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The connective tissue of peripheral nerve: an electron microscope study

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INTRODUCTION

Although much information is now available concerning the structure of nerve fibres as revealed by the electron microscope, little attention has so far been given to the connective tissue elements of peripheral nerve using this technique. In view of the importance of the supporting structures in the processes of repair after nerve injury, it was considered of interest to make an electron microscope study of the connective tissue of normal peripheral nerve, with particular emphasis on the controversial issues of the nature of the sheaths of individual nerve fibres and the cellular content of the endoneurium. Reviews of the findings made by light microscopy have been given by Nageotte (1932), Young (1942) and Holmes & Young (1942). The classical investigations of Key & Retzius (1876) and Ranvier (1878) provided the basis for all subsequent studies in this field.

MATERIAL AND METHODS

All observations were made on the nerve to the medial head of the gastrocnemius muscle (N.G.M.) of adult rabbits. The animals were anaesthetized with Nembutal and ether and the nerves fixed *in situ* for 5 min. in 1 % osmium tetroxide in mammalian Ringer solution, buffered at pH 7·4. The nerve was then removed, cut into short segments and fixed in this solution for 4–6 hr. at 4° C. Following this, the pieces were rinsed in distilled water, dehydrated in ethanol in graded concentrations and then immersed in absolute ethanol containing 1 % phosphotungstic acid for 4 hr. Finally, the pieces were embedded in Araldite, sectioned with a Porter–Blum microtome, mounted on carbon-coated copper grids and examined with a Siemens Elmiskop II microscope.

RESULTS

The N.G.M. in the rabbit is composed of a single fasciculus containing approximately 400 myelinated nerve fibres and relatively few non-myelinated fibres. The three main subdivisions of the connective tissue of the nerve, the epineurium, perineurium and endoneurium (Key & Retzius, 1876) will be described separately. They correspond respectively to the perifascicular tissue, the lamellated sheath and the intrafascicular tissue of Ranvier (1878).

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Epineurium

As in other mammalian nerves, the nerve trunk is surrounded by a dense, collagenous connective tissue layer, the epineurium. Examination with the electron microscope reveals it to contain three types of extracellular fibrillary structure. Of these, the most prominent are the collagen fibres, disposed mainly in the length of the nerve trunk, although obliquely running bundles of fibres are also seen (Pl. 1, figs. 1, 4). The fibres have a diameter which usually lies between 700 and 850 Å. This is similar to the value of 800 Å. reported for the epineurium of the rat by Schmitt, Hall & Jakus (1942).

Elastin fibres are also present, again mainly disposed longitudinally. They are generally unbranched and 0·25–0·5 μ in diameter (Pl. 1, figs. 2–4). They are more densely stained at the periphery, where they are associated with fine filaments about 100 Å. in thickness. The elastin fibres resemble those described in other tissues and in particular those reported by Battig & Low (1961) in the connective tissues of the myocardium.

Fine filaments with a diameter of about 100 Å. are seen independently of elastin fibres, either in small bundles or intermixed with collagen fibres. They exhibit a 'beaded' appearance at times, but no clear periodicity has been noticed. They probably correspond to the 'microfibrils' described in connective tissues in other sites by Low (1961 *b*).

Fibroblasts are seen scattered throughout the epineurium. They have elongated processes and do not possess a basement membrane (Pl. 1, fig. 1).

Perineurium

The perineurium is composed of concentric layers of flattened cells disposed circumferentially around the nerve trunk within the epineurium. About ten laminae are usually present (Pl. 2, figs. 6, 7). The nuclei are also flattened, being seen as elongated structures both in transverse and longitudinal sections. The cells have prominent basement membranes. Between the laminae lie collagen fibres which, as in the epineurium, are mainly longitudinal. Occasional elastin fibres are present, associated with microfibrils. Microfibrils are also seen separately, especially adjacent to the basement membranes of the perineurial cells.

A striking feature of the perineurium is the close apposition between cells within a single lamina, the cells often being accurately 'dove-tailed' together (Pl. 2, fig. 9). Lateral processes making contact between neighbouring laminae and interlocking with each other are also seen (Pl. 2, fig. 8). At the junction between adjacent cells, membrane contacts are observed that are of the type described by Gray (1961) as 'closed contacts'. These are of considerable length at times (see Pl. 2, figs. 8, 9). Part of such a region is shown at higher magnification in Pl. 3, fig. 10. At these sites, the basement membranes are lost and the plasma membranes of the two cells are separated by a gap of 150–170 Å. with a thin intervening line making a three-lined system. Symmetrical densities are present in the cytoplasm beneath the adjacent plasma membranes.

Immediately internal to the innermost layer of the perineurium, there is frequently a flattened cell, but with features that differ from those of the perineurium itself: the nucleus is more compact, the endoplasmic reticulum more prominent and there is no basement membrane (Pl. 2, fig. 7). Such cells are interpreted as being fibroblasts, being similar to those seen within the endoneurium (Pl. 3, figs. 11–13).

