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Electron microscope observations on the human foetal and embryonic spinal cord

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INTRODUCTION

Many of the electron microscope studies of the developing mammalian central nervous system have been directed to the elucidation of the mechanism whereby spiralled lamellae of myelin are spun about the associated axons (e.g. Peters, 1960, 1962, 1964). The development of the ependyma has also been studied, for example, in the rabbit (Tennyson & Pappas, 1962) and in man (Malinský & Brichová, 1967) but other aspects of human central nervous system development do not appear to have been studied by electron microscopy.

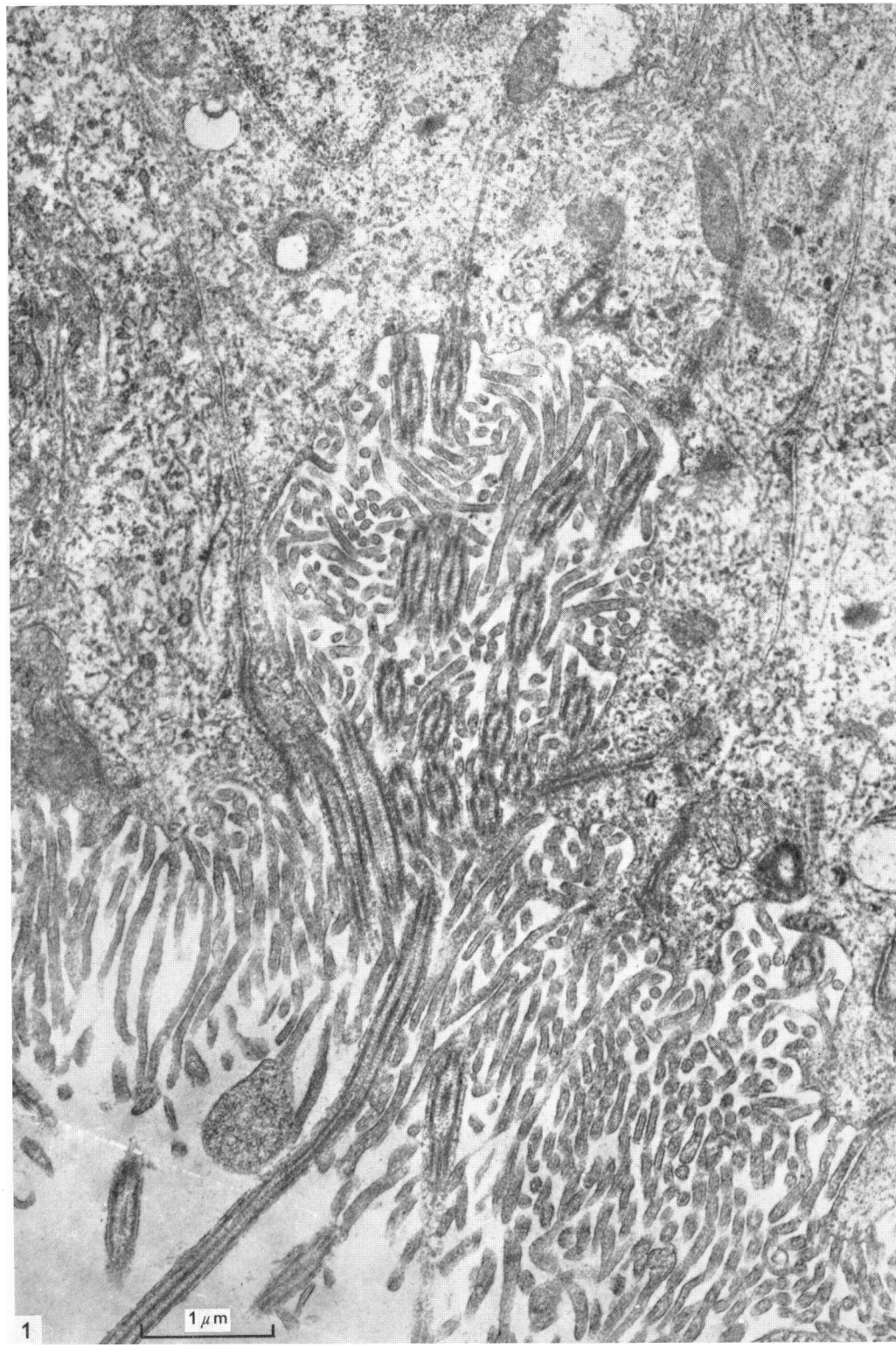
The present observations were made on human foetuses obtained at hysterotomies performed for various reasons. The histories of the mothers never suggested that any foetal abnormality would be present and none was seen. The crown-rump measurements are given but the ages of the foetuses have been estimated using figures given in the literature (Hamilton, Boyd & Mossman, 1952; Fitzgerald & Windle, 1942; Hogg, 1941) for it was clear that little reliance could be placed upon the estimates of foetal age obtained from the mothers.

MATERIALS AND METHODS

Segments of lumbar spinal cord from human foetuses of 1·5, 3, 4 and 12 cm C.R. length were dissected out some 15–20 min after hysterotomy, the foetuses having been chilled with ice cubes from within a minute or two of separation from the mothers. The estimated intra-uterine lives were respectively, 4–6 weeks, 7–8 weeks and 13–16 weeks.

The cord was exposed under the dissecting microscope when it was immersed in chilled 5 % gluteraldehyde in phosphate buffer at pH 7·3. Ten minutes later slices 1 mm thick were cut and immersed first in the buffered glutaraldehyde and then, after several rinses in a 10 % solution of sucrose similarly buffered, for 1 h in a buffered 1 % solution of osmium tetroxide.

After dehydration and embedding in Araldite, thick sections were stained with a mixture of Azur II and Methylene Blue (Richardson, Jarett & Fink, 1960) and examined by light microscopy. Thin sections were stained with uranyl acetate after mounting on uncoated grids and examined in a Metropolitan Vickers EM 6 electron microscope.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RESULTS

The cord of the 12 cm foetus resembled in some respects that of the adult and is here described first.

