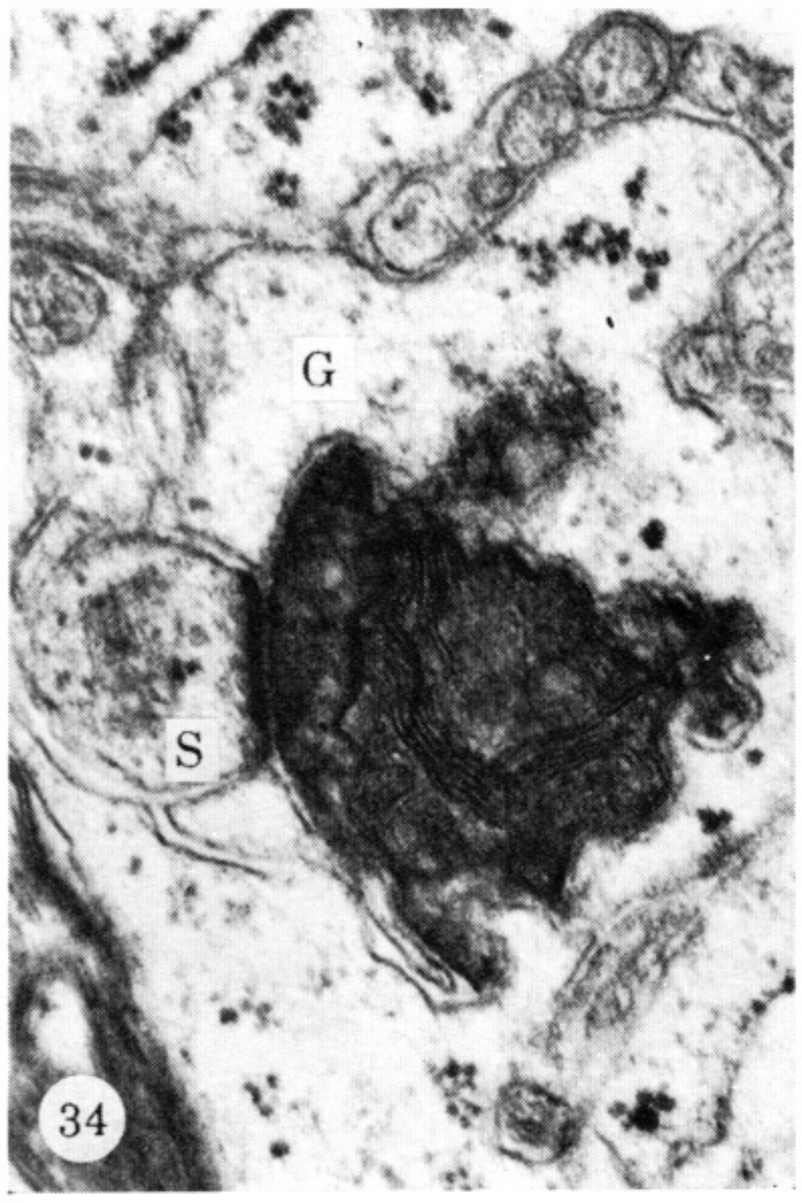
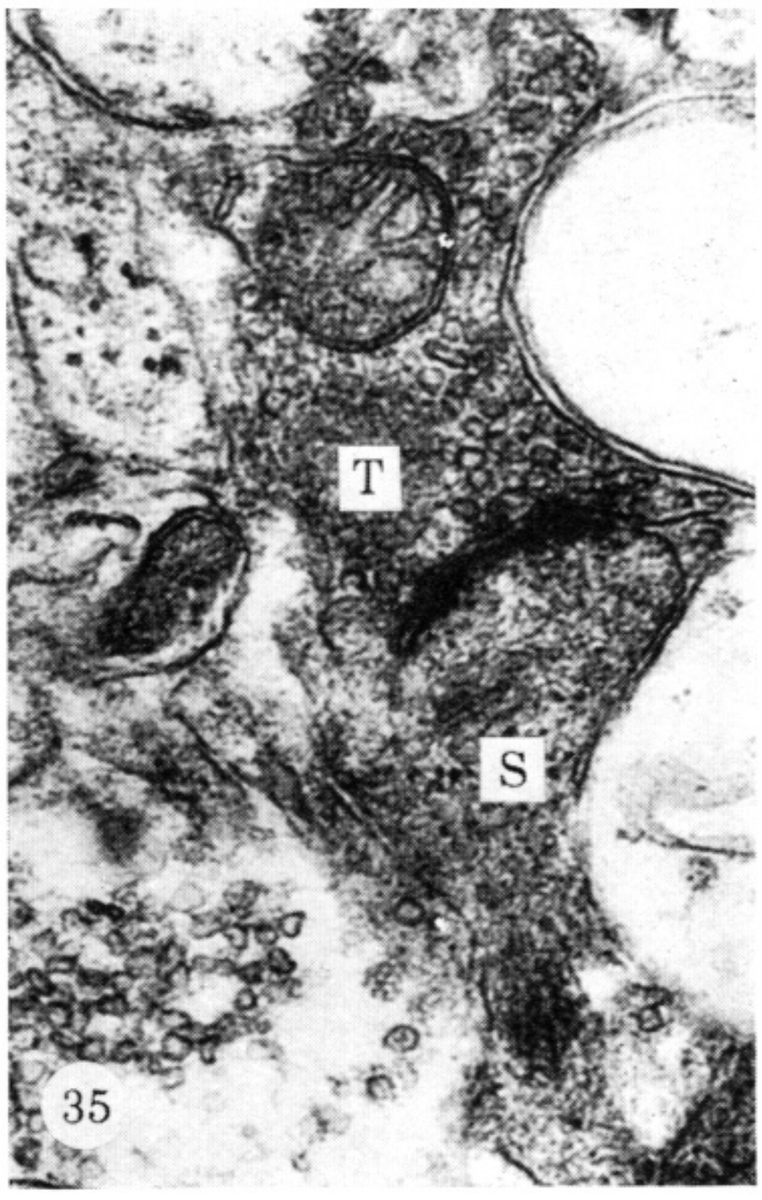
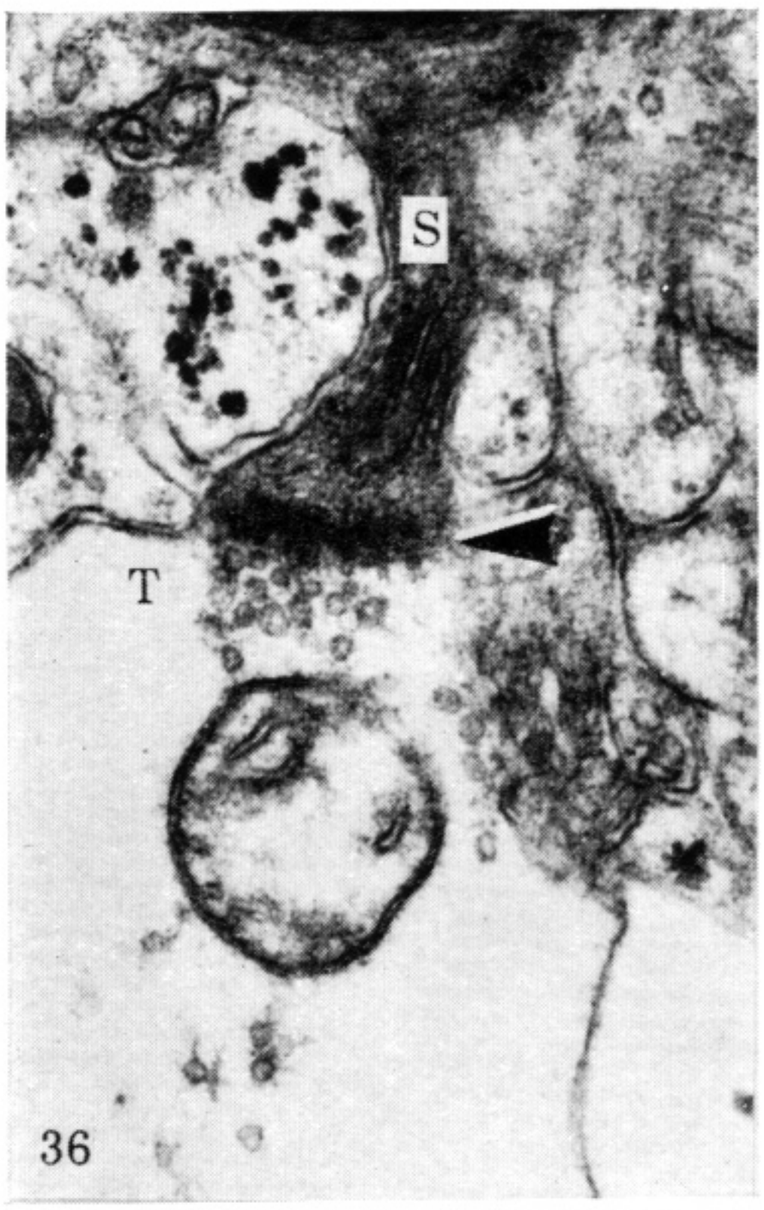
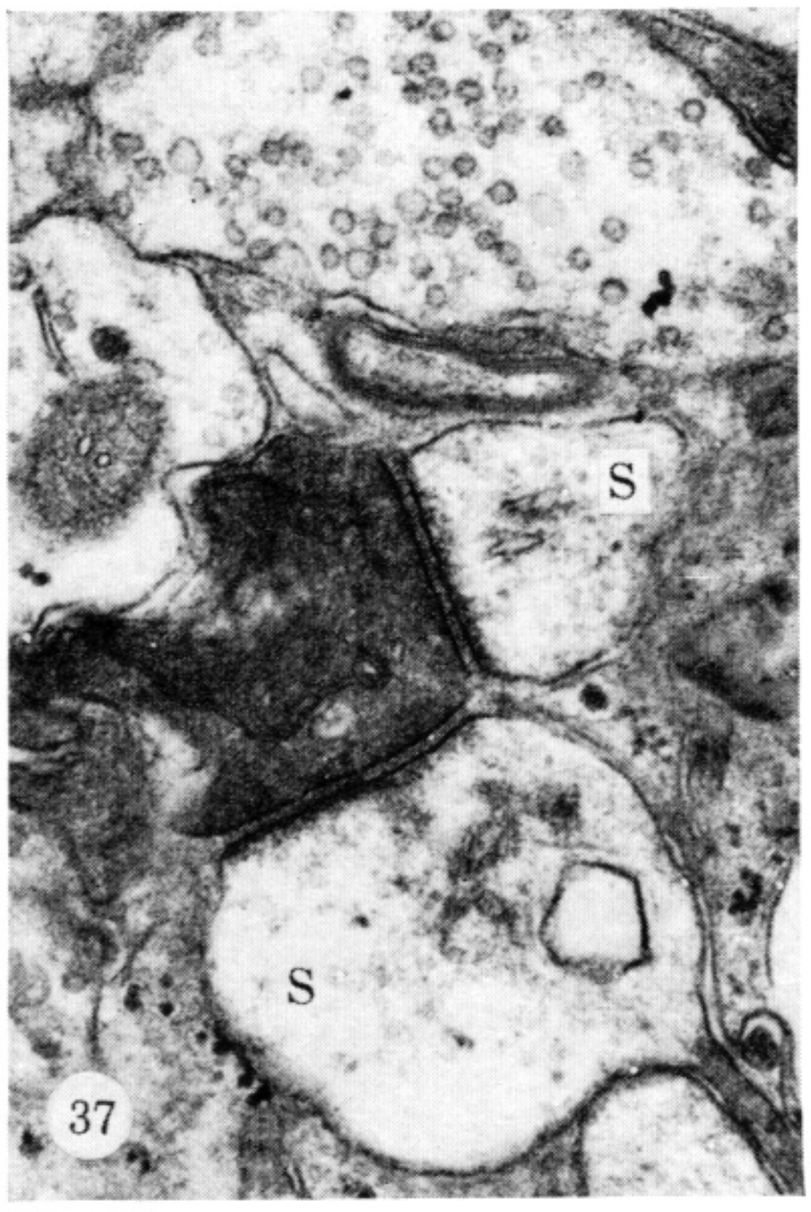
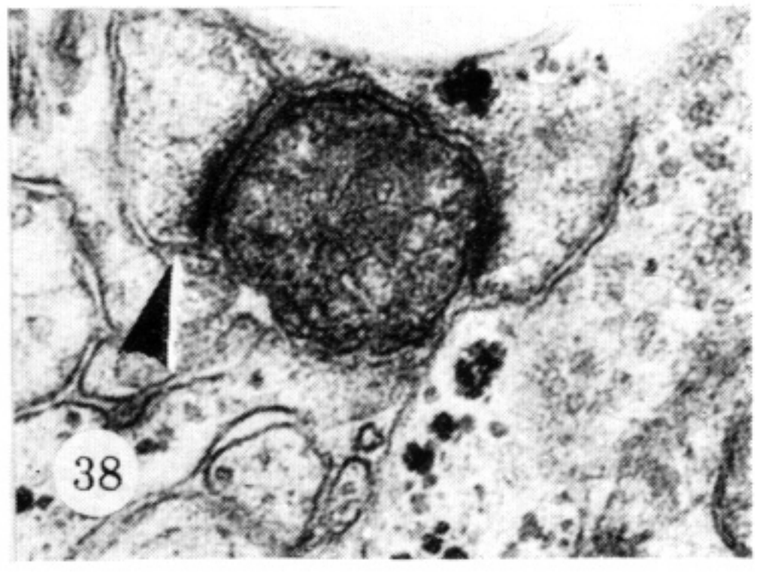