Endoneurium

Extracellular fibrillary structures. The collagen of the endoneurium is again orientated mainly in the length of the nerve trunk and is aggregated around the nerve fibres and blood vessels and also in a zone immediately internal to the perineurium. Elsewhere, the collagen is considerably less densely packed. The fibres are of smaller diameter than those of the epineurium, being 500–600 Å. in thickness (Pl. 2, fig. 6 and cf. Pl. 1, figs. 4, 5). The organization of the endoneurial nerve fibre sheath will be discussed separately.

No elastin fibres have been seen in the endoneurium, although 100 Å. microfibrils are present, either diffusely associated with collagen fibres (Pl. 1, fig. 5) or in small bundles (Pl. 4, fig. 16). The absence of elastin fibres confirms the findings of light microscopy: elastin fibres were described as being present in the epineurium but not in the endoneurium (Stöhr, 1928).

Nerve fibre sheaths. The Schwann cells of both myelinated and non-myelinated nerve fibres are surrounded by a basement membrane approximately 250 Å. in thickness. This is separated from the plasma membrane of the Schwann cell by a gap of 250 Å. which contains some granular material similar to that of which the basement membrane is composed (Pl. 4, fig. 14).

The collagen fibres aggregated around the larger myelinated nerve fibres are separable into two layers, this being most clearly evident in longitudinal sections (Pl. 4, fig. 17). The outer layer consists of fibres running mainly longitudinally and more densely packed than in the inner layer. Those of the inner layer are generally of slightly lesser diameter and are not orientated in any uniform direction: some run circularly, others longitudinally, others obliquely. The same two layers are at times visible around the smaller myelinated fibres and around Schwann cells containing non-myelinated axons, although here the sheath is less distinctly organized. A similar arrangement exists around the endoneurial capillaries.

Cellular content of the endoneurium. Fibroblasts have been noted in the endoneurium by numerous light microscopists (e.g. Cajal, 1928; Nageotte, 1932; Masson, 1932; Denny-Brown, 1946; Thomas, 1948). With the electron microscope, these are observed (Pl. 3, fig. 13) as cells that lie in the interstices between the nerve fibres, having triangular or rectangular cell bodies when seen in transverse section; at times they partially encircle a nerve fibre and are then crescentic in shape. They possess elongated processes that extend either in the length of the nerve trunk or laterally between the nerve fibres. The processes branch and may loosely interdigitate with those from neighbouring fibroblasts. The cytoplasm of these cells contains a prominent endoplasmic reticulum (Pl. 3, fig. 11) which is not infrequently orientated in more or less parallel arrays. In places it is dilated, the cisternae containing granular material. Fine intracellular filaments are also present (Pl. 3, fig. 12). The cells do not possess a basement membrane. These features correspond to those described for fibroblasts in other sites (see Wasserman, 1954; Porter & Pappas, 1959; Gieseking, 1960).

In view of the statements by Causey & Barton (1959) and Palmer, Rees & Weddell (1961) that less than 5 % cells within the perineurium are fibroblasts, it was considered desirable to make counts of the number of nuclear profiles belonging to the different cell types observed in the endoneurium. Counts of nuclear profiles were made in whole transverse sections of five nerves by the technique described by Causey & Barton. All the nuclear profiles within the perineurium were counted, except those obscured by grid bars; it was assumed that those obscured were distributed randomly between the different cell types. The nuclei were classified into those belonging to Schwann cells containing myelinated and non-myelinated fibres, fibroblasts, capillary endothelial cells, capillary pericytes and perineurial extensions into the endoneurium. A small number of nuclei remained unclassified, belonging to cells of unrecognizable type.

Schwann cells were clearly identifiable by virtue of their relationship to myelinated or non-myelinated axons. In addition, they possess a basement membrane and contain 100 Å. filaments within their cytoplasm. Elfvin (1961) demonstrated the presence of 100 Å. filaments in the Schwann cells associated with non-myelinated axons. They are also present in those associated with myelinated axons (see Pl. 4, figs. 14, 17), but are usually less conspicuous. The features of the endoneurial fibroblast have already been described. The endothelial cells forming the walls of capillaries were also easily recognizable (Pl. 4, fig. 15). A further type of cell encountered in the endoneurium lies in close proximity to the walls of the capillaries; an example is shown in Pl. 4, fig. 15. These cells frequently have a crescentic shape when seen in transverse section and partially encircle the capillaries. They will be referred to as capillary pericytes. Both these cells and the capillary endothelial cells possess basement membranes. Such capillary pericytes were noted in the endoneurium by Causey & Barton (1959) and closely resemble cells described as occurring in relation to capillaries in the connective tissue of the myocardium by Battig & Low (1961). Their nature is uncertain. The extensions of perineurial cells into the endoneurium are usually associated with the entry of blood vessels (Pl. 4, fig. 18).