The lumbar cord was approximately 2·5 mm wide and 2 mm deep with a conspicuous anterior fissure. The central canal was small and lined with a columnar ependyma. Grey matter was disposed in anterior and posterior columns, and in a central mass surrounding the canal. Nissl substance was present in the larger cells of the grey matter, especially in the anterior horns. Scattered glial cells and myelinated nerve fibres lay in the marginal zone. The distribution of the fibres appeared to be random and although small groups of three or more sometimes occurred, fibre tracts could not be recognized.

Electron microscopic observations in this cord were limited to the central canal, the medial part of the anterior horn of the grey matter and the anterior funiculus of the marginal zone.

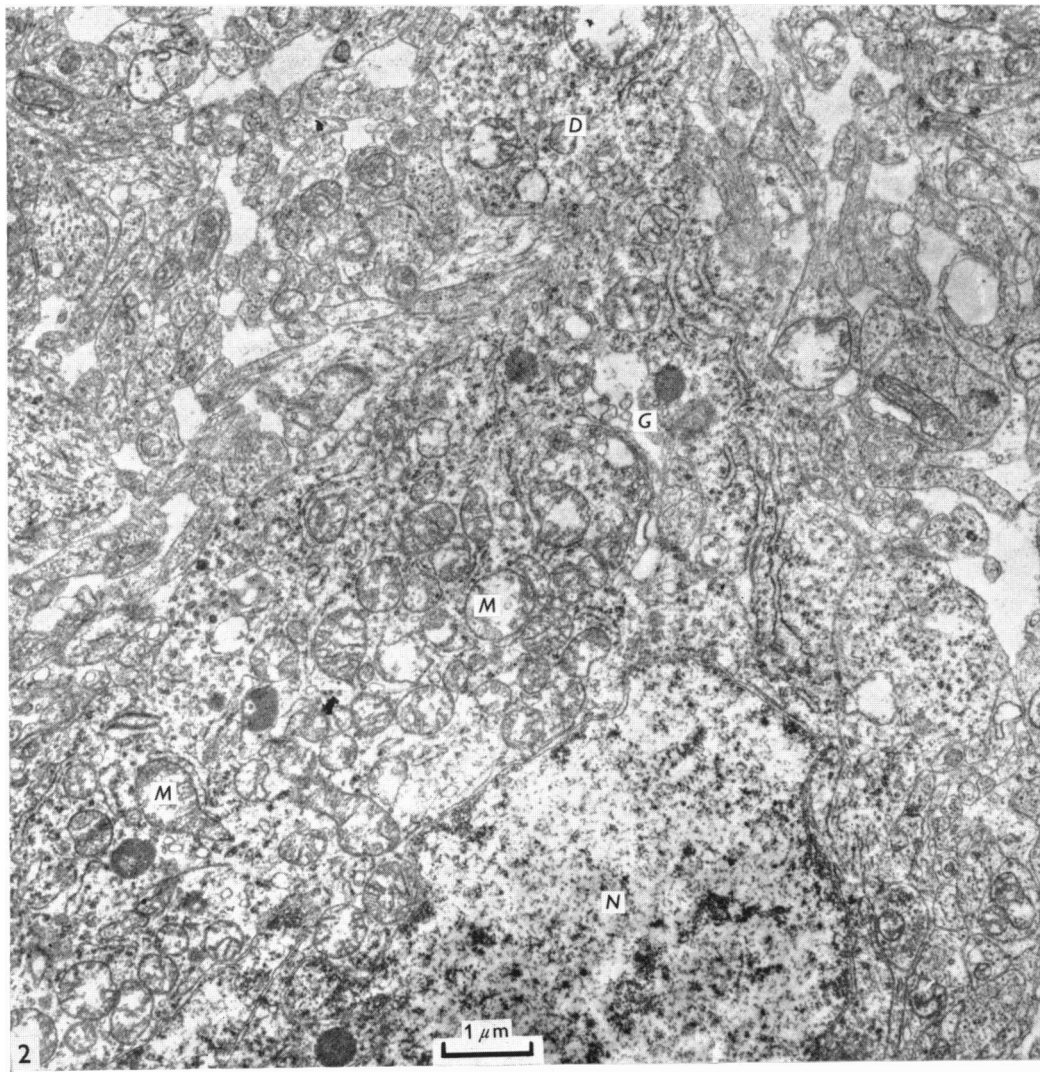
The ependyma exhibited conspicuous junctional complexes close to the lumen: elsewhere contacts between neighbouring cells were uncomplicated, with an electron-lucent gap of *c.* 20 nm everywhere present. At junctional complexes the adjacent membranes were of increased density and apparent thickness, and the gap between them in places widened and in other places disappeared, but whether this appearance was due to actual fusion or to the plane of section is not clear (Fig. 1). The cytoplasm contained a moderately dense ground substance in which lay free and aggregated ribosomes, tubular or filamentous structures, extensive areas of Golgi apparatus, and mitochondria which often appeared swollen. Granular endoplasmic reticulum was present but nowhere extensive. Numerous microvilli extended into the lumen of the canal as did cilia and, much less frequently, extensive bleb-like projections. Two or more cilia often arose from the same ependymal cell where each was equipped with the usual basal apparatus. All cilia seen showed the central as well as the peripheral tubules characteristic of kinocilia.

The bulk of the grey matter was a complex neuropil in which most of the cytoplasmic processes could hardly be identified. Scattered through it were cell bodies, some of which, by their large size and cytoplasmic inclusions, could be identified as neurons (Fig. 2).