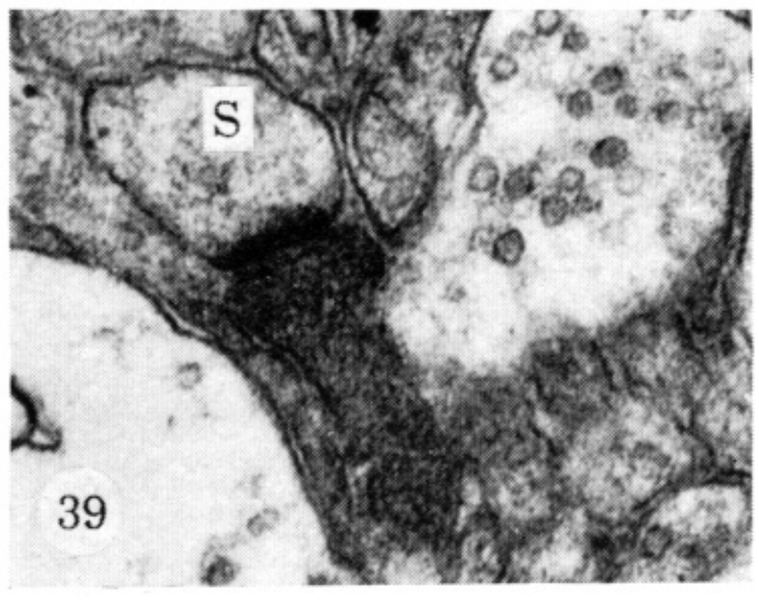


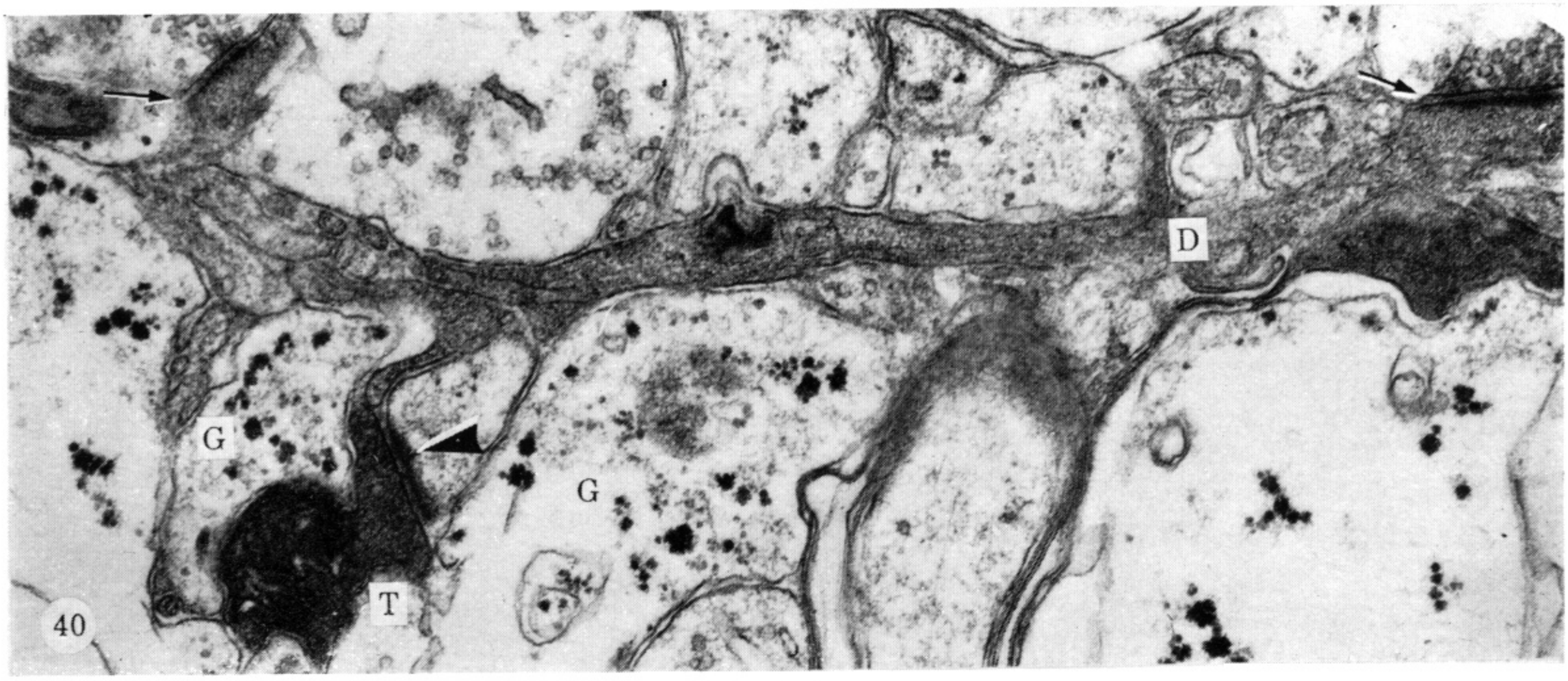




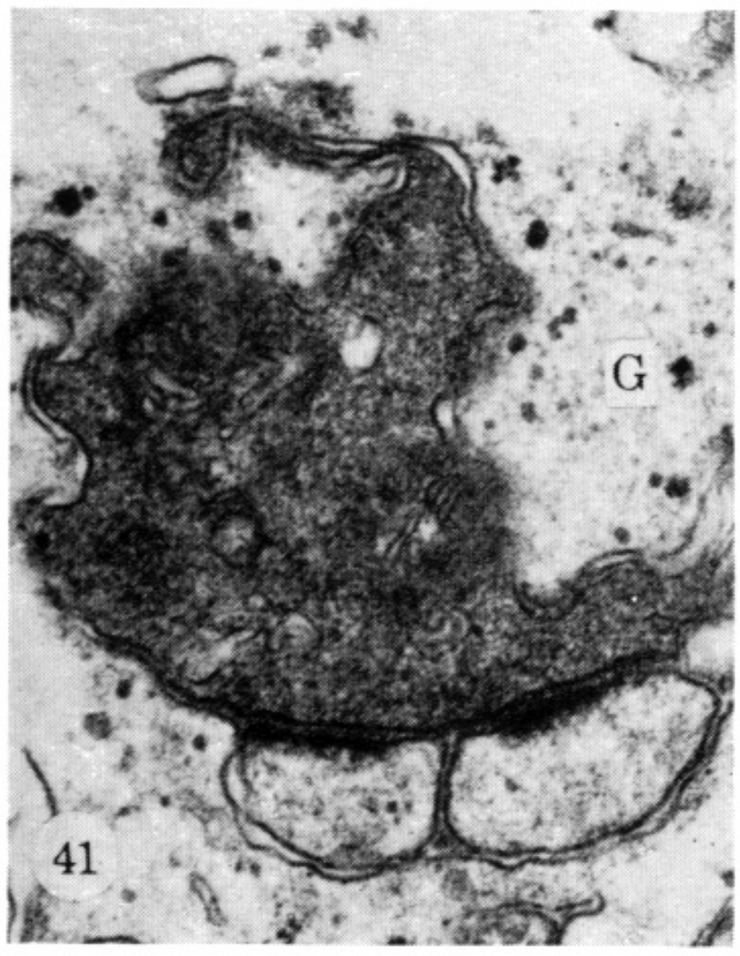


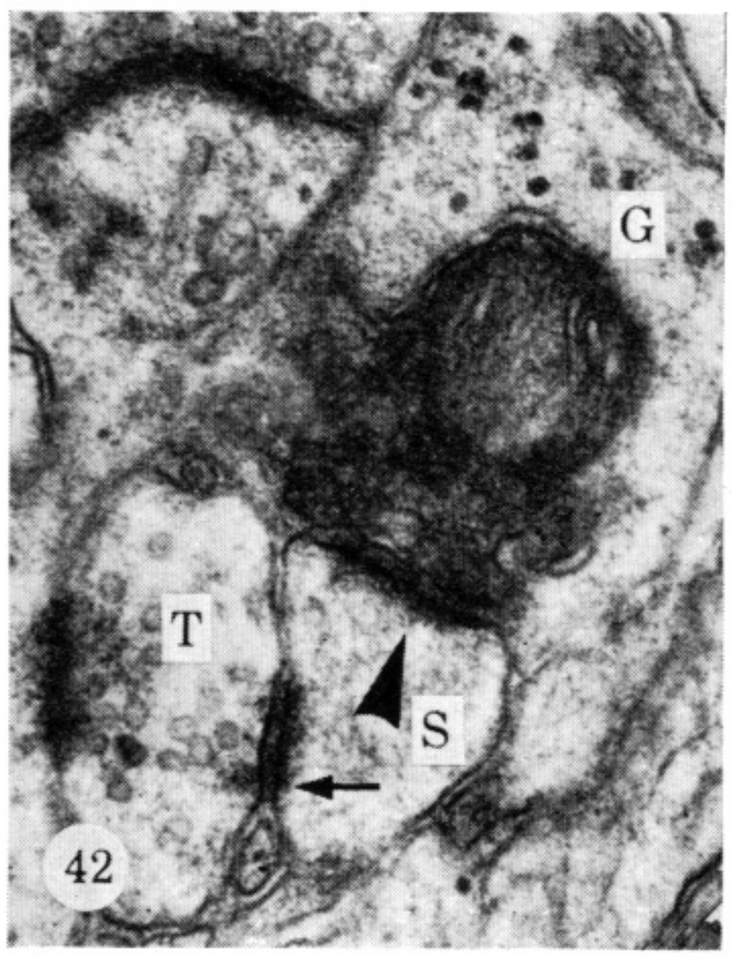


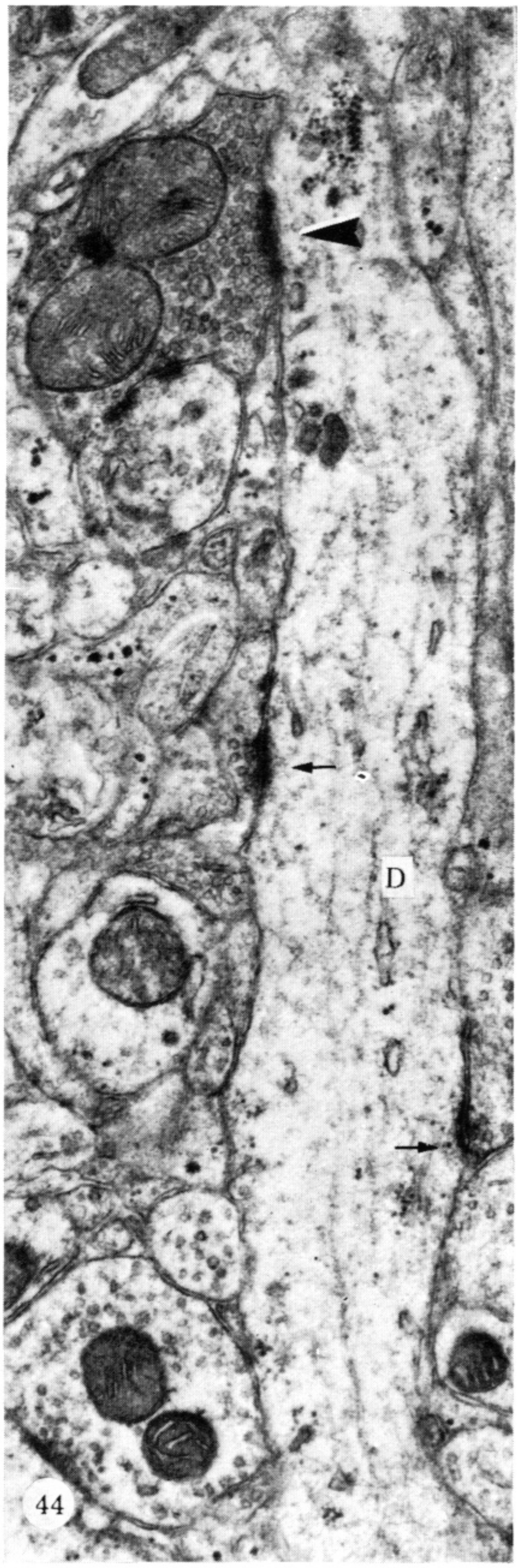


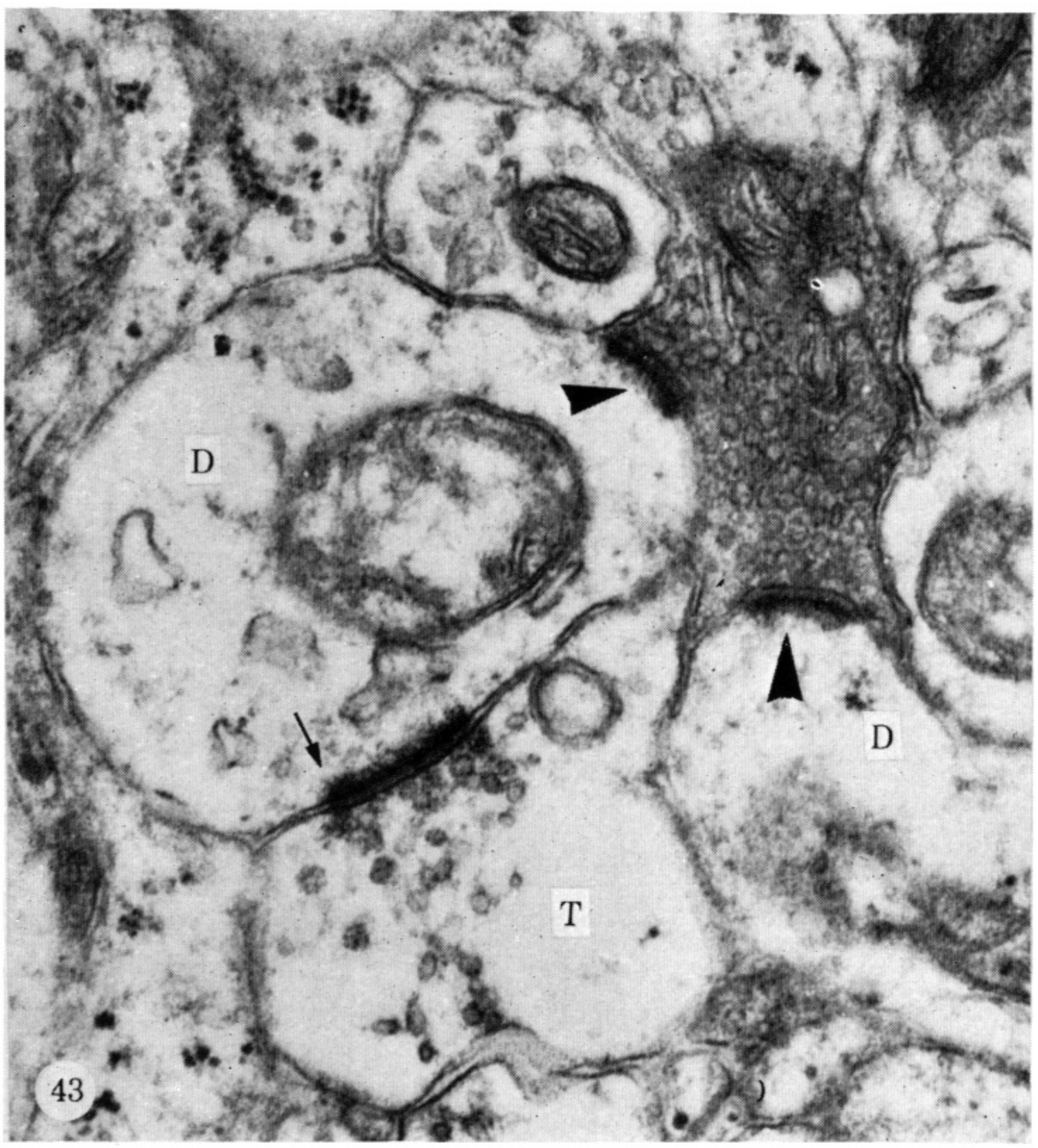


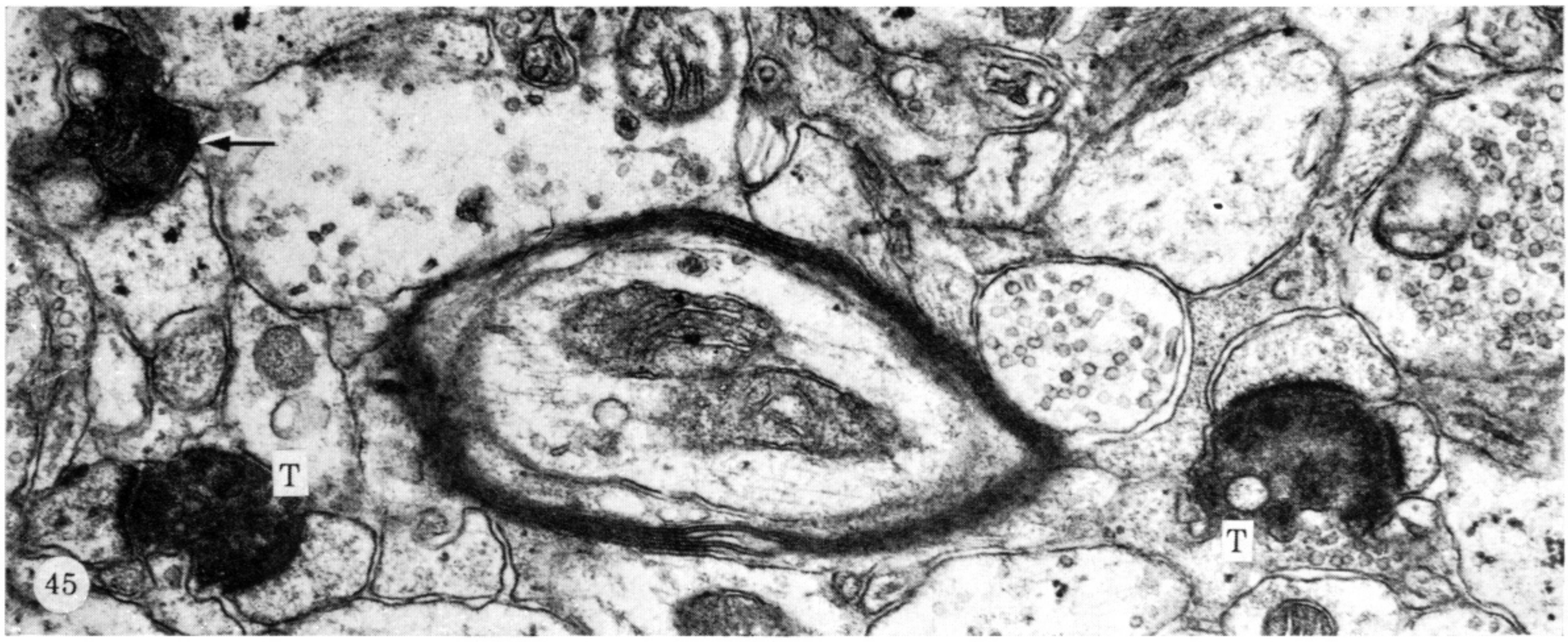
FIGURES 33–40. For description see opposite.