Table 1. *Counts of nuclear profiles within perineurium of rabbit* N.G.M.

(Numbers of nuclei examined with percentage values given in parentheses.)

Serial no. of rabbit	A81	A324	A351	A433	A434	Totals
Schwann cells (total)	20 (39·2)	67 (45·9)	84 (45·7)	60 (43·5)	63 (46·0)	294 (44·8)
Schwann cells (myelinated)	9 (17·6)	24 (16·4)	28 (15·2)	13 (9·4)	38 (27·7)	112 (17·4)
Schwann cells (non-myelinated)	11 (21·6)	43 (29·5)	56 (30·4)	47 (34·1)	25 (18·2)	182 (27·7)
Endoneurial fibroblasts	18 (35·3)	47 (32·2)	33 (17·9)	33 (23·9)	29 (21·2)	160 (24·4)
Capillary endothelial cells	7 (13·7)	11 (7·5)	37 (20·1)	23 (16·7)	22 (16·1)	100 (15·2)
Capillary pericytes	3 (5·9)	4 (2·7)	8 (4·3)	10 (7·2)	9 (6·6)	34 (5·2)
Perineurial cells	0	8 (5·5)	0	0	0	8 (1·2)
Unclassified	3 (5·9)	9 (6·2)	22 (12·0)	12 (8·7)	14 (10·2)	60 (9·2)
Totals	51	146	184	138	137	656

The results of the nuclear profile counts are shown in Table 1. It will be seen that approximately 45 % of the profiles belonged to Schwann cells, approximately 25 % to fibroblasts and 15 % to capillary endothelial cells.

Palmer *et al.* (1961) reported that in the sural nerve of unoperated rats, very few endoneurial fibroblasts were present, whereas in the contralateral nerves of animals in which one sural nerve had been sectioned 5 days previously, up to 25 % of the nuclei might belong to fibroblasts. In the present series, the nerves of rabbits A 433 and A 434 were from unoperated animals, whereas those from A 81, A 324 and A 351 were from animals in which the opposite N.G.M. had been crushed 300, 14 and 133 days before, respectively. In view of the possible contralateral effect of nerve injury, the proportion of endoneurial fibroblasts to other nuclei was compared by the χ^2 test. No significant difference was present between the nerves from the unoperated animals and the unoperated nerves from the operated animals ($P > 0{\cdot}1$).

DISCUSSION

Although Lorente de Nó (1950) was of the opinion that the connective tissue sheaths of peripheral nerves do not significantly impede diffusion, it has now been established that they provide an effective diffusion barrier (see Feng & Gerard, 1930; Feng & Liu, 1949; Rashbass & Rushton, 1949; Crescitelli, 1951). There have been some differences of opinion as to the anatomical site of the barrier, but it is now evident that it is provided not by the epineurium, but by the perineurium (Krnjević, 1954), as would indeed be expected in view of its cellular composition. The present electron microscope study shows that the cells of the perineurium are closely interlocked and intimately attached to one another by multiple closed contacts, this being in keeping with their action as a diffusion barrier. Gray (1961) has demonstrated that in closed contacts between glial cell processes in the brain, the extracellular space is reduced or obliterated. In osmium tetroxide fixed material, the closed contact appears as a three-lined system corresponding with the 'external compound membrane' seen after fixation with potassium permanganate (see Robertson, 1959). Gray has postulated that closed contacts, in sealing off the extracellular space, force metabolites to traverse a cytoplasmic pathway. The perineurium can thus be considered as insulating the environment of the nerve fibres from the external tissues. Masson (1942) considered that the perineurium represented the junction between mesoderm and ectoderm. He believed that, in addition to the Schwann cells, the cells of the endoneurium and the perineurium were of ectodermal origin from neural crest tissue, whereas the epineurium was derived from mesoderm.

The epineurium is composed of densely packed collagen fibres. In the endoneurium, on the other hand, apart from the condensations around the nerve fibres and blood vessels, and subperineurially, the collagen is loosely packed, leaving substantial extracellular fluid spaces. The experiments of Weiss (1943) and Weiss, Wang, Taylor & Edds (1945) have indicated that the endoneurium contains fluid that flows in a proximo-distal direction along the nerve trunk. Low (1961*a*) has introduced the concept that the basement membrane of cells defines the limits of the extracellular tissue space. This space contains formed elements, such as connective tissue fibres, and cells that lack any membranous ensheathment. Applying this concept to peripheral nerve, the perineurial, Schwann, capillary and capillary pericytes all possess basement membranes and thus lie outside the extracellular tissue space. The endoneurial fibroblasts, not possessing basement membranes, along with the extracellular fibrillary structures, lie within this space.