Close to the neuronal nucleus were many mitochondria and an area of Golgi apparatus, while the more peripheral cytoplasm contained extensive flattened cisternae of granular endoplasmic reticulum associated with free and aggregated ribosomes to form Nissl bodies. A cytoplasmic process of the cell extended beyond the section, and from its content of Nissl bodies was identified as a dendrite. Similar processes seen elsewhere in the neuropil were likewise identified (see, for example, Fig. 3). The nucleus of the neuron was large and may have been deeply indented. No process identifiable as an axon was seen arising from this or any other neuron.

A second population of cell bodies present in the gray matter was presumed to consist of neuroglial cells. These were smaller and had less extensive and less

Fig. 1. Ependymal cells of 12 cm specimen. Cilia, microvilli and a club-ended pseudopodium project into the lumen of the central canal. Junctional complexes lie close to the lumen but elsewhere the side-walls of the cells are smooth.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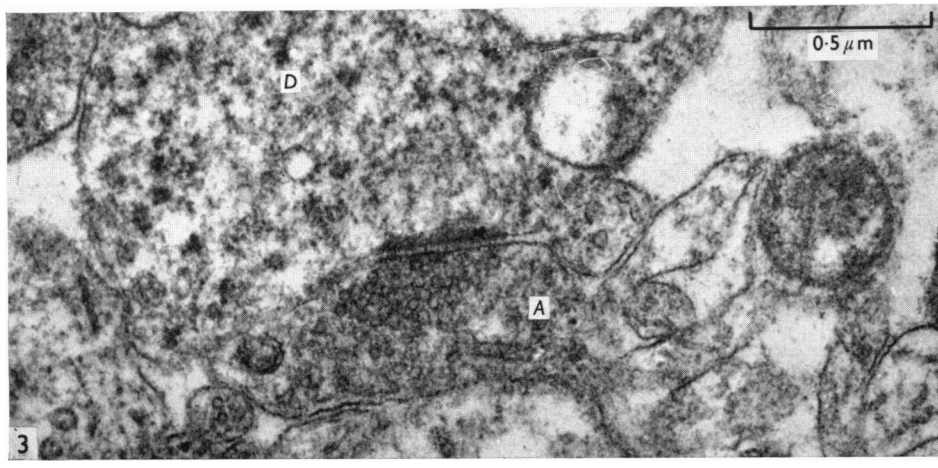
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D
A
3

differentiated cytoplasm: in particular nothing resembling a Nissl body was seen. It was not possible to distinguish astrocytes from oligodendrocytes. Similar cells were present in the marginal zone also and there entered into complex relationships with axons and with one another.

Figure 3 illustrates other features of anterior horn neuropil. The large cytoplasmic process containing swollen mitochondria and polyribosomes was identified as a dendrite and it was in synaptic relationship with a vesicle-containing process identified as an axonal terminal. The plasma membrane of the dendrite was thickened and of increased electron density opposite the concentration of synaptic vesicles and some cross-striation was visible in the gap separating the two plasma membranes. The vesicles were of *c.* 30 nm in diameter. Thickened electron-dense patches of plasma membrane were frequently seen unassociated with other characteristics of synapses and their significance is not known.

Myelinated axons were scattered through the marginal layer, usually singly, but sometimes in groups of three to five closely adjacent. Usually an internal mesaxon was present but on the outer aspect of the sheath only a glial process was seen where some were extensive (see Figs. 4 and 5).

Much of the marginal zone was a complex of cytoplasmic processes which could not certainly be identified. Occasionally, as in Fig. 4, their inter-relationships allowed identification. Here the cytoplasmic processes of a glial cell enwrapped a bundle of small axons and also provided separate coverings for each of several larger axons. Fig. 5 is a line drawing to show these inter-relationships more clearly. Axons identified by their relationships with glia usually contained cross-sections of tubules of 23–25 nm diameter and, more rarely, filaments of 7–10 nm diameter. Similar structures occurred also in undoubted glial processes but here were less regularly orientated and were usually set in a more electron-dense cytoplasm.

The outer surface of the marginal layer was a mosaic of cytoplasmic processes which expanded on reaching the surface and there, with a continuous covering of basement membrane, formed the 'outer limiting membrane'. They were assumed to have arisen from glial cells or even from ependymal cells, but connexions were not observed. A similar arrangement of cytoplasmic processes and basement membranes was found in relation to blood vessels in the cord.