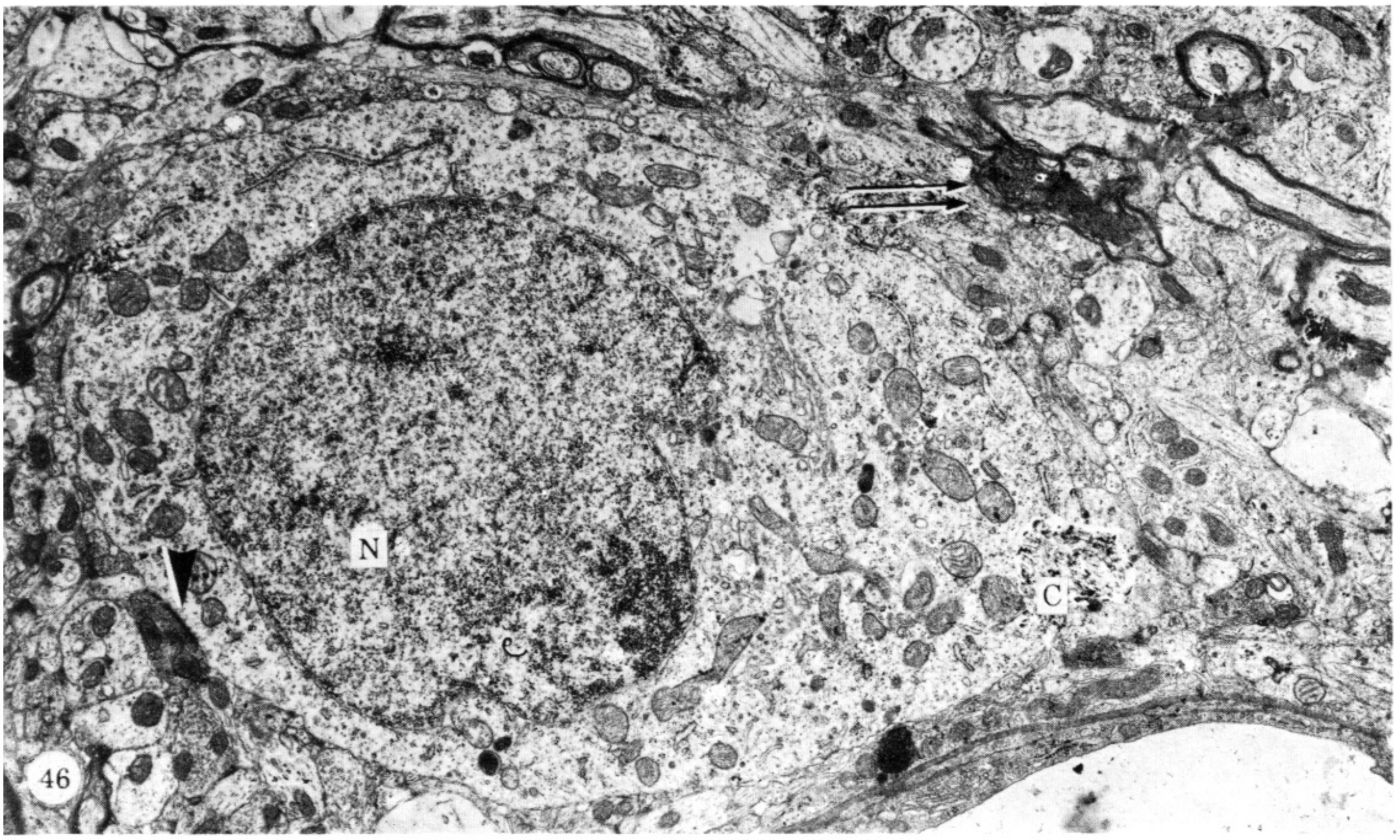


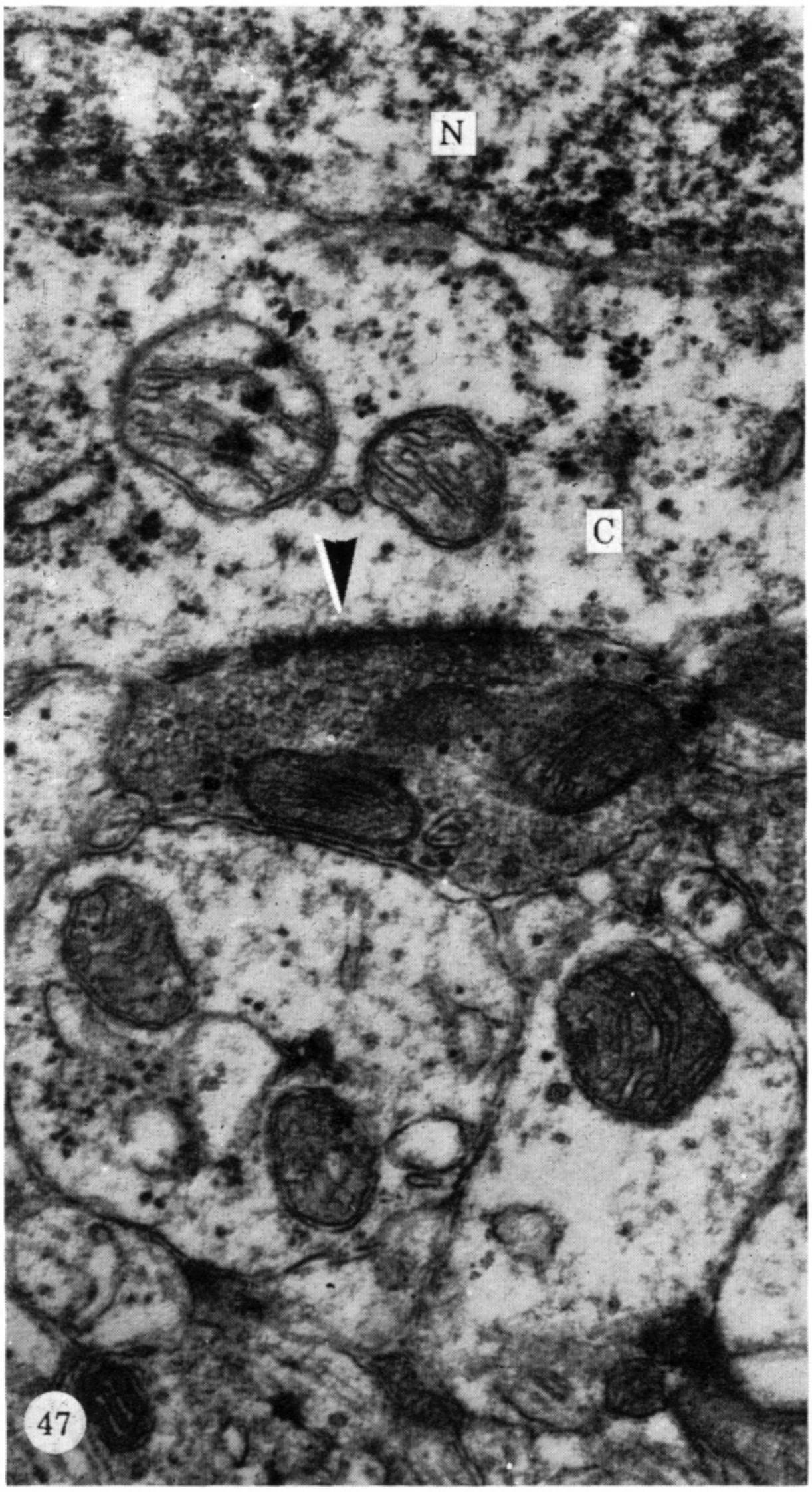


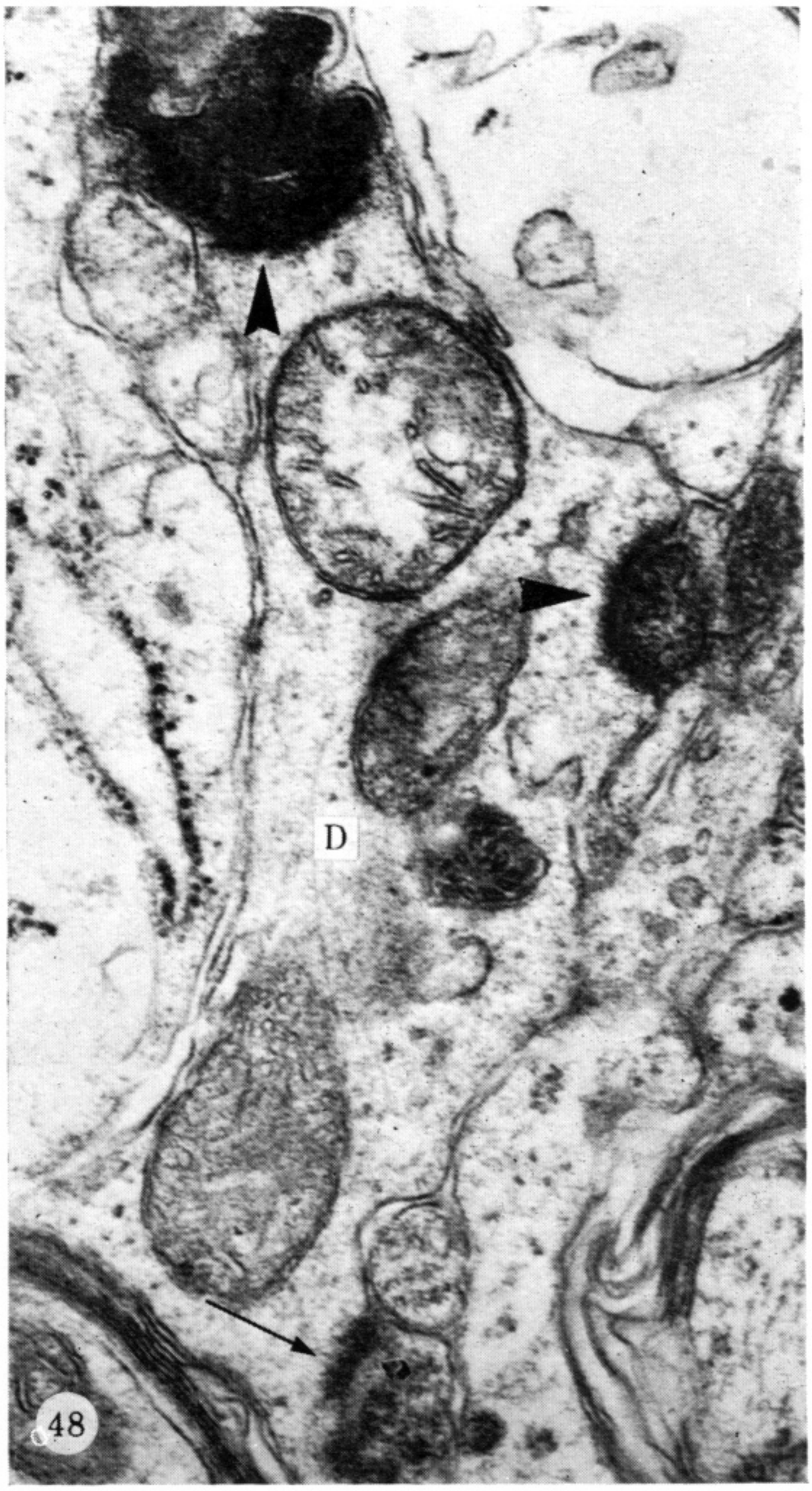




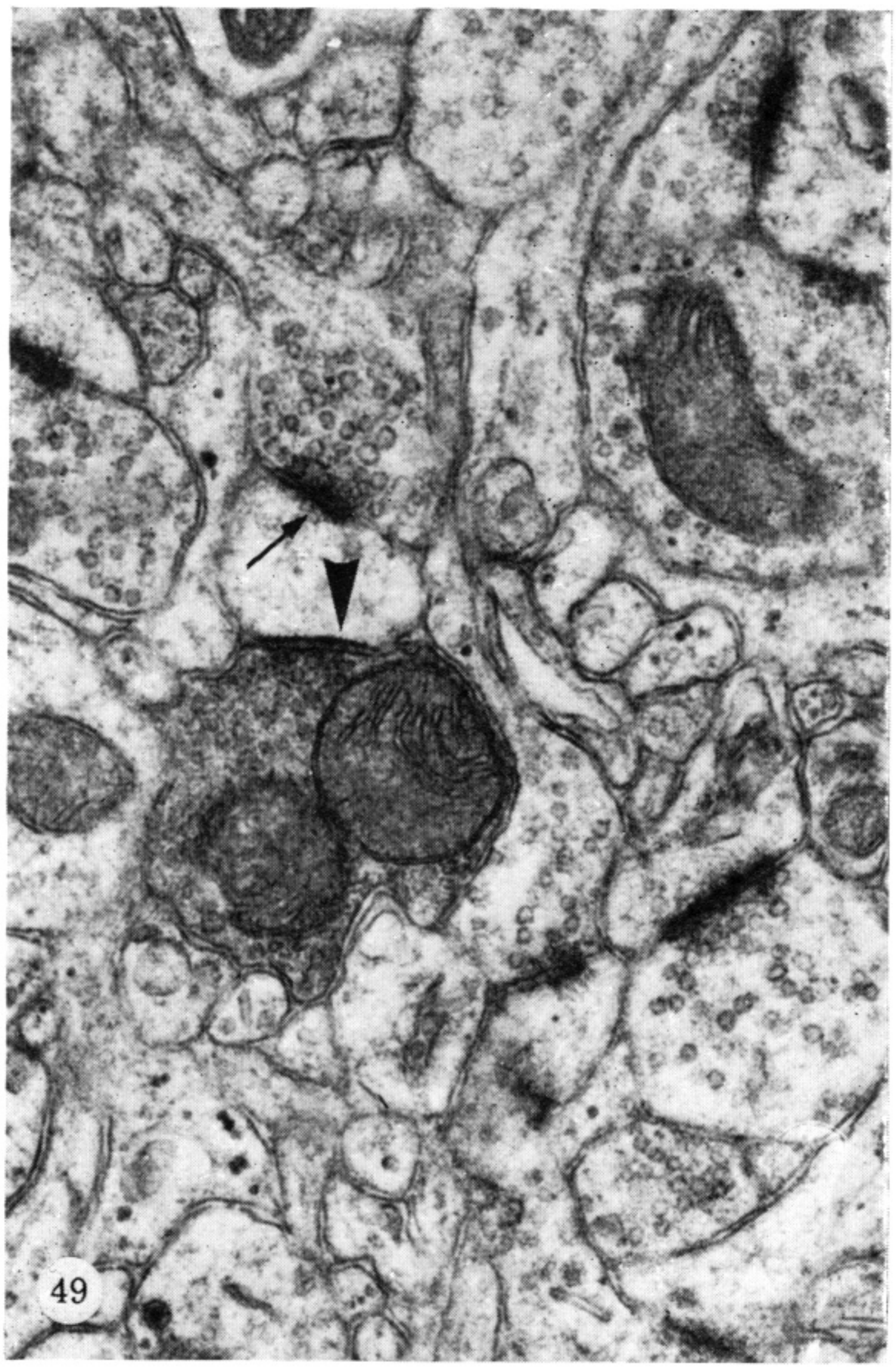
FIGURES 41–45. For description see opposite.



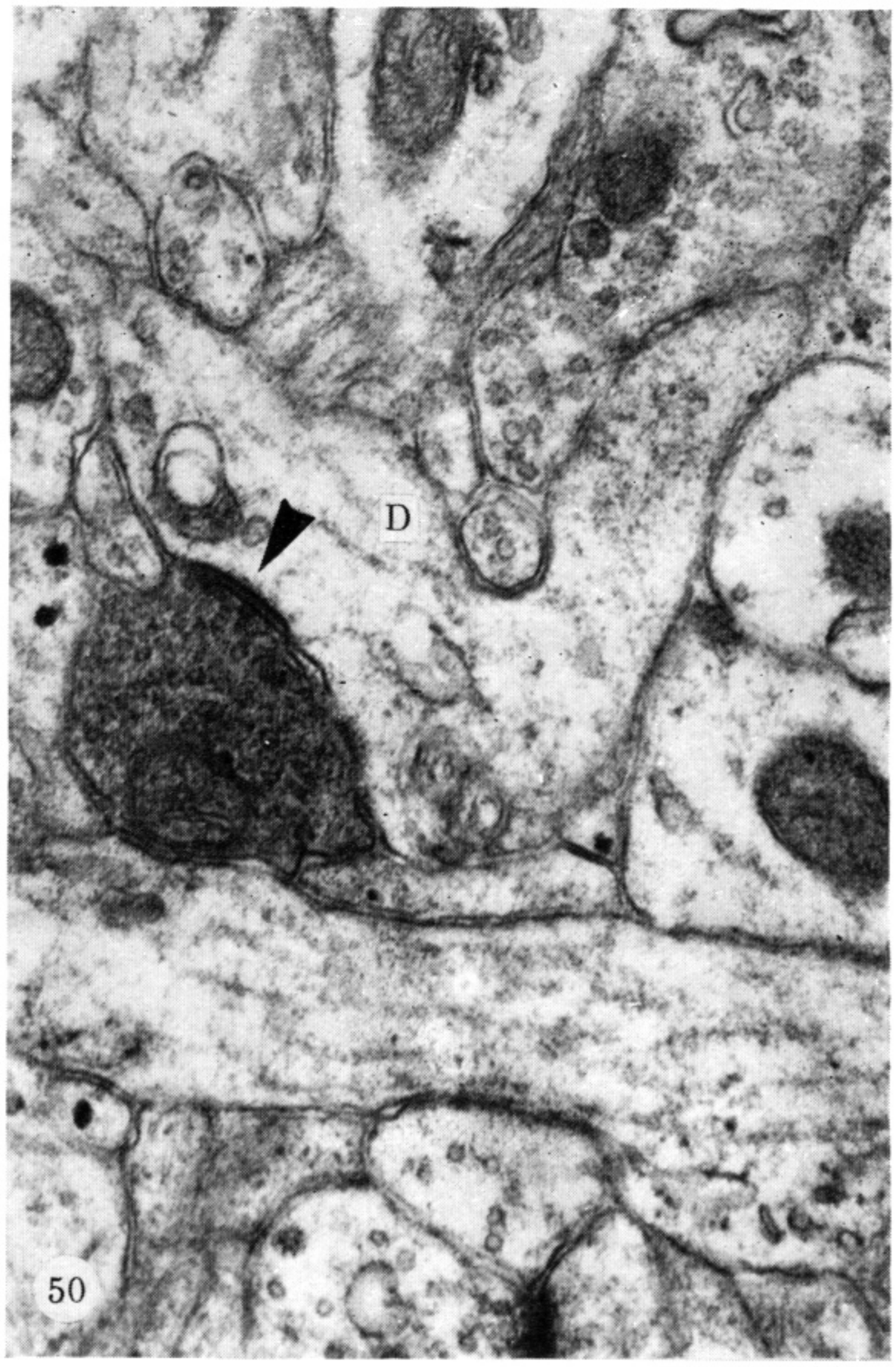




FIGURES 46–48. For description see opposite.