The nature of the sheaths of peripheral nerve fibres has long been the subject of debate, an added difficulty being confusion over terminology (see Young, 1942; Holmes & Young, 1942). It is of interest to relate the findings obtained by electron microscopy to those derived from light microscopy. In 1839, Schwann (see Münzer, 1939) described the cell which bears his name and which he observed as a thin layer immediately outside the myelin, bounded externally by a membrane. This membrane, the 'membrane (or sheath) of Schwann', was described by Young (1942) as a 'thin layer, closely adherent to the myelin, and curving in at the nodes of Ranvier'. External to the 'membrane of Schwann', Key & Retzius (1876) defined a layer of longitudinally orientated collagen fibres, which was considered to be part of the endoneurium. The 'sheath of Key and Retzius', sometimes referred to as the 'sheath of Henle', is not inflected at the nodes. It is to be noted that the term 'sheath of Schwann' has also been employed to refer to the layer of Schwann cell cytoplasm external to the myelin.

Plenk (1927) described a network of fine argyrophil fibres around the nerve fibre and this was confirmed by Laidlaw (1930). Later Plenk (1934) observed that he could not demonstrate this network simultaneously with the 'membrane of Schwann' and considered that the two were identical, as was thought possible by Masson (1932). Plenk suggested that there was an inner endoneurial sheath (the 'sheath of Plenk and Laidlaw') made up of a network of fine argyrophil fibres, and an outer endoneurial sheath composed of longitudinal collagen fibres.

The present electron microscope observations confirm the interpretation made by Plenk. It is likely that the inner endoneurial sheath corresponds to the system of collagen fibres seen with the electron microscope immediately outside the basement membrane of the Schwann cell containing circular, longitudinal and oblique fibres, and that the outer endoneurial sheath corresponds to the external layer of longitudinal collagen fibres. It would be desirable to have electron microscope observations on the appearances at the nodes of Ranvier, but satisfactory longitudinal sections through nodes of large myelinated fibres have not so far been obtained. This is being further studied.

Glees (1943), when examining the connective tissue sheaths of cutaneous nerves, failed to demonstrate any distinction between inner and outer endoneurial sheaths. This finding is possibly explained by the observation made in the present study that the separation between the inner and outer endoneurial sheaths is less definite for small myelinated nerve fibres than for larger fibres. In the cutaneous nerve plexus, fibre diameter is likely to be small.

The term 'neurilemma' has been used in several different senses. In recent years it has been employed to refer either to the inner endoneurial sheath (e.g. Young, 1942) or to the layer of Schwann cytoplasm outside the myelin (e.g. Guth, 1956). In electron microscope examinations of peripheral nerve, Hess (1956) considered that it consisted of the plasma membrane of the Schwann cell, together with the basement membrane and a variable amount of connective tissue ground substance between. Terry & Harkin (1957) thought that it also included some collagen fibres external to the basement membrane. It is here advocated that the term be now abandoned as no longer serving any useful descriptive purpose.

The present study has demonstrated that an appreciable proportion of cells within the perineurium of the rabbit N.G.M. are fibroblasts. No absolute figures can be given as total counts were not made. Moreover, correction for nuclear length (see Abercrombie, 1946) is difficult to apply to electron microscope sections. However, the present values for the relative proportions of different cell types agree very closely with those reported by Thomas (1948) on the basis of light microscope examination of the N.G.M. of the rabbit. This author found that at 5 days of degeneration, when there would have been little change in nuclear numbers, 45 % were tubal nuclei (nuclei within Schwann tubes), 41 % endoneurial connective tissue nuclei and 14 % blood vessel wall nuclei. The values for tubal and blood vessel wall nuclei are almost identical with the present results, and the value for the endoneurial connective tissue nuclei agrees if the figures for endoneurial fibroblasts, capillary pericytes and cells of uncertain nature are taken together. Thomas did not distinguish between the different endoneurial connective tissue nuclei.

With regard to the apparent discrepancy between the findings of the present study and those of Causey & Barton (1959), this is probably due to the fact that these workers mainly examined the sural nerve. This nerve contains a far greater number of non-myelinated nerve fibres; moreover, the myelinated fibres are of generally smaller size with shorter internodal lengths and will therefore possess more numerous Schwann cell nuclei. For these two reasons, the relative proportion of Schwann cell nuclei to other nuclei will be greater.

SUMMARY

1. An electron microscope study of the connective tissue of the nerve to the medial head of the gastrocnemius muscle in the rabbit has been made after fixation with osmium tetroxide and staining with phosphotungstic acid.

2. The epineurium consists predominantly of longitudinal collagen fibres with a diameter of 700–850 Å., associated with fibroblasts. Elastin fibres and microfibrils are also present.

3. The perineurium is a concentrically laminated structure composed of flattened cells of endothelial type which are closely interlocked with each other. Closed contacts are present at the junctions between neighbouring cells.