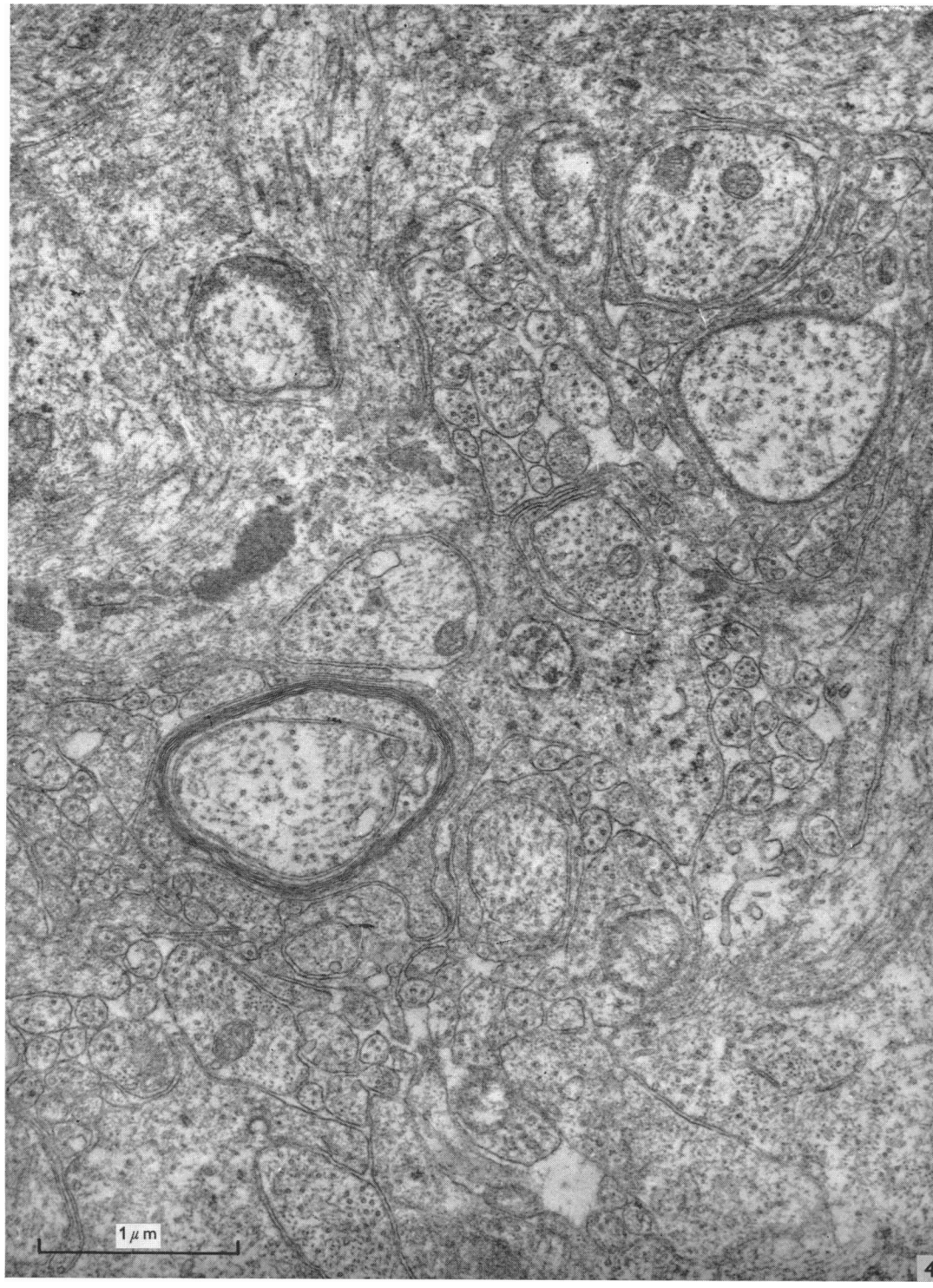
The segments of spinal cord from the 3 and 4 cm foetuses were very similar and will be considered together.

The lumen of the central canal was extremely narrow and in places difficult to make out by light microscopy, except ventrally where a small part remained patent. The ependymal layer blended indistinctly with the mantle, but the junction of mantle and marginal layers was more clearly marked.

By electron microscopy the ependymal epithelium was seen to be characterized

Fig. 2. Anterior horn neuron from 12 cm specimen. Many mitochondria (*M*) and some Golgi apparatus (*G*) lie to one side of the nucleus (*N*) while Nissl bodies, as flattened cisternae and clumps of ribosomes, occupy the periphery of the cytoplasm and extend into a dendritic process in the upper part of the field (*D*). The neuron lies in a complex neuropil.

Fig. 3. Synaptic contact in anterior horn neuropil from 12 cm specimen. An axonal terminal (*A*) contains many vesicles of *c.* 30 nm diameter. Beside it, a larger dendritic process (*D*) contains clumps of ribosomes and its plasma membrane is thickened and of increased electron density opposite the aggregation of vesicles. Some cross-striation is visible in the synaptic cleft.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by extensive flattened cisternae of granular endoplasmic reticulum close to one or other pole of the nucleus. (Similar stacking was seen also in ependymal cells of the 1·5 cm embryo, Figs. 9 and 10.) The ependymal cytoplasm was rich in other organ-