49



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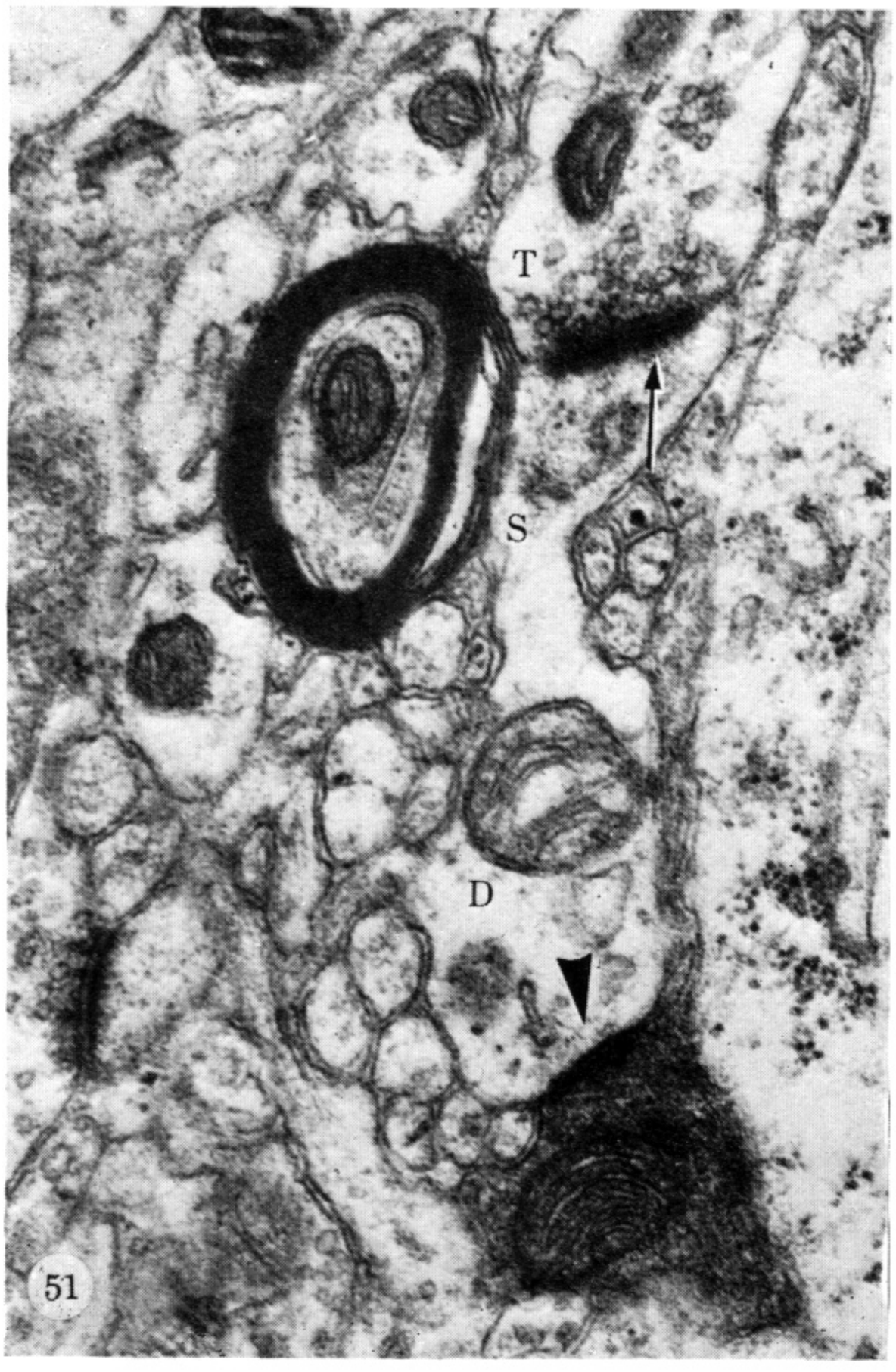
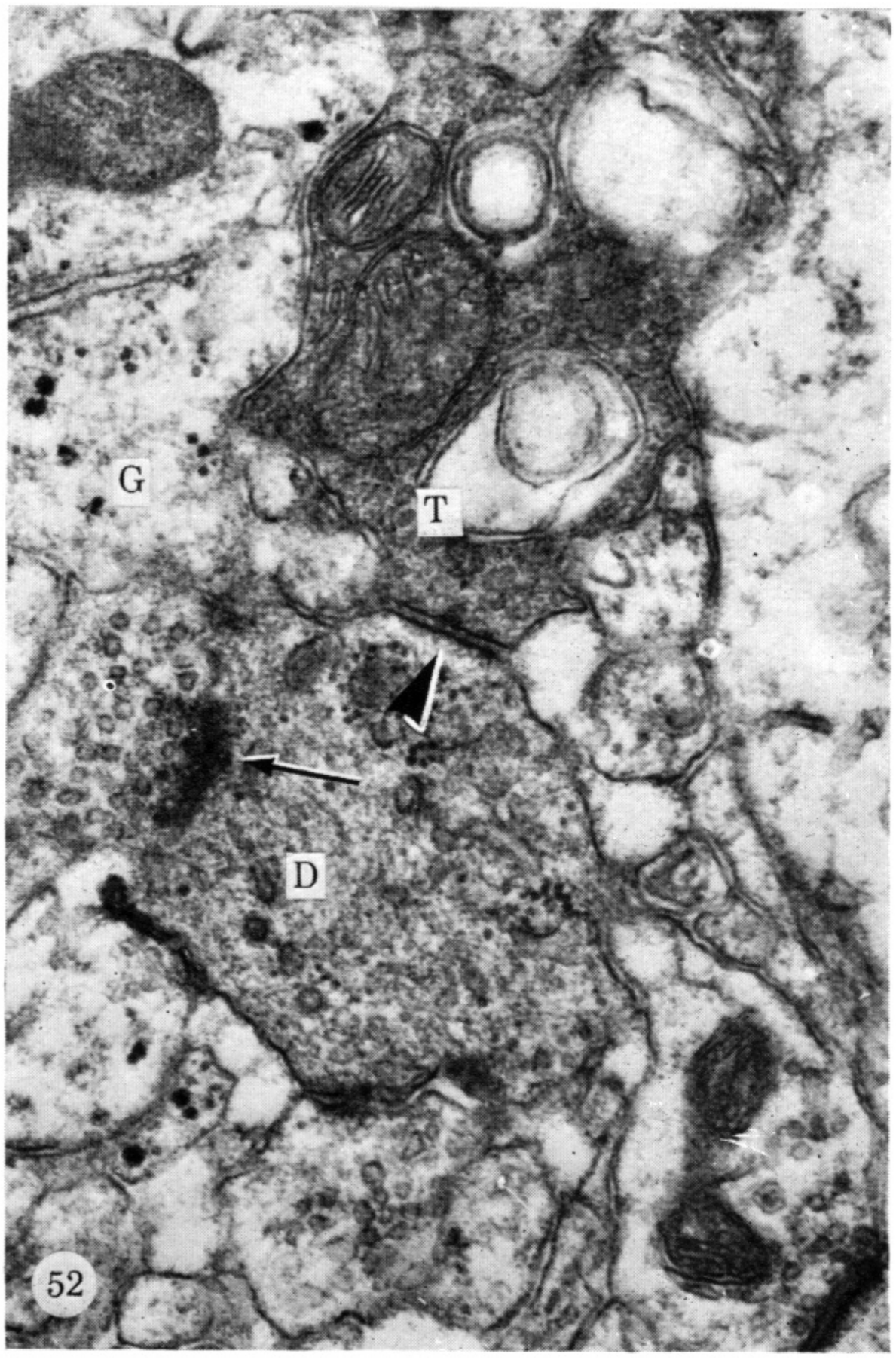
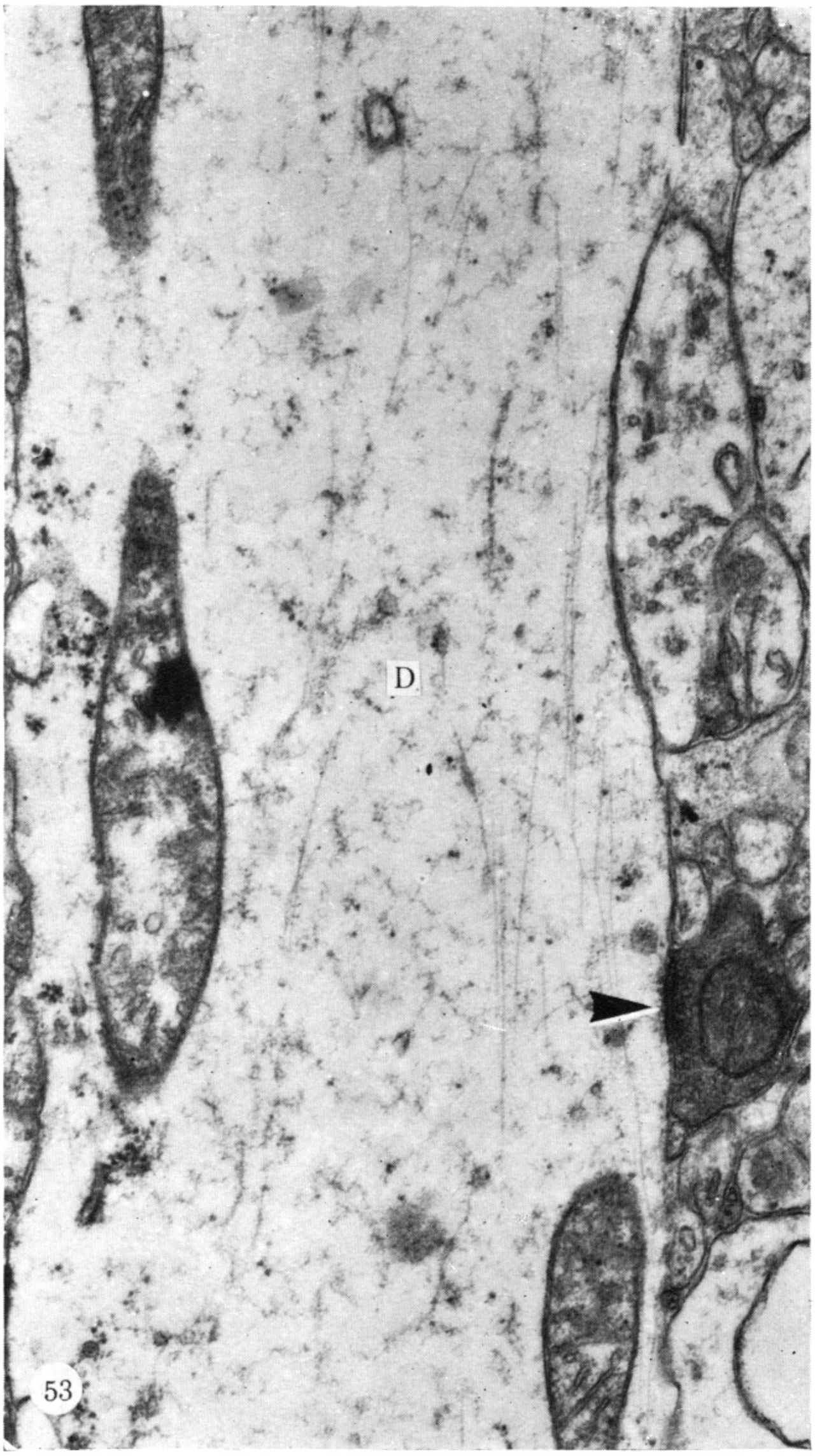


51

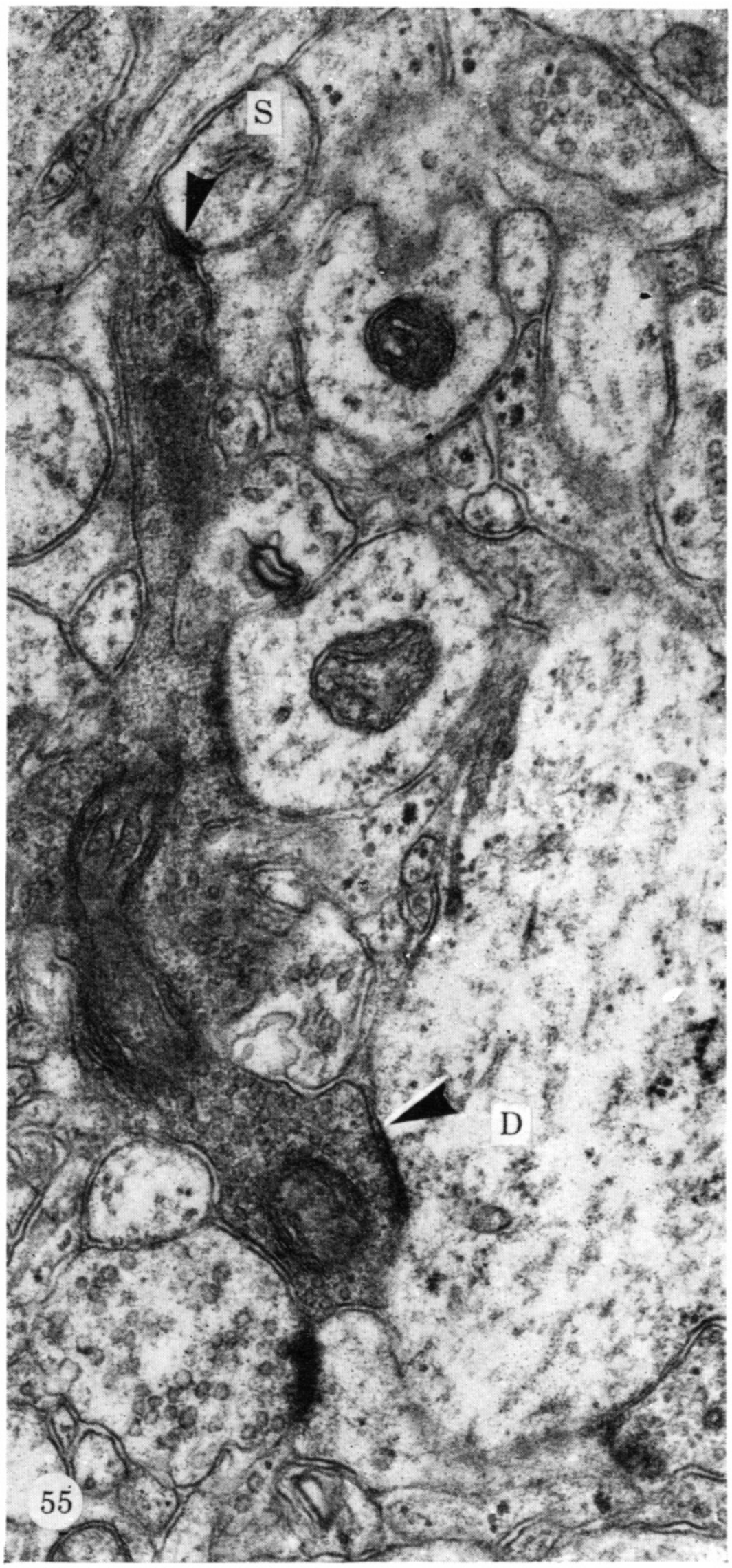


52

FIGURES 49–52. For description see opposite.