4. The endoneurium is composed of longitudinally arranged collagen fibres with a diameter of 500–600 Å. Condensations are present around the nerve fibres and capillaries, and subperineurially. The collagen is associated with microfibrils, but no elastin fibres are present.

5. Schwann cells of large myelinated nerve fibres are surrounded by a basement membrane outside which the endoneurium is organized into two layers. The inner layer is composed of collagen fibres of slightly smaller diameter than those of the outer layer and which run longitudinally, circularly and obliquely. The outer layer consists solely of longitudinal collagen fibres. A similar sheath surrounds the Schwann cells containing small myelinated and non-myelinated axons, but is less clearly organized into two layers.

6. Counts of the cellular content of the nerve trunk within the perineurium revealed that, in this nerve, approximately 45 % of the nuclei seen in transverse sections are those of Schwann cells, approximately 25 % those of fibroblasts, and

the remainder belong to capillary endothelial cells, capillary pericytes, perineurial extensions into the endoneurium and unidentified cells.

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Key to Lettering

b.m.	basement membrane	i.en.	inner endoneurium
b.v.	blood vessel	mes.	mesaxon
cap.	capillary	mf.	microfibrils
c.c.	closed contact	my.	myelin
c.f.	collagen fibres	o.en.	outer endoneurium
e.f.	elastin fibre	pc.	capillary pericyte
en.	endoneurium	pn.	perineurium
epn.	epineurium	p.m.	plasma membrane
e.r.	endoplasmic reticulum	pr.	lateral process of perineurial cell
f.	intracellular filaments	S.c.	Schwann cell
fb.	fibroblast		

EXPLANATION OF PLATES

PLATE 1

Fig. 1. Transverse section through epineurium showing collagen fibres and fibroblast.

Fig. 2. Longitudinal section through epineurium showing elastin fibre.

Fig. 3. Transverse section through epineurium showing collagen fibres and elastin fibres with associated microfibrils.

Fig. 4. Longitudinal section through epineurium showing collagen fibres and an obliquely sectioned elastin fibre.

Fig. 5. Longitudinal section through endoneurium showing collagen fibres and microfibrils.

PLATE 2

Fig. 6. Transverse section through perineurium showing laminated structure. The difference in the diameter of the epineurial and endoneurial collagen fibres is seen.

Fig. 7. Transverse section through perineurium. A fibroblast lies immediately internal to the innermost lamina.

Fig. 8. Contacts between perineurial cells. An elongated closed contact is seen at the region of apposition between the two cells on the right. The two cells on the left display interlocking lateral processes.

Fig. 9. Transverse section through perineurium. Three interlocking cells are seen on the left with multiple closed contacts.

PLATE 3

Fig. 10. Portion of a closed contact between two perineurial cells formed by three parallel dense lines with an overall dimension of 150–170 Å. Symmetrical densities are present in the cytoplasm beneath the plasma membranes.

Fig. 11. Portion of endoneurial fibroblast showing endoplasmic reticulum.

Fig. 12. Portion of endoneurial fibroblast showing intracellular filaments and dilated endoplasmic reticulum.

Fig. 13. Endoneurial fibroblast.