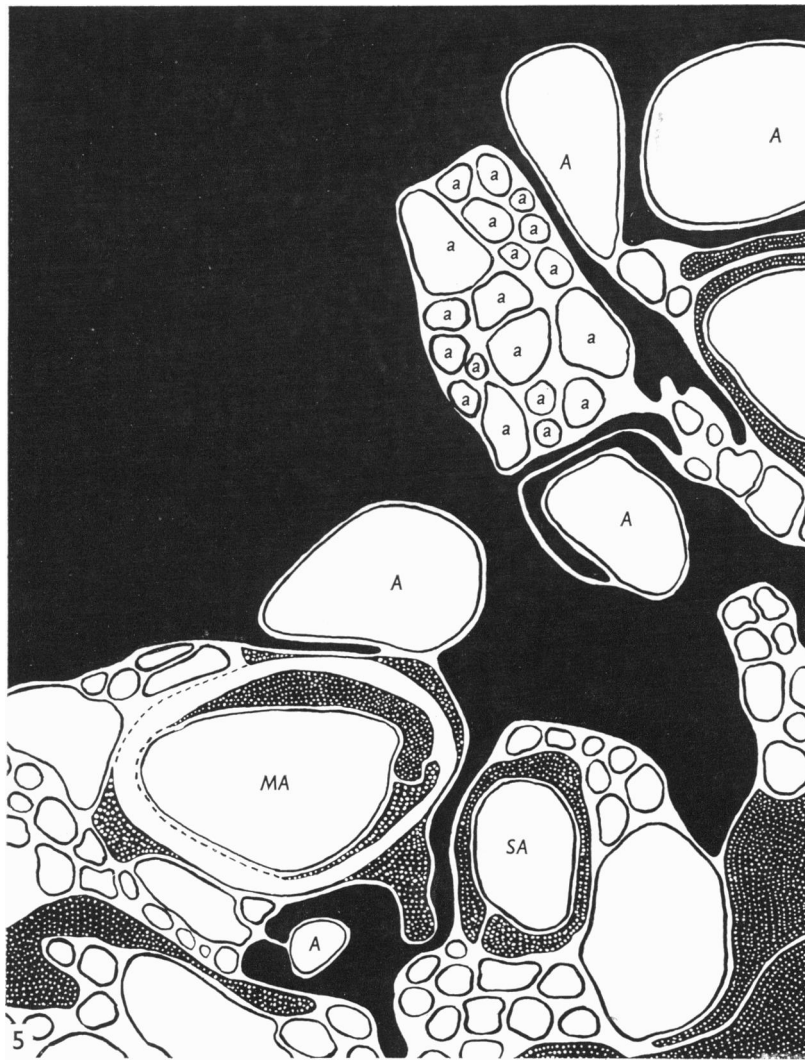
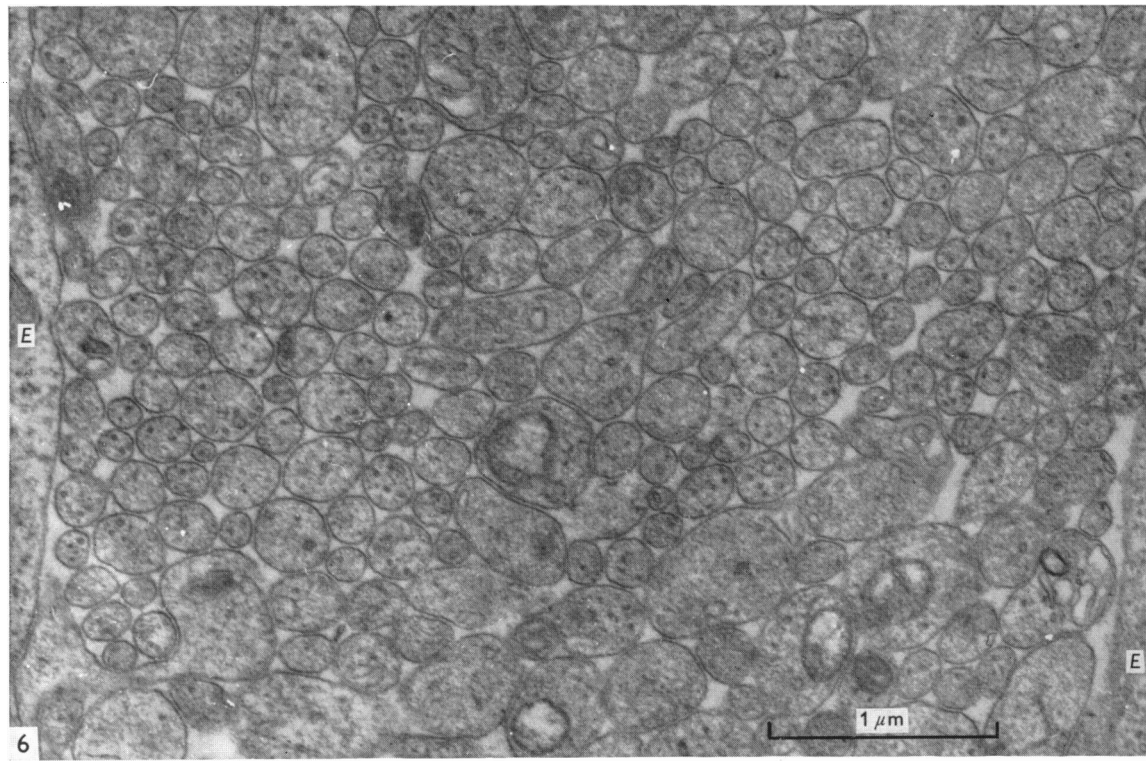


Fig. 5. Tracing made from a print of Fig. 4. Solid black indicates partial extent of a glial cell which provides individual wrapping for five axons (*A*) and a common investment for some 20 others (*a*). Stippling indicates other glial cells, one on inner and outer aspects of the myelin sheath of axon *MA*, another more simply investing axon *SA*.

Fig. 4. Marginal zone from 12 cm specimen. A small myelinated axon and many unmyelinated axons lie associated with glial processes. Some of the axon/glial relationships are indicated in Fig. 5.



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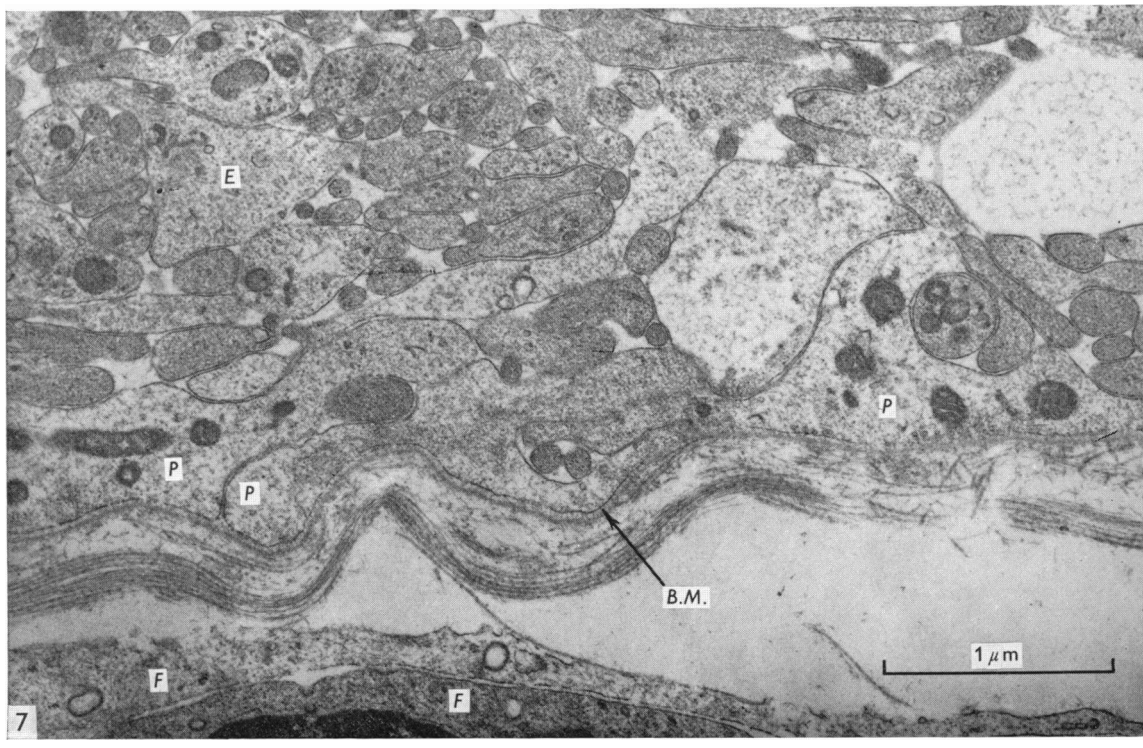