53



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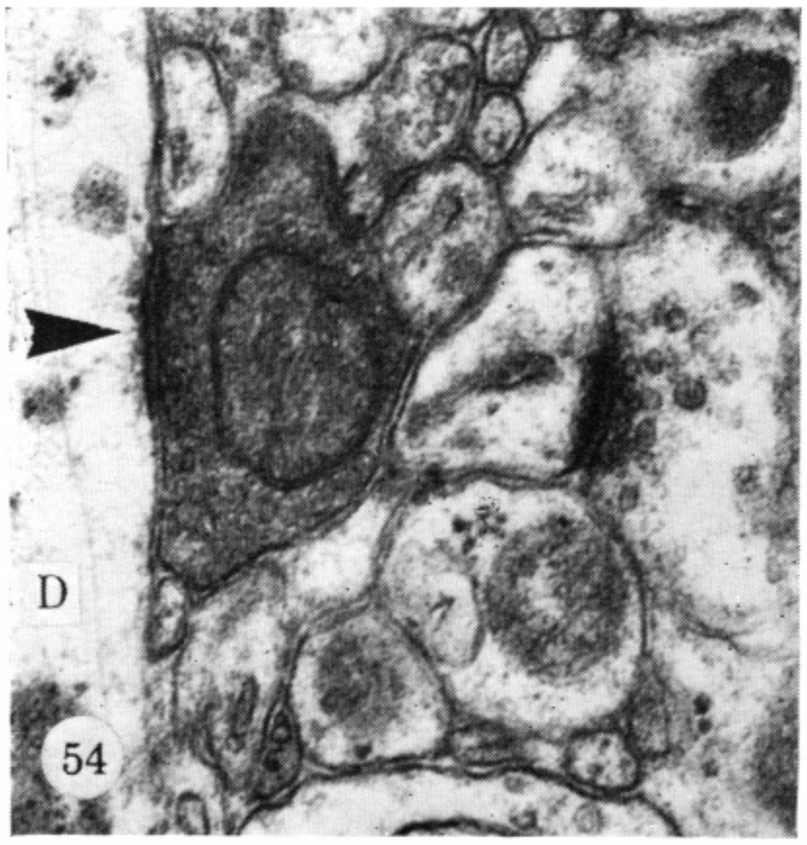
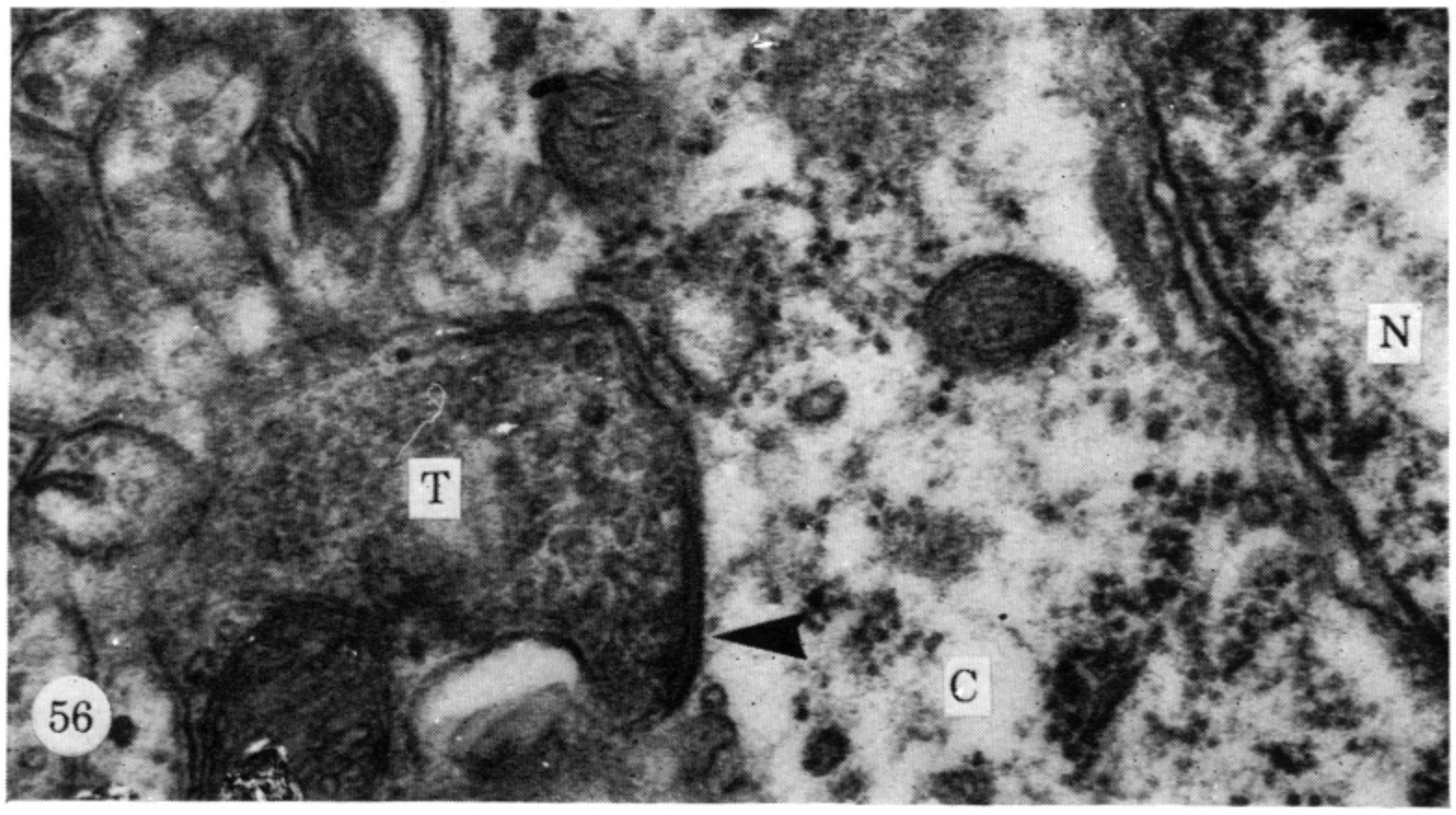


54



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FIGURES 53–56. For description see opposite.

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FIGURES 57 AND 58. For description see opposite.

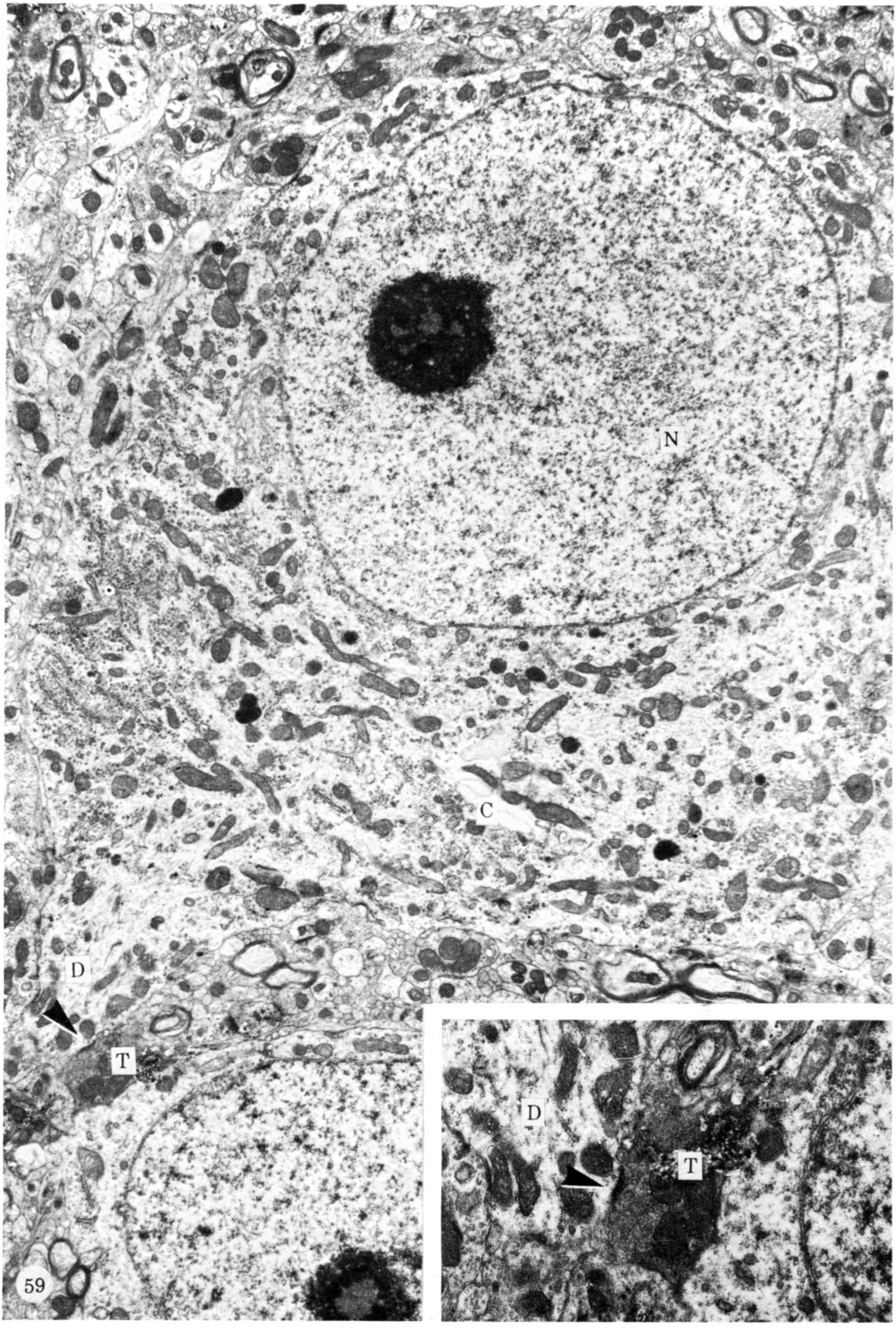
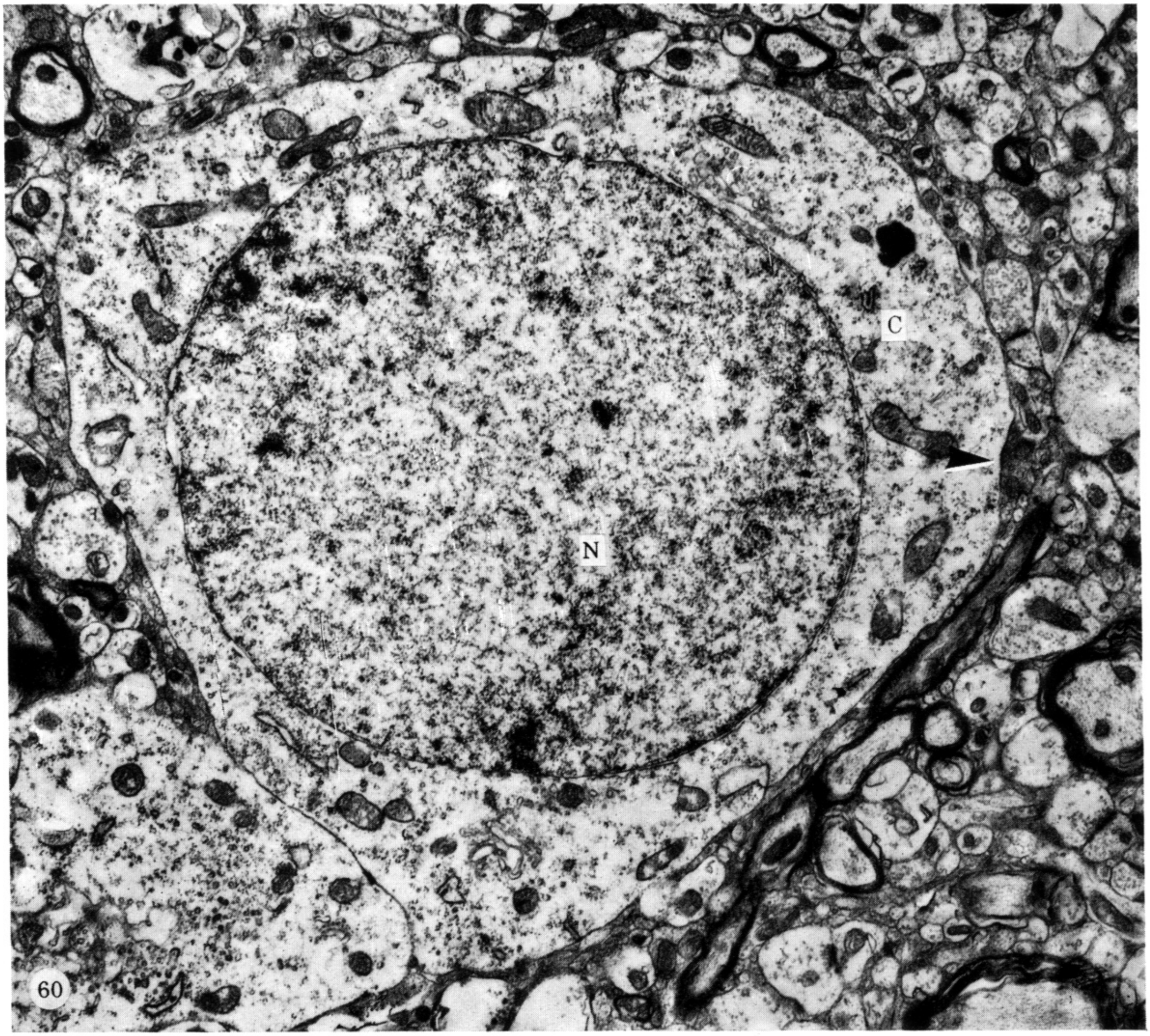
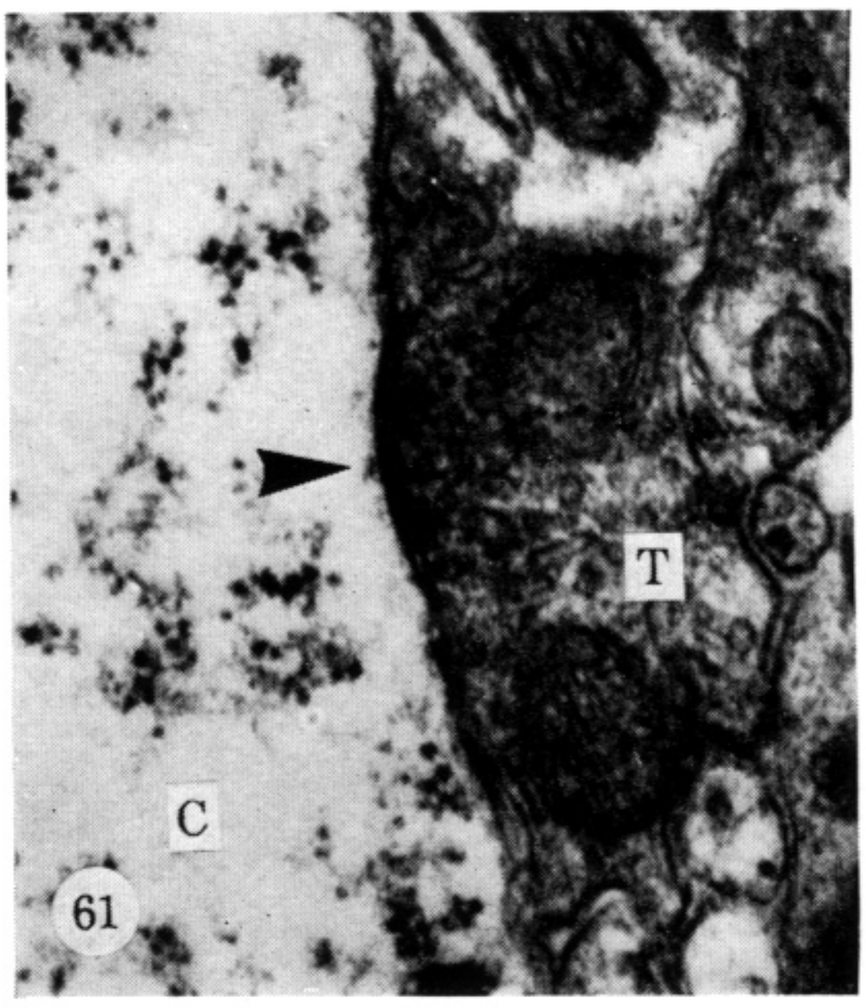
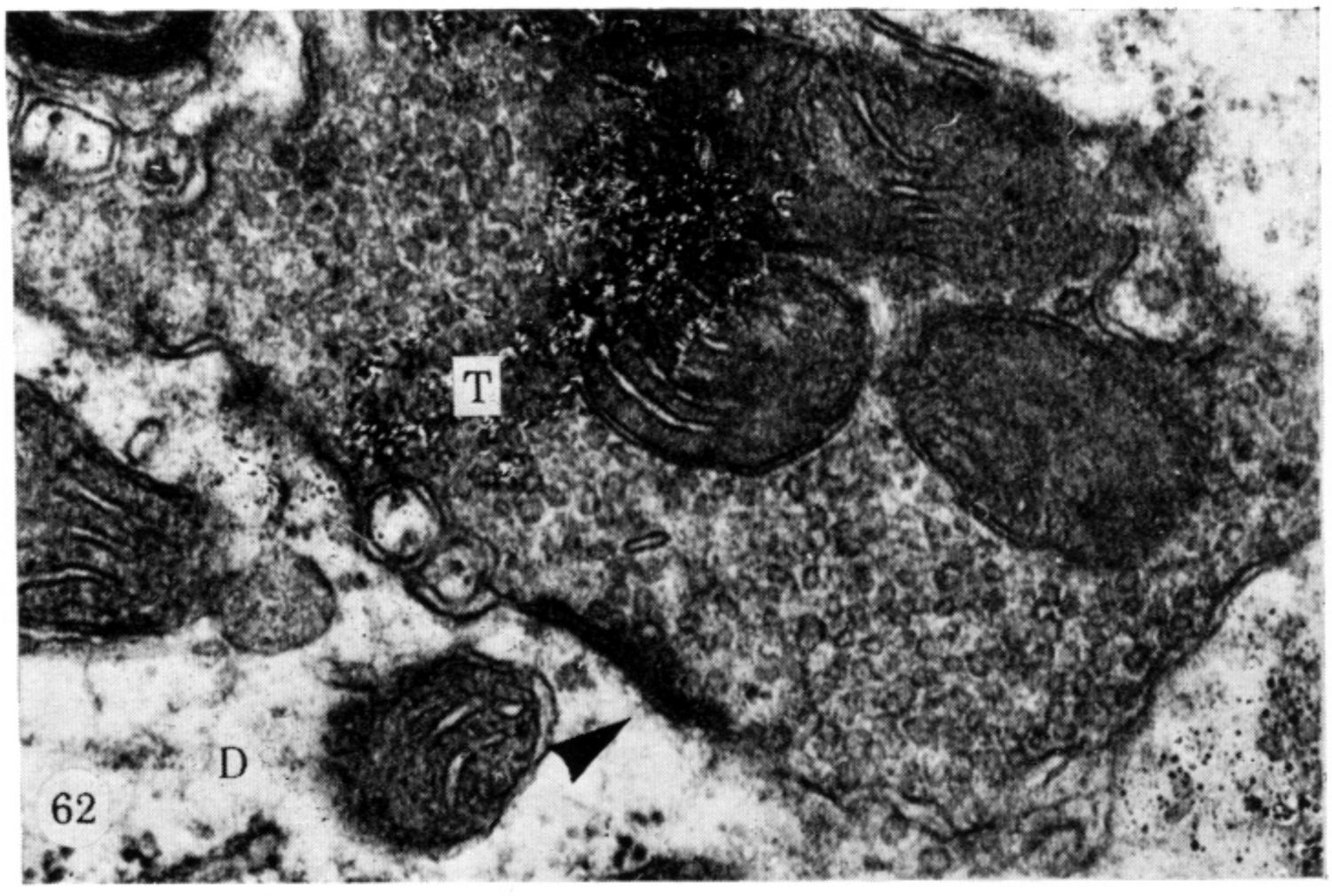