PLATE 4

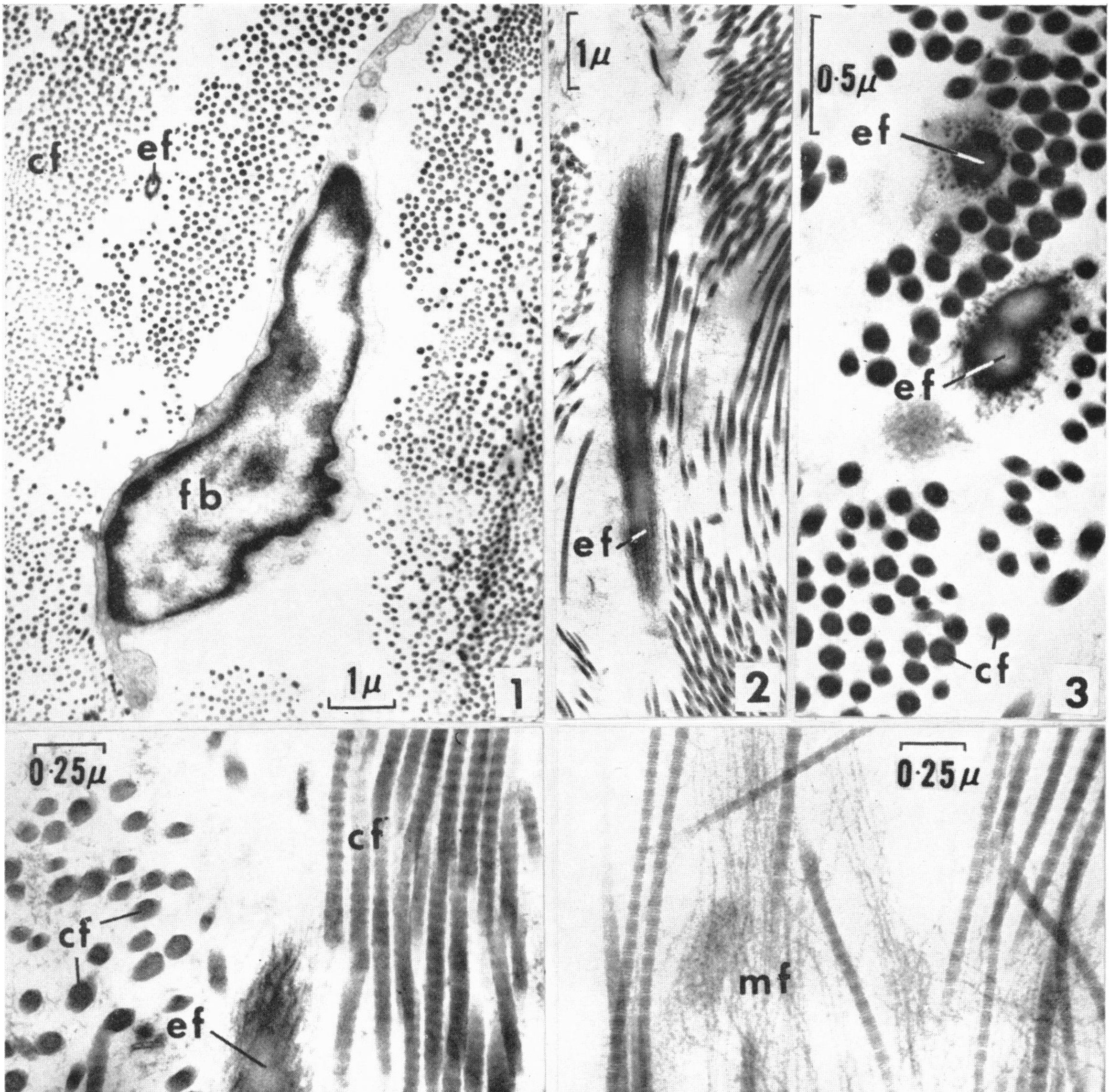
Fig. 14. Margin of Schwann cell, showing basement membrane and transversely sectioned intracytoplasmic filaments. The outer myelin lamellae only have been stained by the phosphotungstic acid.

Fig. 15. Endoneurial capillary with pericyte.

Fig. 16. Bundle of microfibrils in endoneurium.

Fig. 17. Longitudinal section of nerve showing inner and outer layers of endoneurium lying outside basement membrane of Schwann cell of a myelinated nerve fibre. Fine longitudinal filaments are visible in the Schwann cell cytoplasm.

Fig. 18. Two perineurial cells within endoneurium associated with entry of a blood vessel.



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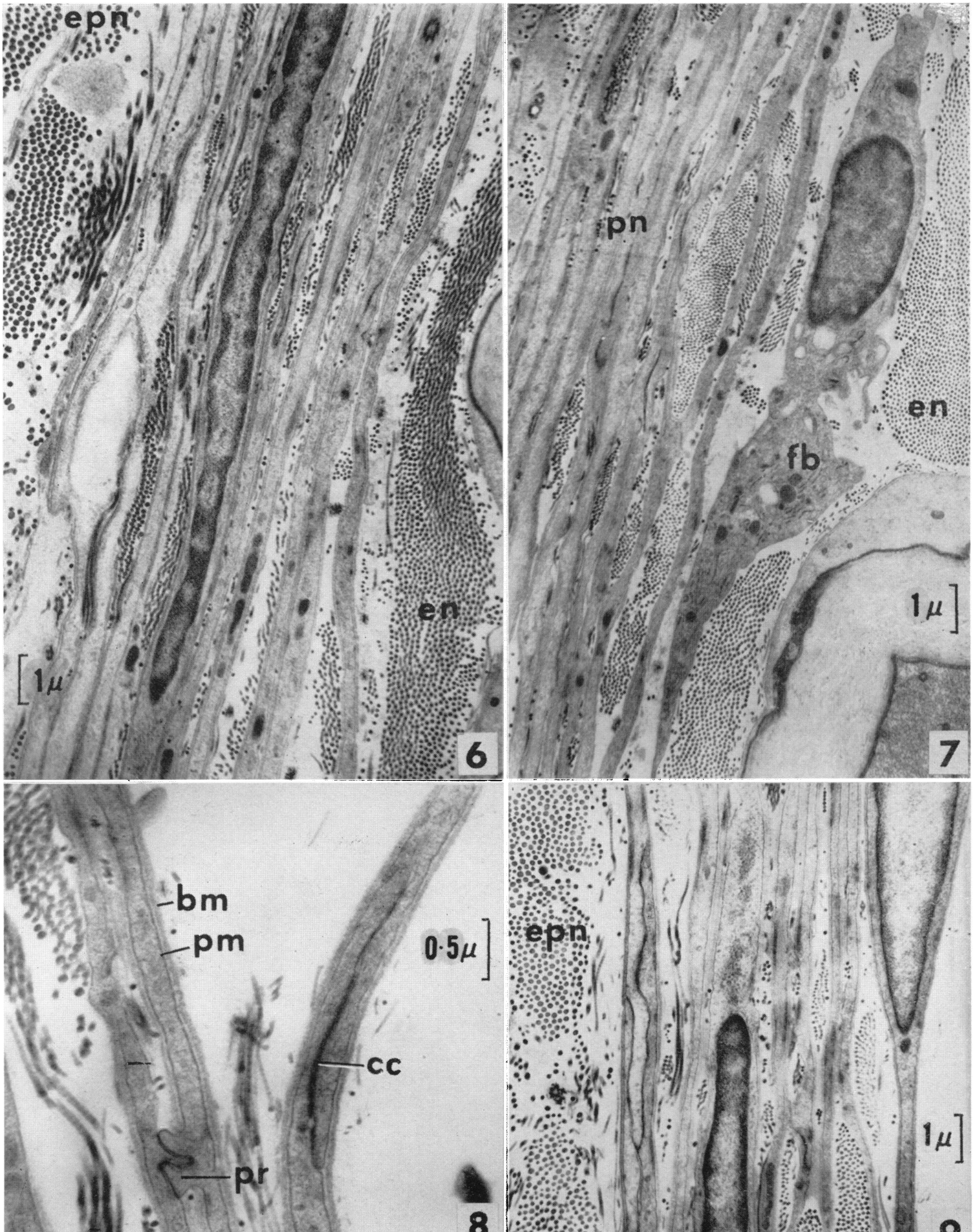