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elles, including mitochondria, dense bodies and Golgi apparatus, and the luminal surface of the cells bore numerous microvilli together with a few bleb-like projections and fewer cilia. Ventrally, where the canal was patent, these projected freely into the lumen where they abutted upon cells or debris. In the slit-like part of the canal the lumen was reduced to narrow spaces into which projecting processes of ependymal cells were bent. Between these narrowly patent spaces the 'central canal' was reduced to a gap comparable only with that between epithelial cells generally. The lateral surfaces of the ependymal cells were smooth and equipped with conspicuous junctional complexes close to their luminal ends, whether there was lumen persisting there or not.

There is no easy means of distinguishing outer ependymal cells from inner cells of the mantle. Some of the cells of the outer parts of the mantle contained granular endoplasmic reticulum and aggregates of ribosomes and others apparently did not. There was thus a hint of differentiation towards the adult forms of neurons and glia. The mantle cells lay in a neuropil whose individual parts largely defied identification, although local accumulations of vesicles in some processes and locally increased density in some plasma membranes suggested that synapses were present.

In the marginal zone were numerous cytoplasmic processes, of round or oval profile in transverse section, of 0·1–0·6 μm diameter, and of moderate electron density. Many of them contained longitudinally orientated tubules of *c.* 23 nm diameter (Fig. 6) and occurred for the most part, in large bundles of 500 or more. Other cytoplasmic processes, of similar or of slightly less electron-density and usually lacking tubular inclusions, formed partitions through the marginal zone which passed toward its outer surface where they expanded to form the outer limiting membrane.

Neither in the marginal layer nor in the neuropil of the mantle layer was any sign of myelination seen. Excepting the marginal layer of the floor plate (to which further reference is made below), no sign of glial invagination of axons was seen either.

The segment of spinal cord obtained from the 1·5 cm embryo was *c.* 0·8 mm wide and *c.* 0·9 mm deep, invested completely by leptomeninges; dorsal and ventral rootlets were attached. The central canal was a narrow slit dilated very slightly at its ventral extremity and the outer limits of the ependymal layer could be made out only in the floor plate where they abutted directly upon the marginal layer. The marginal layer was thin, but slightly expanded dorso-laterally close to the attachment of dorsal nerve rootlets. The mantle layer showed some differentiation into basal and alar laminae but no obvious differentiation into neurons and glia nor any sharp distinction from the underlying ependymal layer.

Electron microscopic examination of the marginal layer showed it to be bounded

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Fig. 6. Marginal layer (lateral funiculus) from 3 cm specimen. Small rounded profiles contain tubules of *c.* 23 nm diameter and are believed to be axons. Paler radiating processes (*E*) are thought to be glial or ependymal in origin.

Fig. 7. Marginal layer (lateral funiculus) from 1·5 cm specimen. The leptomeninx is represented by fibroblast-like cells (*F*) and collagen fibrils. The external limiting membrane is composed of pale cytoplasmic processes (*P*), and a continuous basement membrane (*B.M.*). More deeply situated are small axons containing tubules of *c.* 23 nm diameter and larger paler processes (*E*) believed to be ependymal in origin.