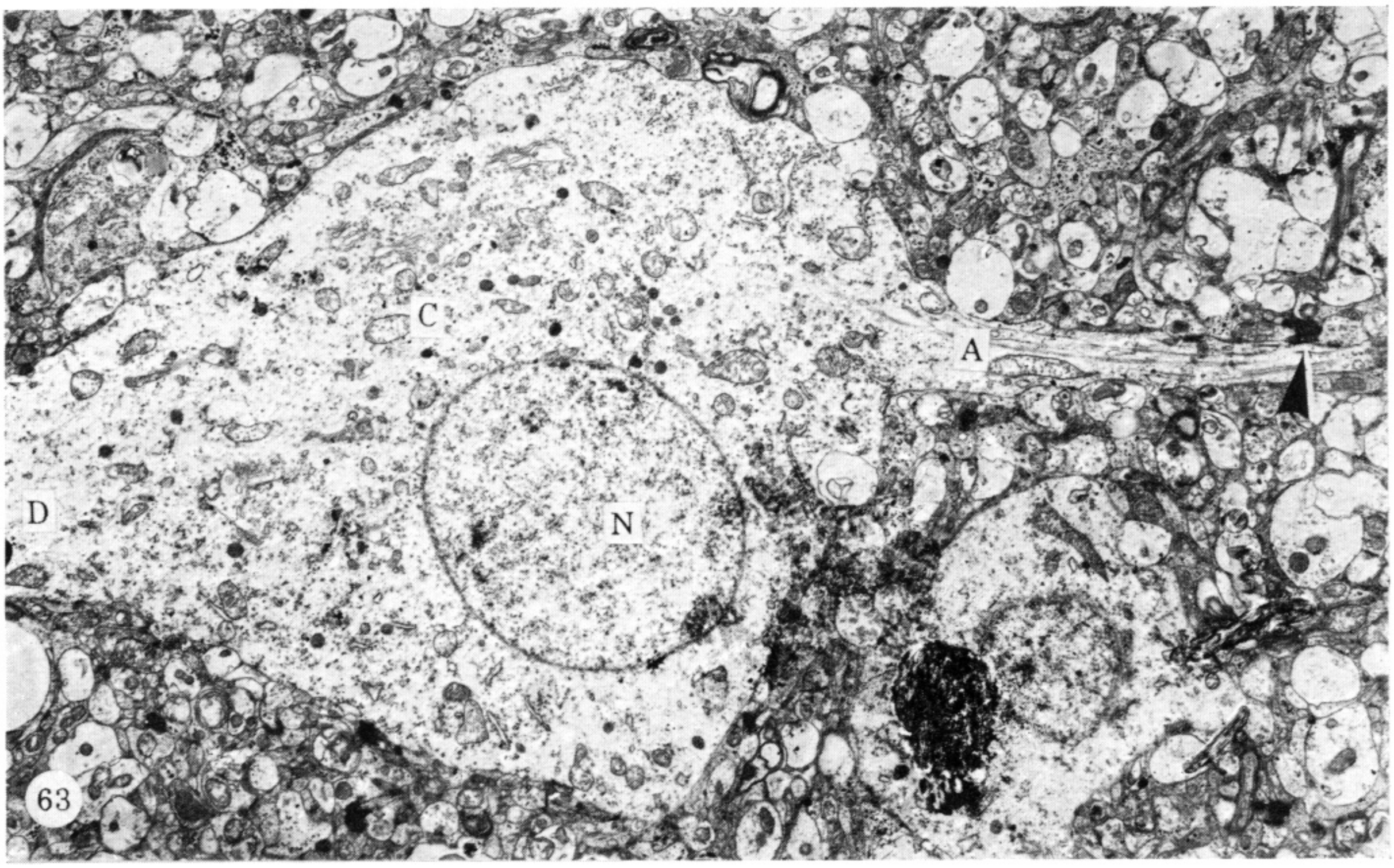
FIGURE 59. For description see opposite.

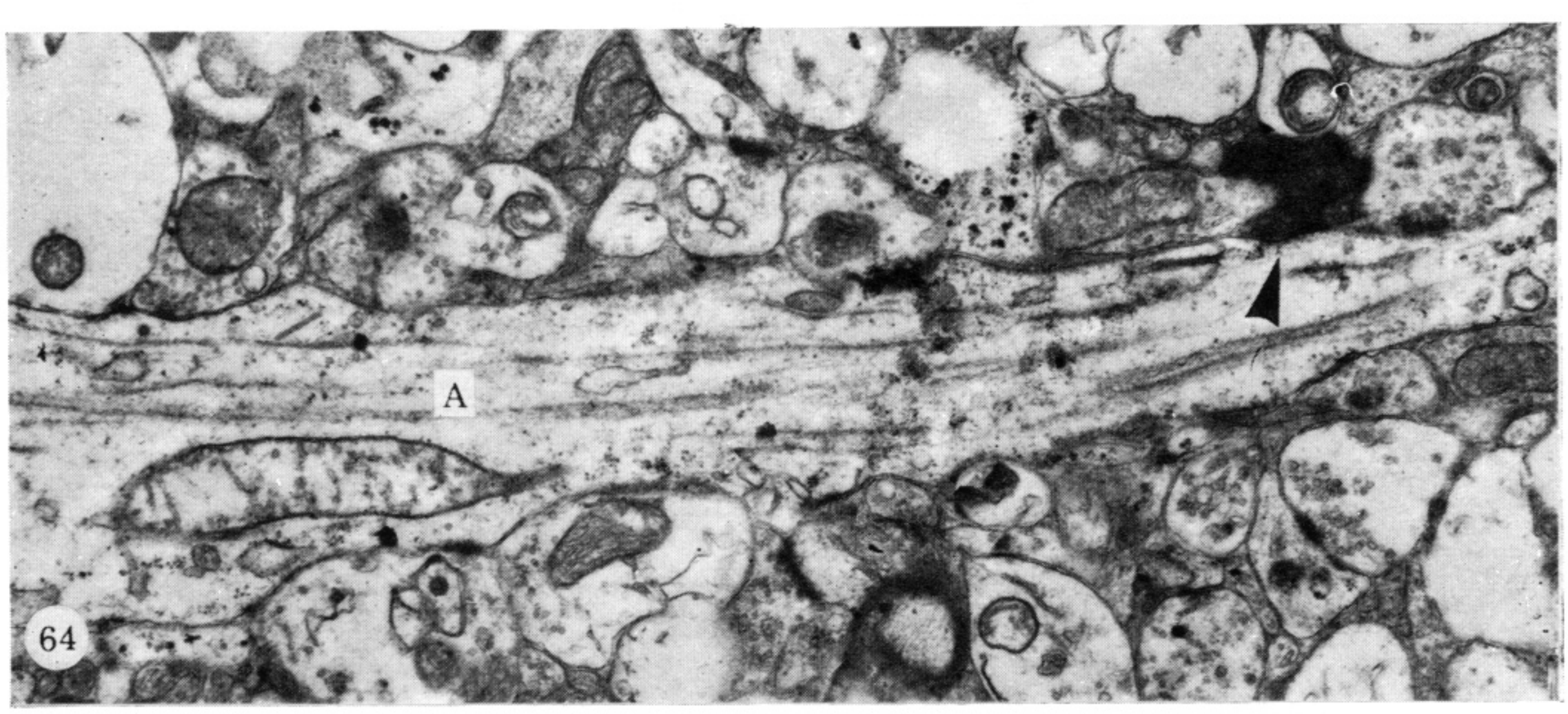


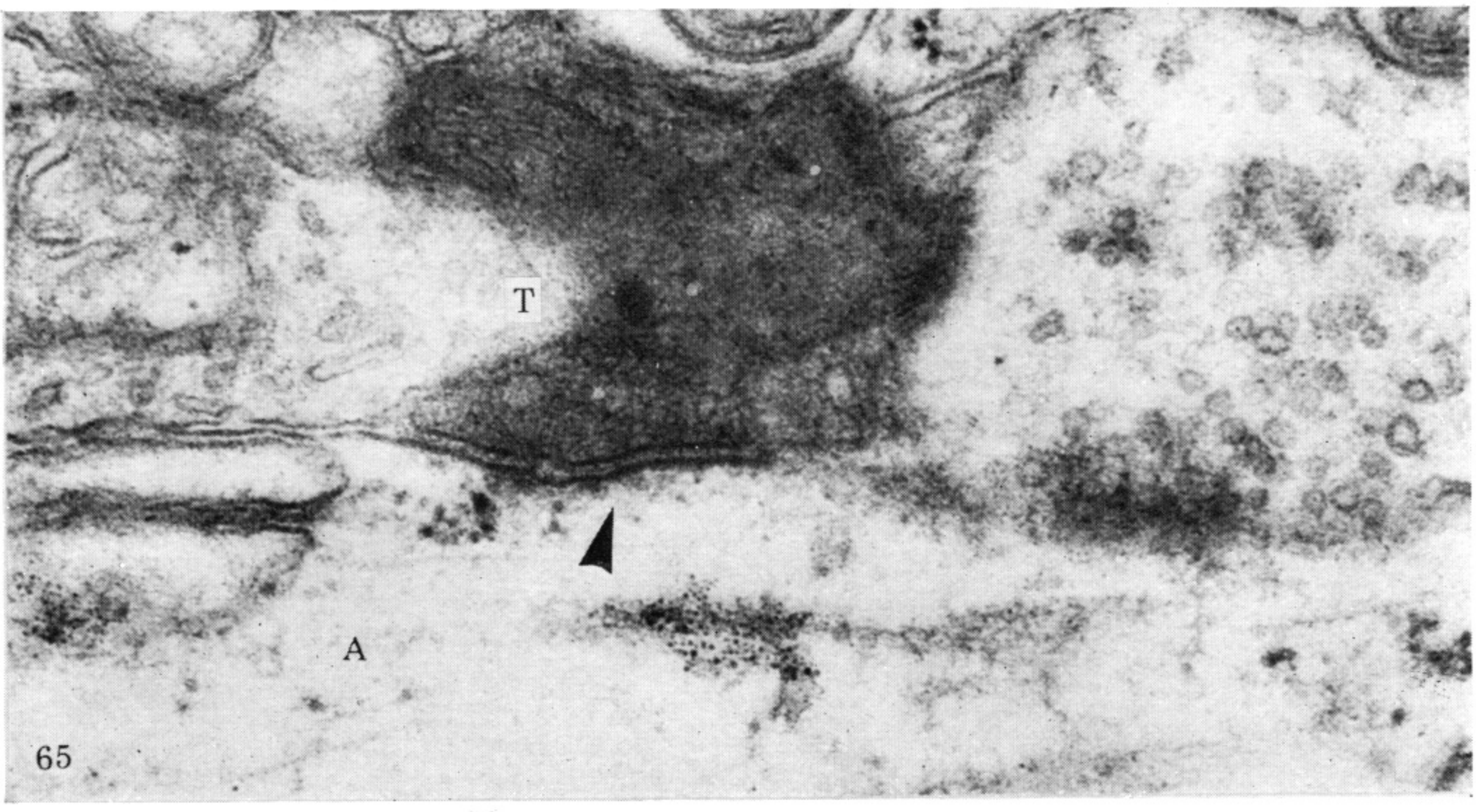




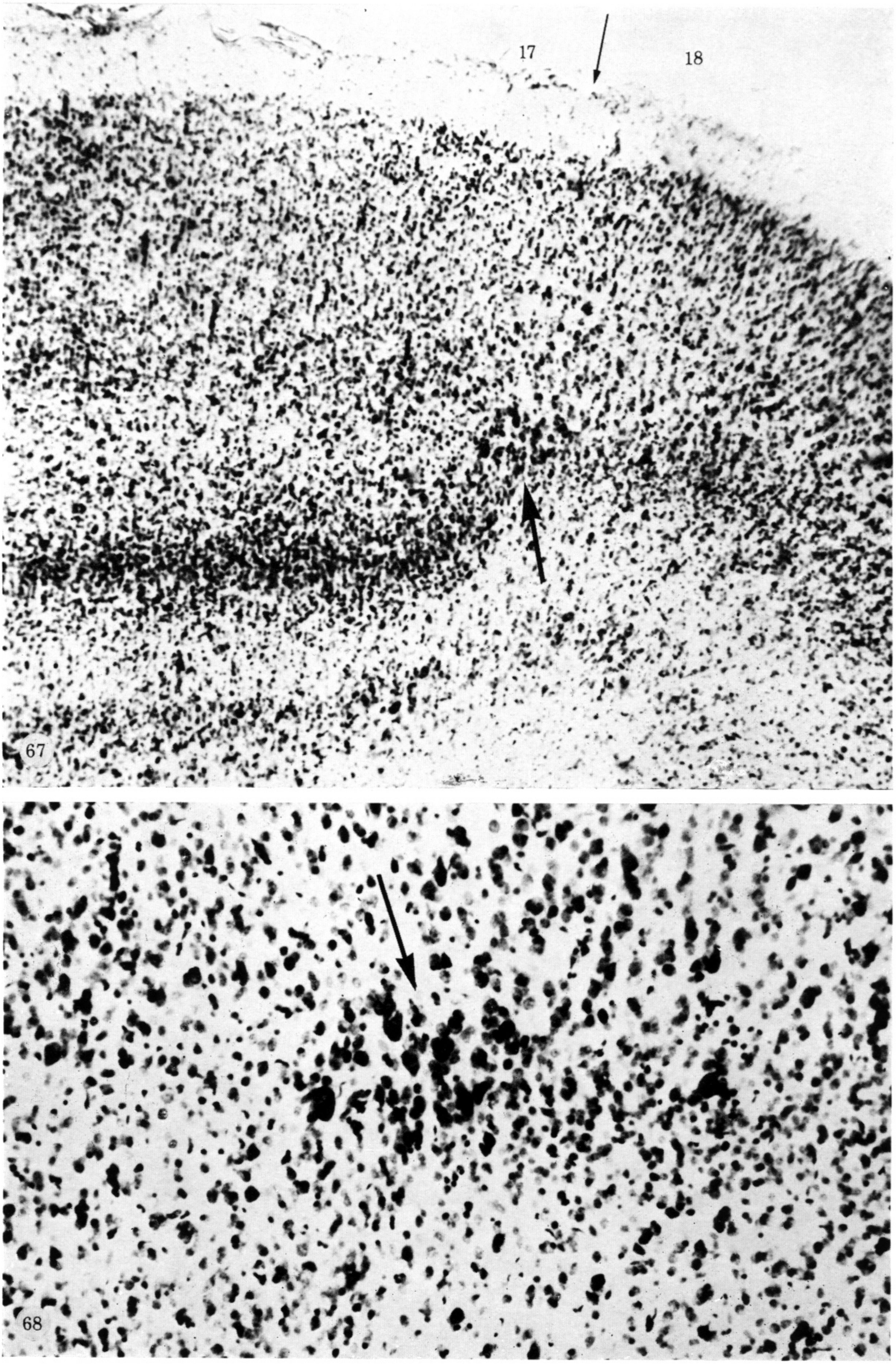
FIGURES 60–62. For description see opposite.