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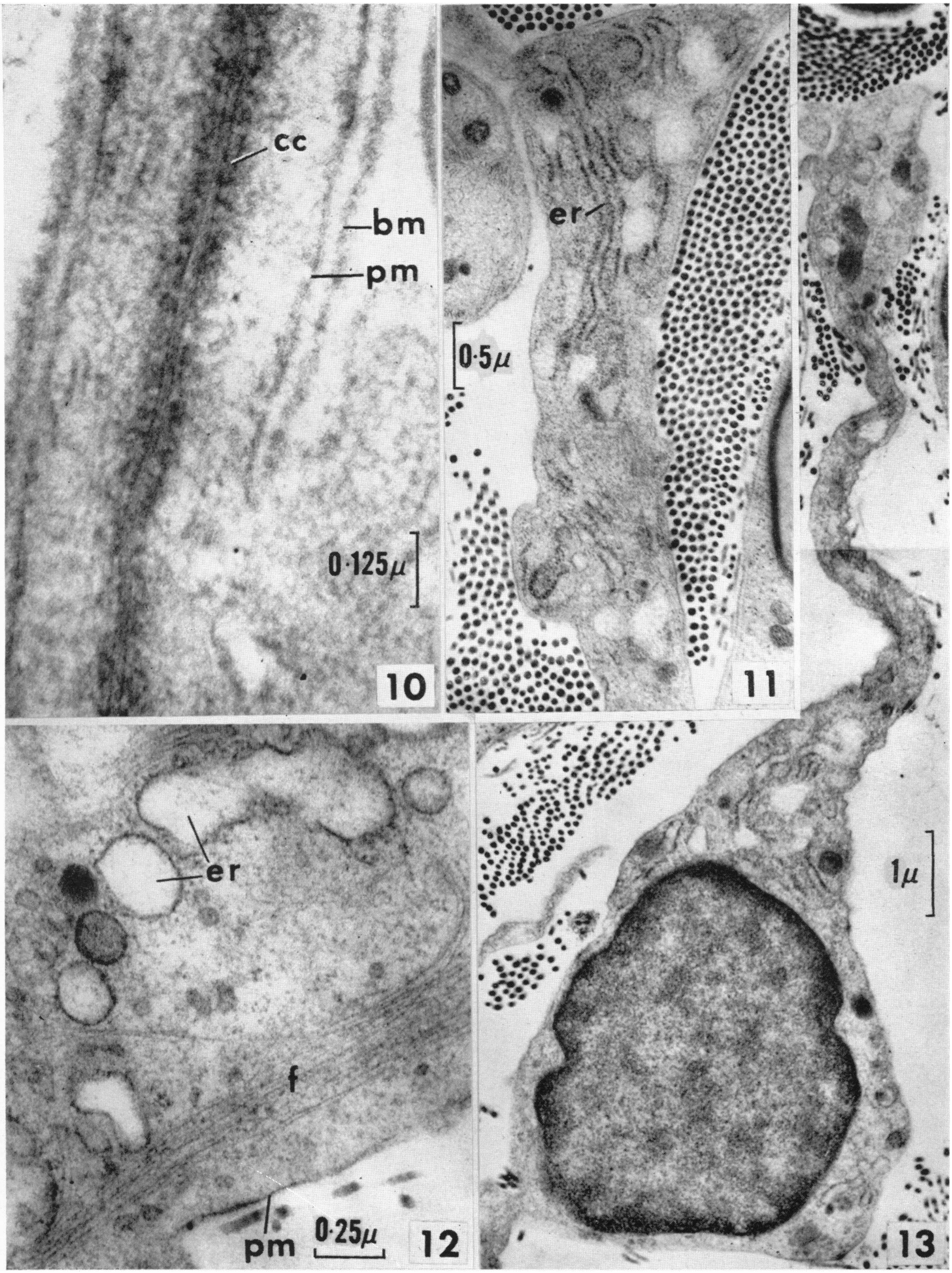