1 μm
8

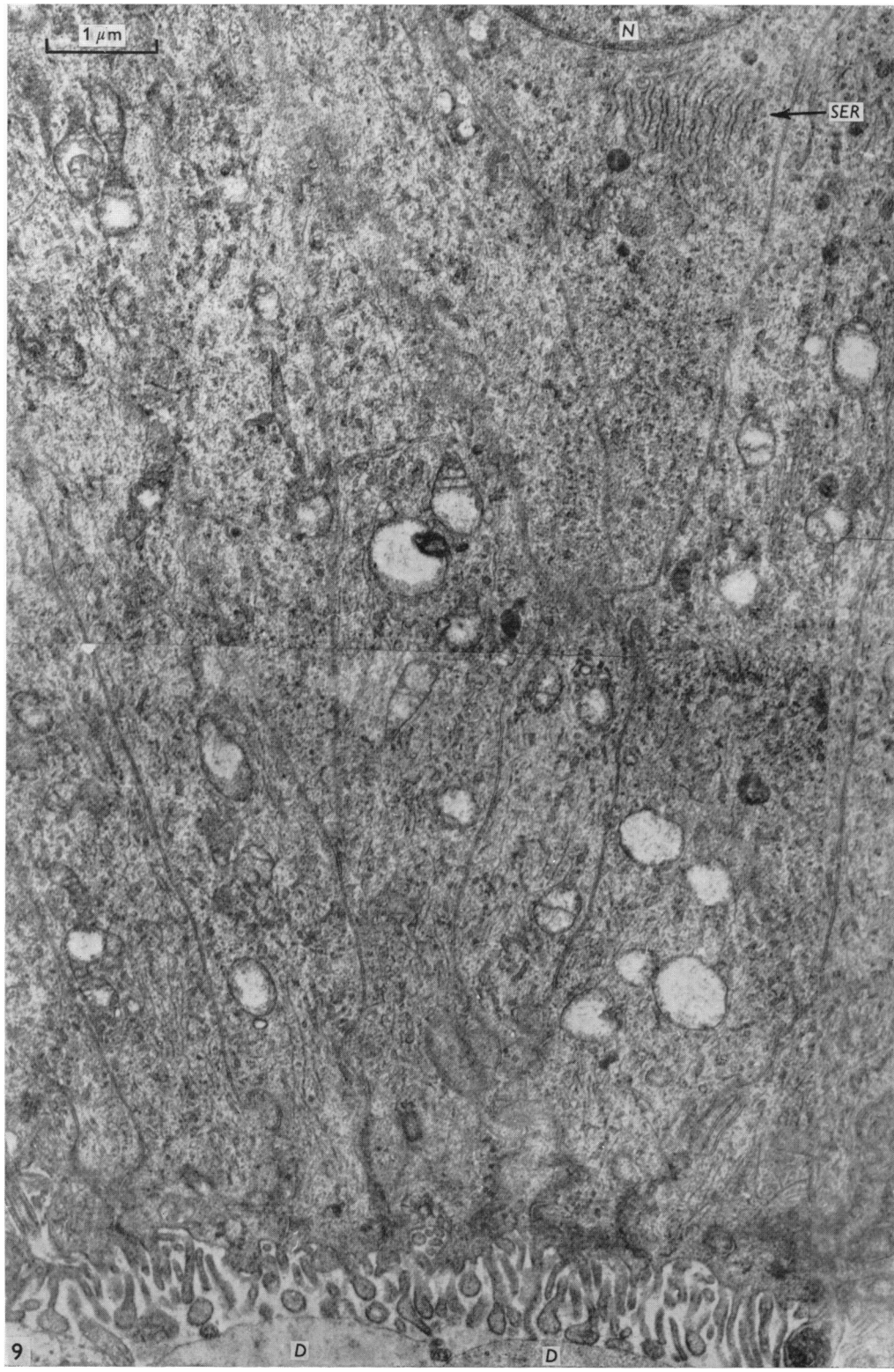
externally by pale cytoplasmic processes overlaid by a continuous basement membrane as in the older specimens (Fig. 7). Occasionally these processes were seen to be expanded outer ends of narrow processes radiating outwards through the marginal zone. In the region of the floor plate, where only ependymal cells were present, it must be assumed that this 'outer limiting membrane' was of ependymal cell origin. At the point of attachment of a nerve rootlet the processes, complete with basement membrane, formed a short cylindrical investment for the emerging or entering rootlet. The axons in these rootlets were *c.* 0·15–0·4 μm in diameter and none larger than 0·4 μm were seen.

The greater part of the marginal zone was formed by a mass of longitudinally orientated cytoplasmic processes with rounded profiles in cross section, of moderate electron density and often equipped with longitudinally disposed tubules of *c.* 23 nm diameter. Most of these processes fell into a size range of 0·1–0·4 μm diameter. In electron density they were very similar to the cytoplasm of the scattered glial (or spongioblastic) cells, which also occurred in the marginal zone (Fig. 8) so that their identification was uncertain. The glial cells of the marginal layer were never seen to give off extensive or numerous processes. In Fig. 9, a few short processes, some containing tubules, can be seen extending from the perikaryonal cytoplasm. The marginal zone also contained much larger, often pale, cytoplasmic processes which were presumably glial in nature, but their connexions with perikaryonal cytoplasm were not observed. There was no evidence of glial invagination of axons, except in the region of the floor plate, to which further reference will be made.

The mantle zone was sharply demarcated from the marginal layer but blended imperceptibly with the ependymal layer. In the outer mantle, perikarya lay close together, separated by far fewer cytoplasmic processes than were found in the neuropil of the older foetuses. Most of the nuclei were of similar size, shape and electron density, and, usually, surrounded only by rather scanty perikaryonal cytoplasm. Some of these cells, however, were equipped with quite extensive polar cytoplasm in which vesicles of granular endoplasmic reticulum, Golgi apparatus and mitochondria were aggregated. Nothing resembling synaptic contacts was seen so that a useful clue to the identification of dendrites is lacking.

The ependyma exhibited the usual conspicuous junctional complexes close to the lumen of the central canal (Fig. 9). The cytoplasm was rich in organelles including mitochondria (usually swollen), granular endoplasmic reticulum arranged as stacks of flattened vesicles close to either pole of the nucleus, extensive regions of Golgi apparatus, dense bodies and filamentous as well as tubular inclusions. The side walls of the cells were for the most part smooth but were sometimes indented by processes of neighbouring cells close to the junctional complexes. The luminal surfaces bore large numbers of microvilli which often were expanded at their luminal ends, as well as occasional bleb-like projections and cilia. The lumen of the central canal was narrow in most of its extent so that apposed walls lay in or nearly in contact, or in contact with cytoplasmic processes, or cell debris, apparently lying free in the lumen of the canal.

Fig. 8. Marginal layer (lateral funiculus) of 1·5 cm specimen. A small cell, presumably glial, with deeply indented nucleus, a few lipid droplets but few other cytoplasmic inclusions, lies among small unmyelinated axons. It gives off tiny processes which are not big enough to effect axonal invaginations.



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The ependymal cells tapered and extended outward among the overlying mantle cells where they were lost, excepting only in the floor plate where there was only a marginal layer. Here too the outer ends of the ependymal cells tapered, but were immediately related to axons; some axons coursed longitudinally and were invaginated into the ependymal cells, with the formation of mesaxons. More superficially placed axons coursed transversely (possibly the forerunner of the 'anterior white commissure'), their bundles being broken up by the radially directed apical processes of the ependymal cells which appeared to expand to form the external limiting membrane. Figs. 10–12 illustrate longitudinally coursing axons invaginated into ependymal cells: as many as six axons invaginate into one cell; up to $1\frac{1}{2}$ spirals of mesaxon suspend an axon; adjacent mesaxons, formed by the same ependymal cell, spiral in opposite senses.

In brief, ependymal cells were related to axons in ways exactly similar to those well known to occur between glial cells and axons in the central nervous system and between Schwann cells and axons in the peripheral nervous system.