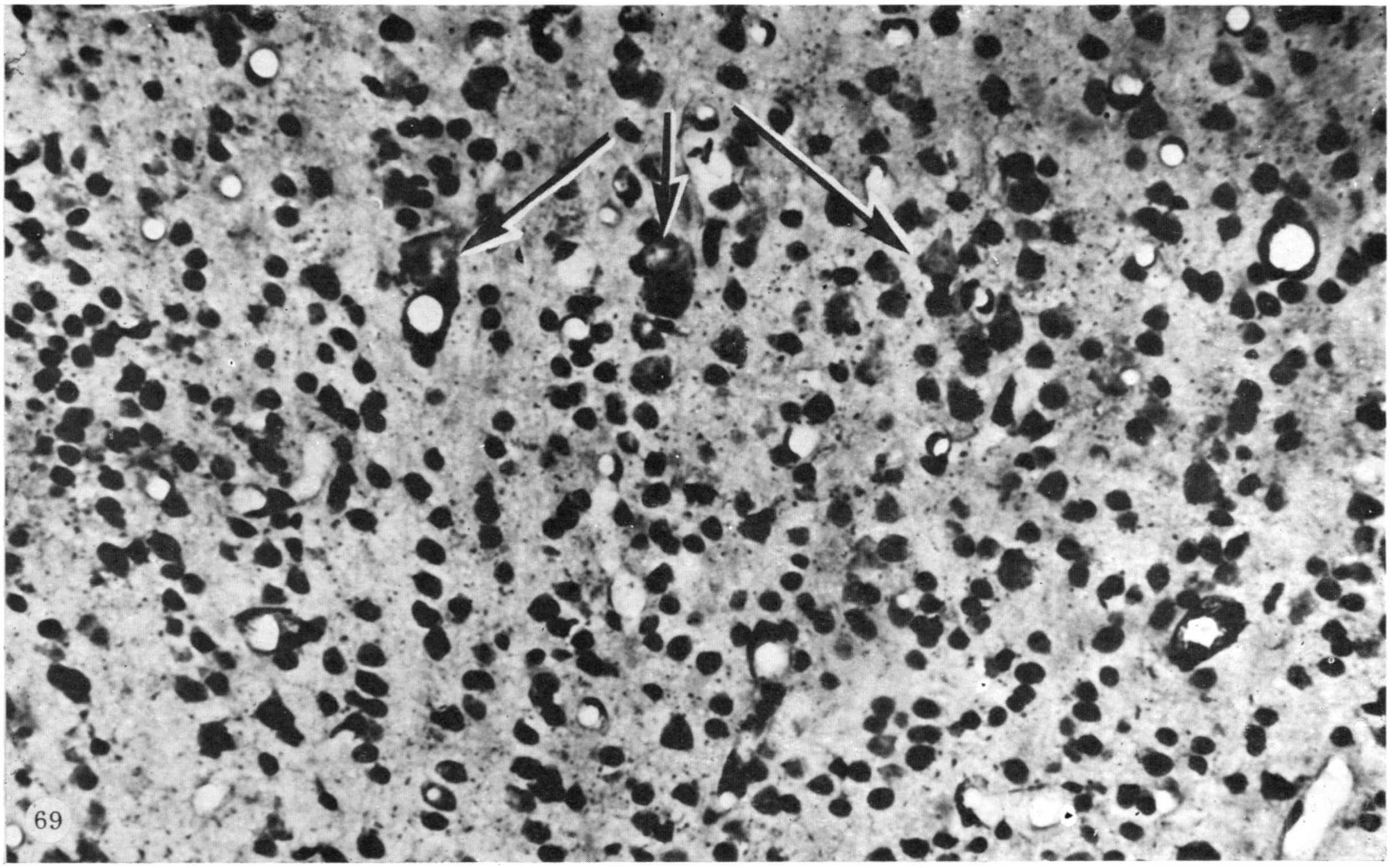


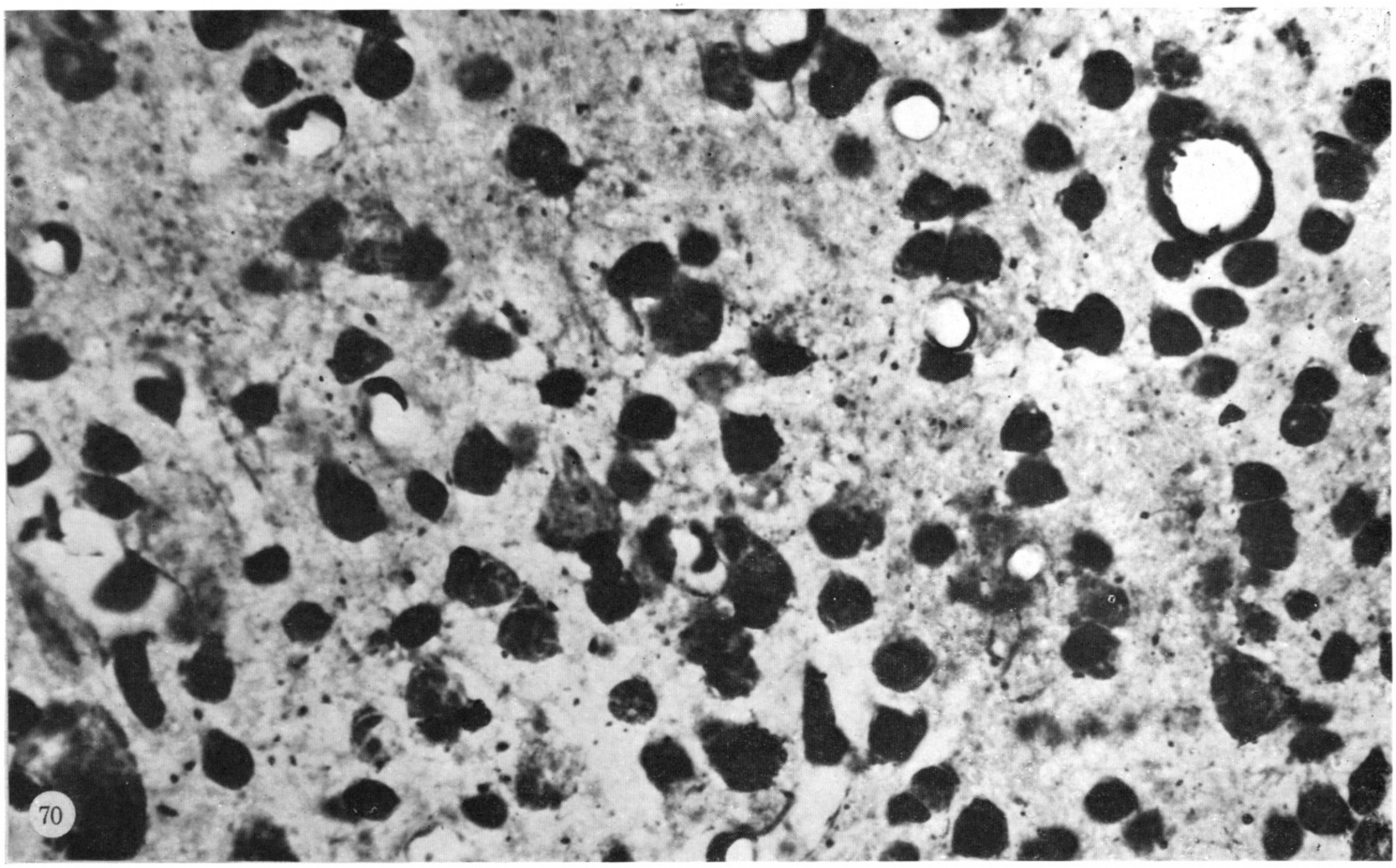


FIGURES 63–65. For description see opposite.

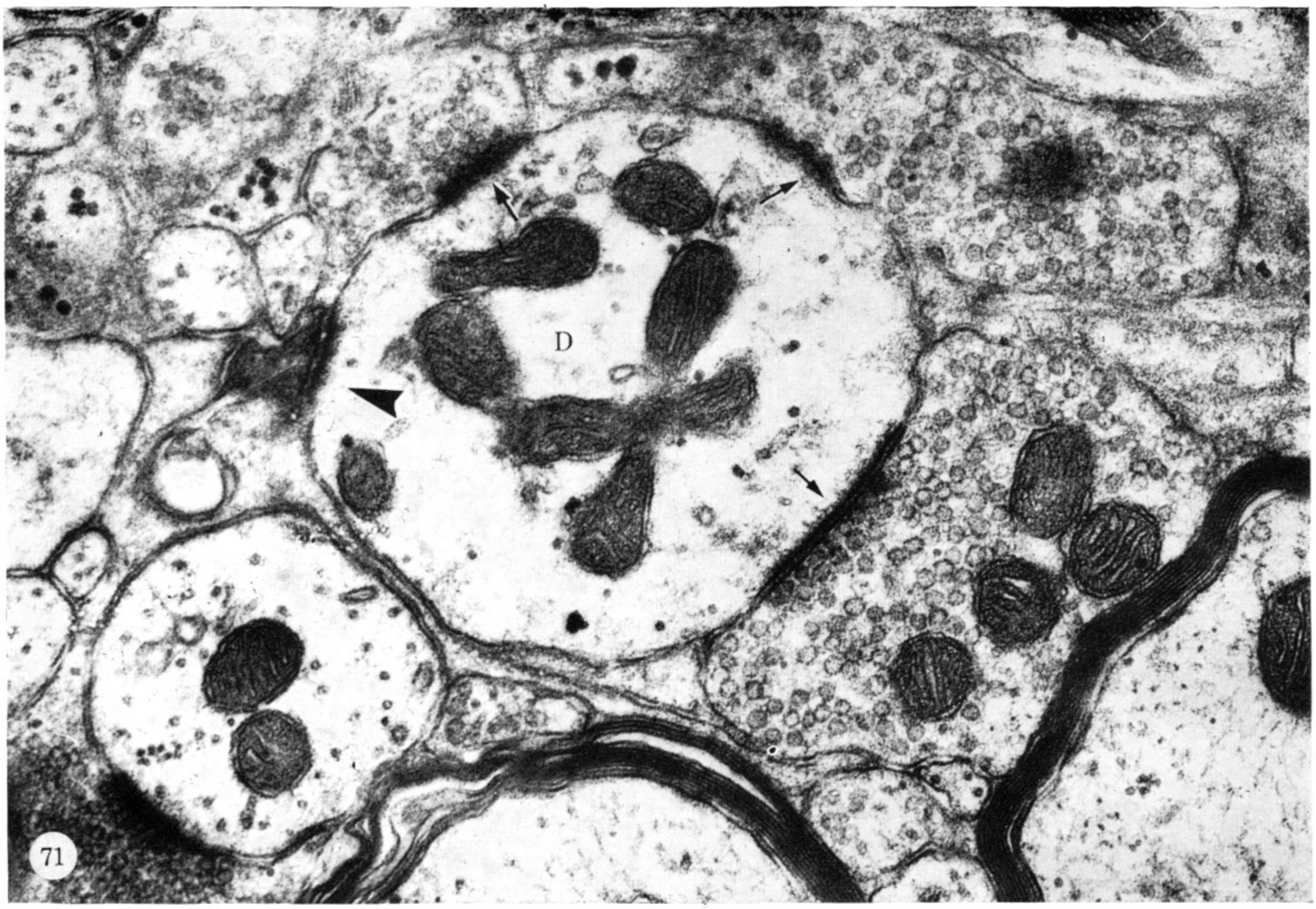


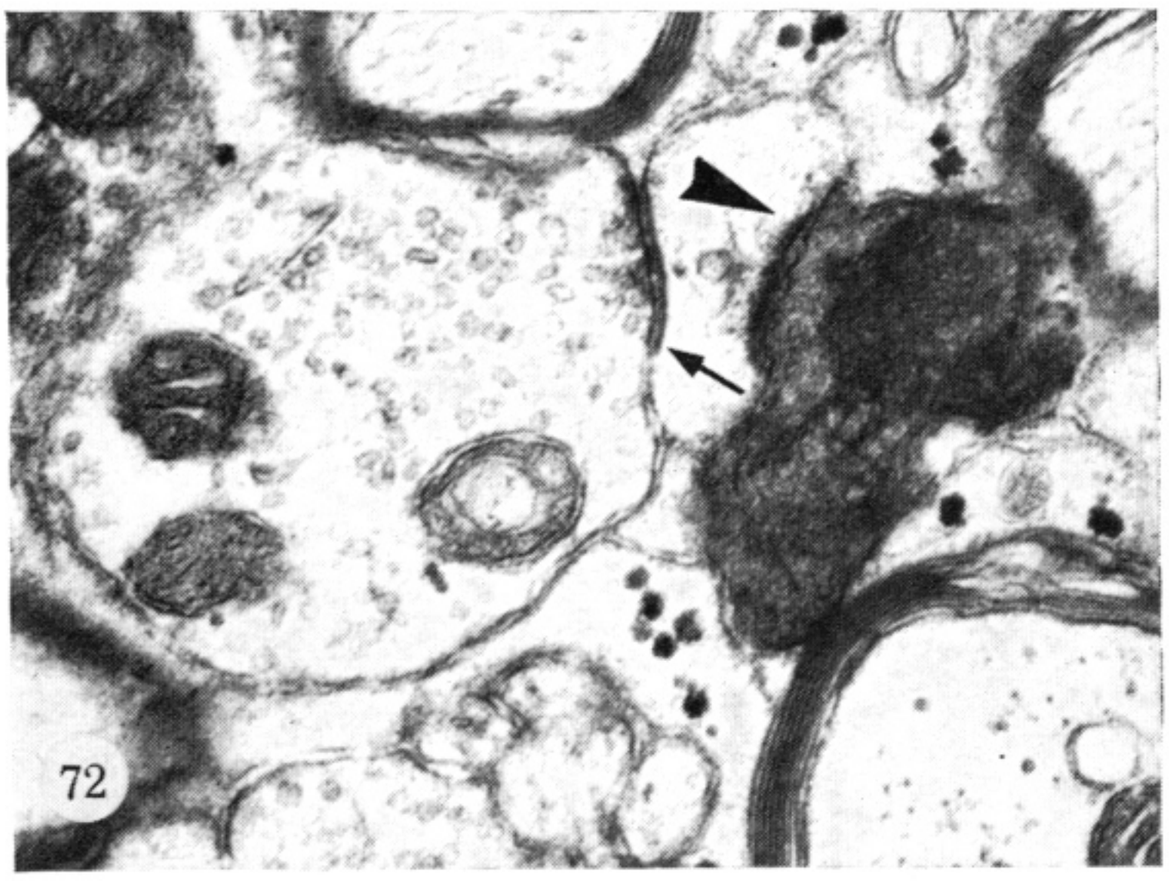
FIGURES 67 AND 68. For description see opposite.