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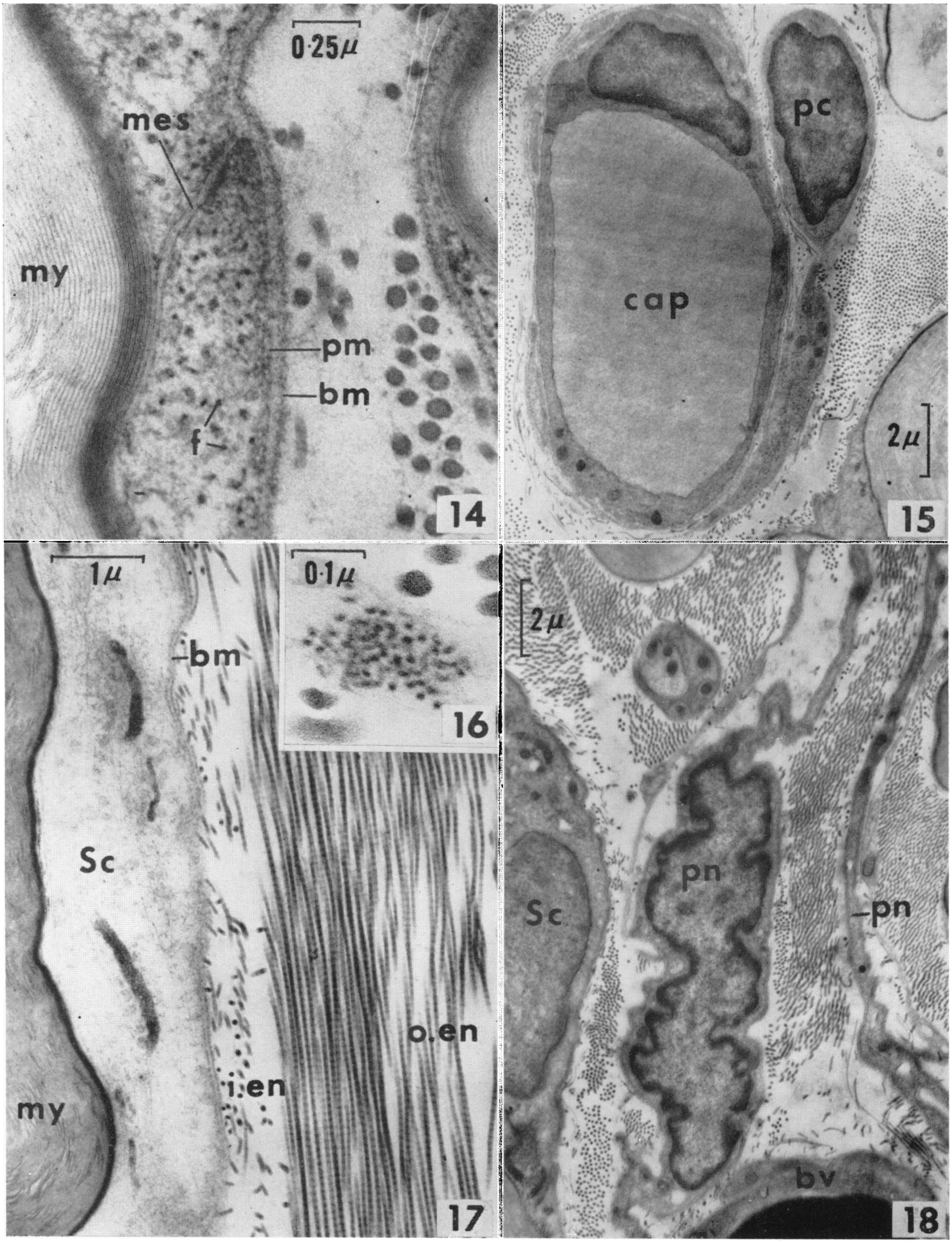
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