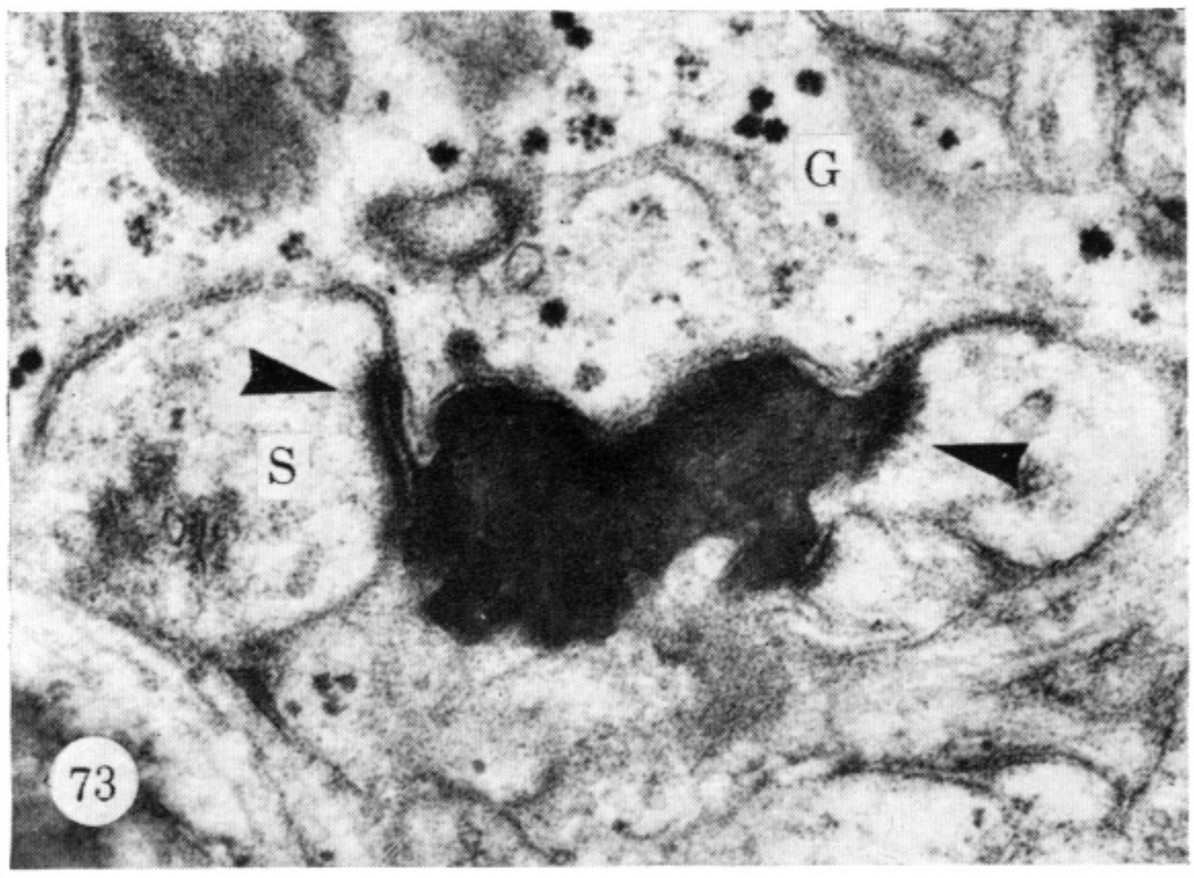


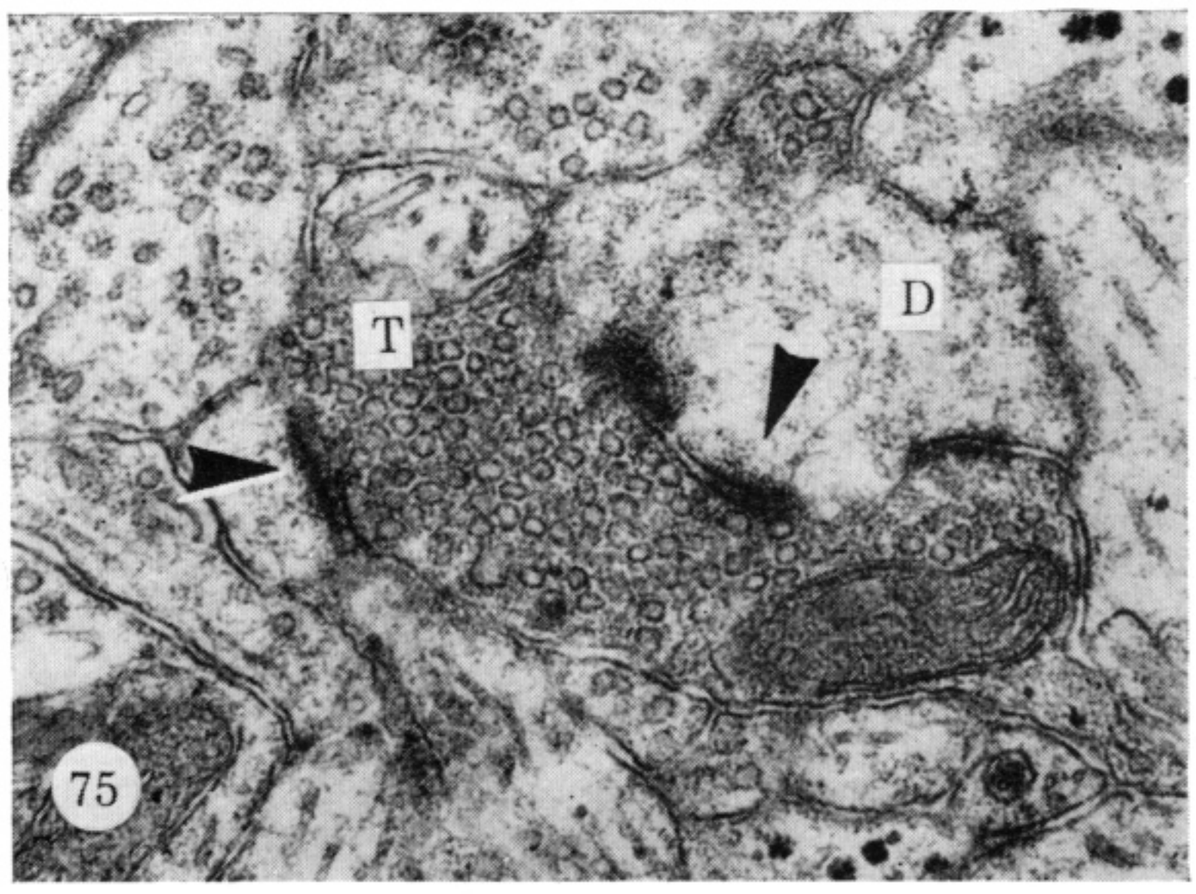


FIGURES 69 AND 70. For description see opposite.

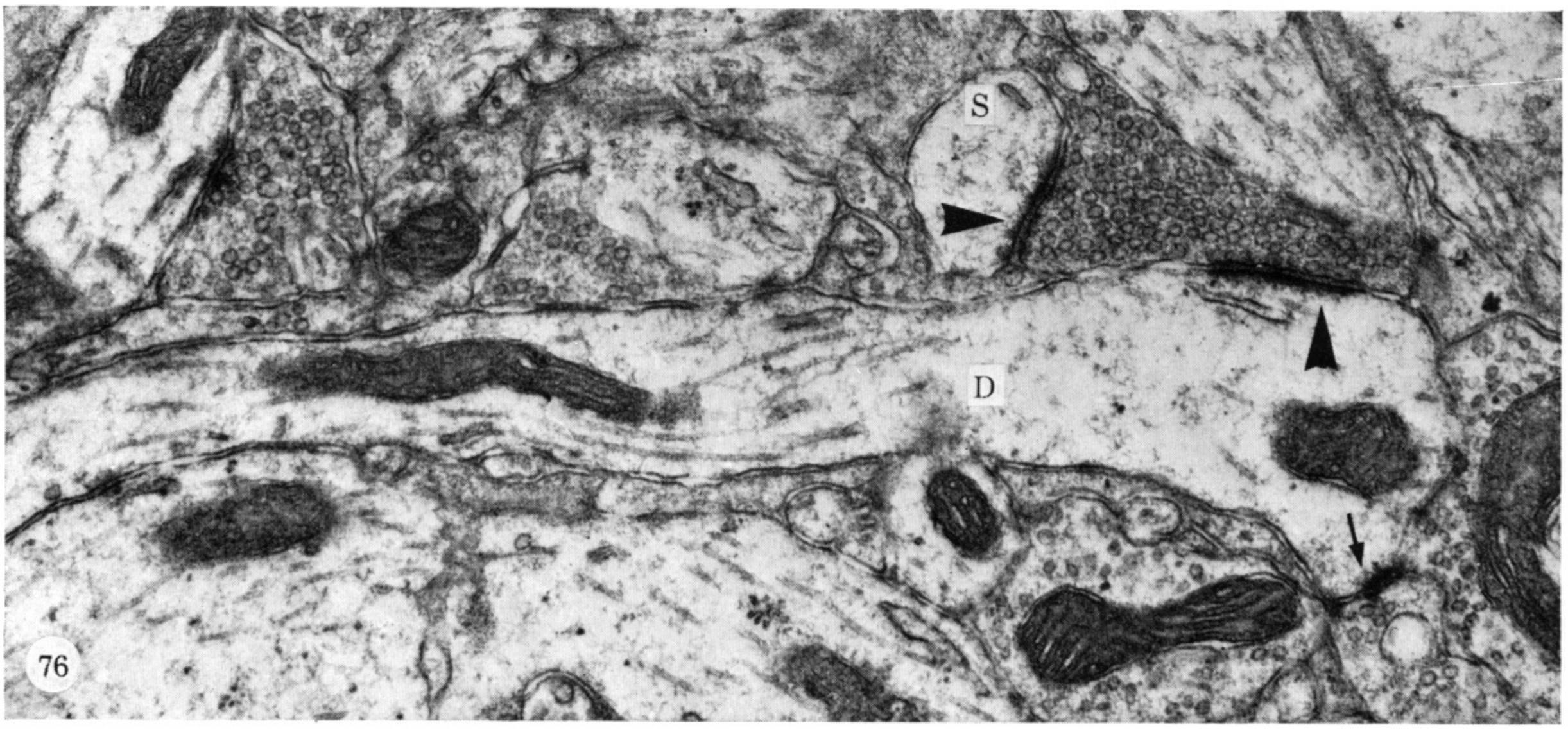


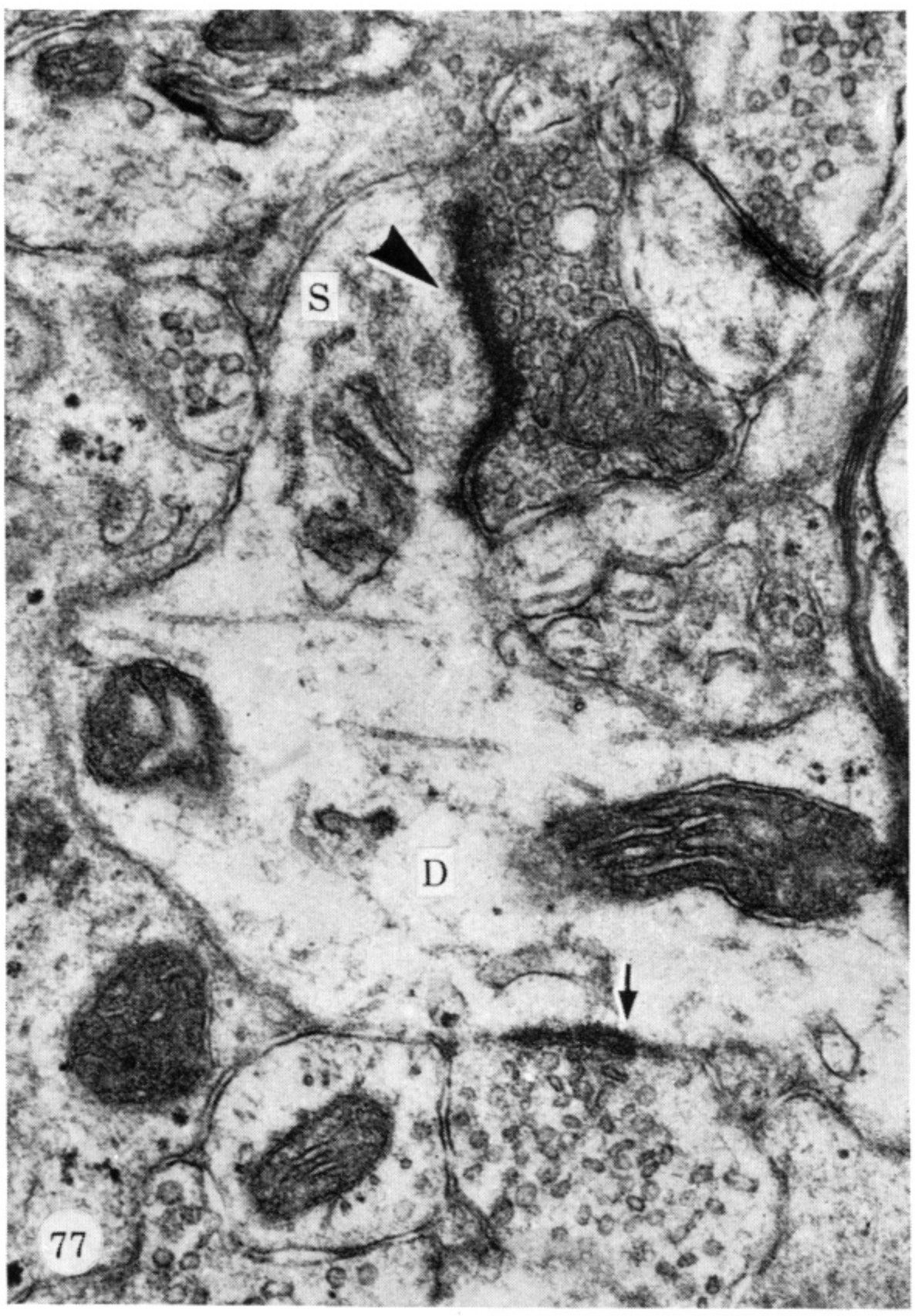


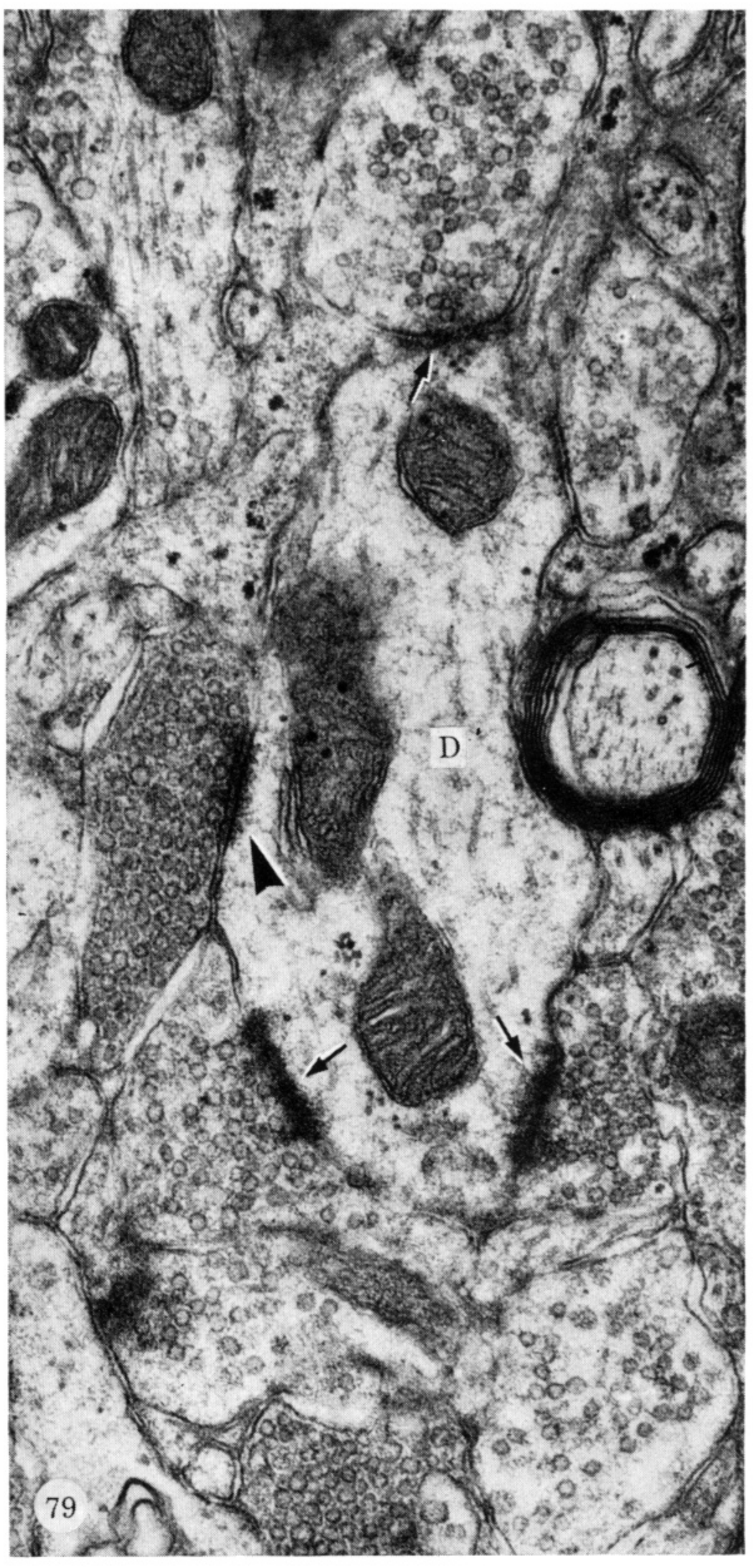


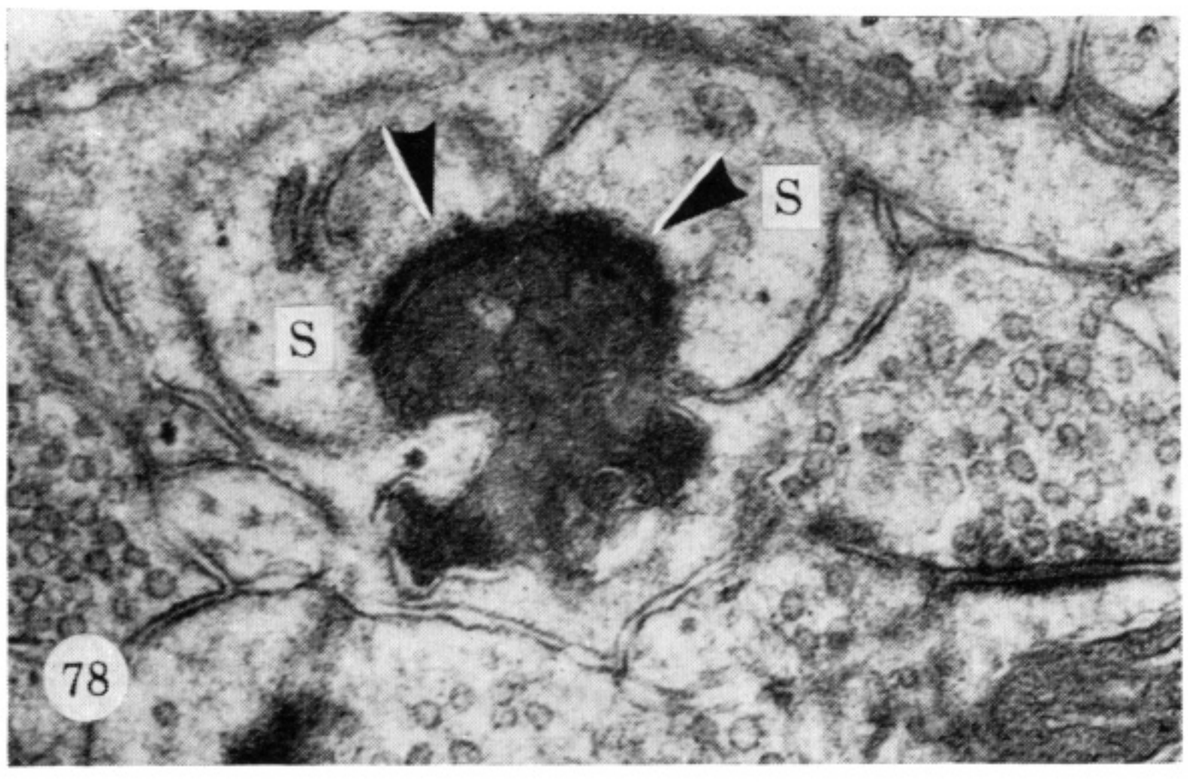


FIGURES 71–75. For description see opposite.









FIGURES 76–79. For description see opposite.