A similar, but smaller region of ependymal/axon invagination was found in the floor plates of each of the other two small foetal spinal cords. In the largest specimen the floor plate of the spinal cord no longer consisted only of ependyma and cell-free marginal zone; nor did it exhibit any aggregation of myelinated or separately invaginated axons in this region.

DISCUSSION

The most interesting of the present results is the observation that ependymal cells of the spinal cord may take on a function previously attributed exclusively to the macroglia, namely, the invagination of axons with the formation of mesaxons from the invaginating plasma membrane. The ependymal cells involved were few in number and occurred only in the floor plate of the neural tube. Their location is probably an important factor in permitting the recognition of this property of the cells, for elsewhere ependymal cells in the smaller spinal cords blended with the mantle layer and if axon invagination occurred here its identification would be difficult. It is well known (see Davies, 1967) that the floor plate of the early neural tube consists only of ependymal cells and a narrow marginal layer, as the present study confirms. Even so, it could not be seen that all of the invaginating processes were in continuity with the nucleated part of an ependymal cell: some could have been glial processes which extended into the floor plate from the basal parts of the mantle layer.

Axons ensheathed by ependymal cells were apparently absent from the largest specimen, and there was no concentration of unmyelinated axons singly invaginated by glial cells, nor any concentration of myelinated axons immediately ventral to the central canal. It may be that this tract is not only precocious in the development of singly invaginated axons but is also temporary in its existence. In its position it

Fig. 9. Floor plate ependyma of 1·5 cm specimen. Pseudopodia, a cilium and a bleb-like structure project into the lumen of the central canal in which debris (*D*) is present. The cytoplasm contains many mitochondria, which are often swollen: and the stacked arrangement of flattened cisternae of endoplasmic reticulum (*SER*) close to the nucleus (*N*) is almost always seen in these cells.

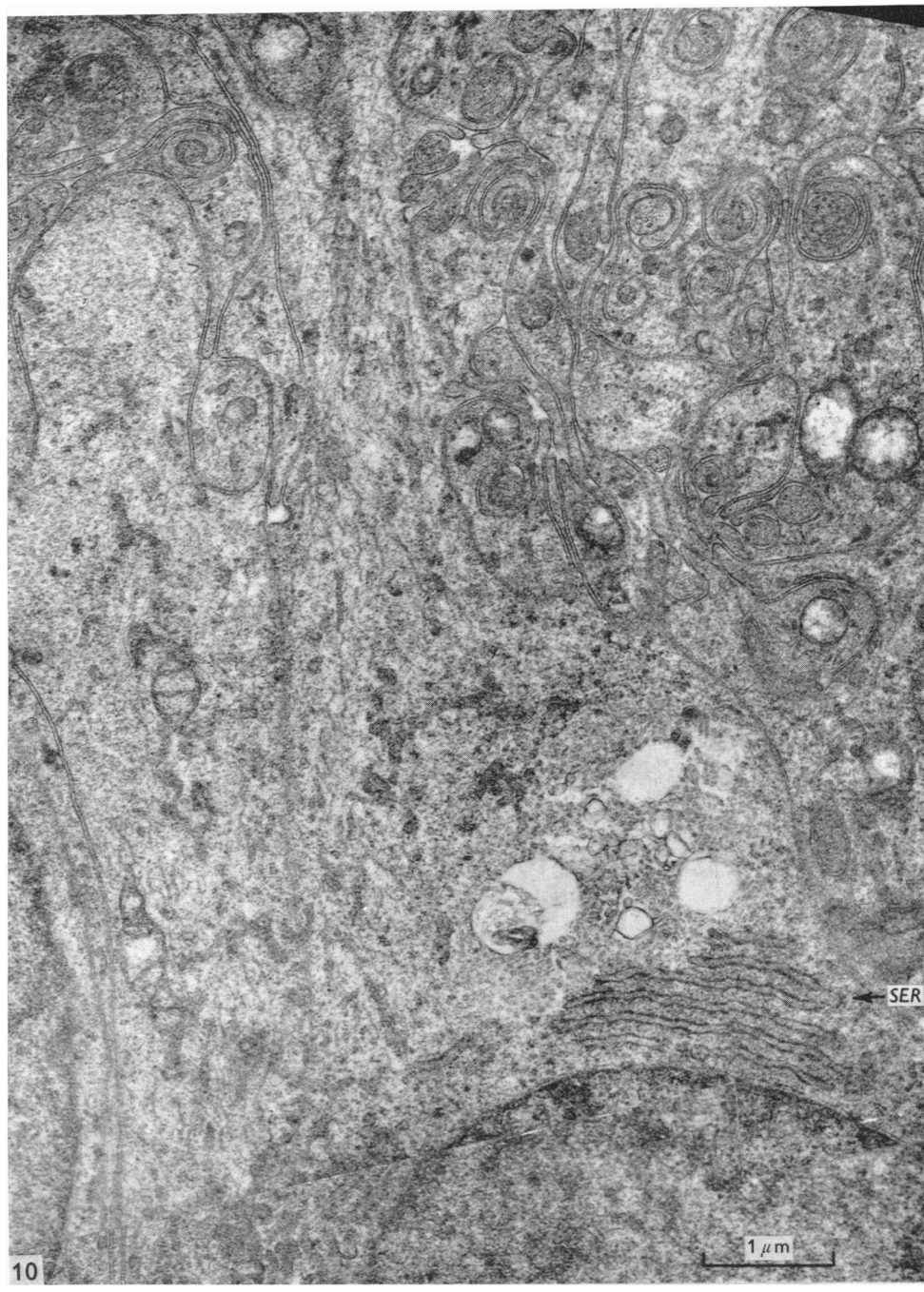


Fig. 10. Ependymal and marginal layers of floor plate of 1·5 cm specimen. A stack of flattened cisternae of granular endoplasmic reticulum (*SER*) lies close to an ependymal cell nucleus. Toward the upper part of the field small axons, running longitudinally, are invaginated into ependymal cell cytoplasm.

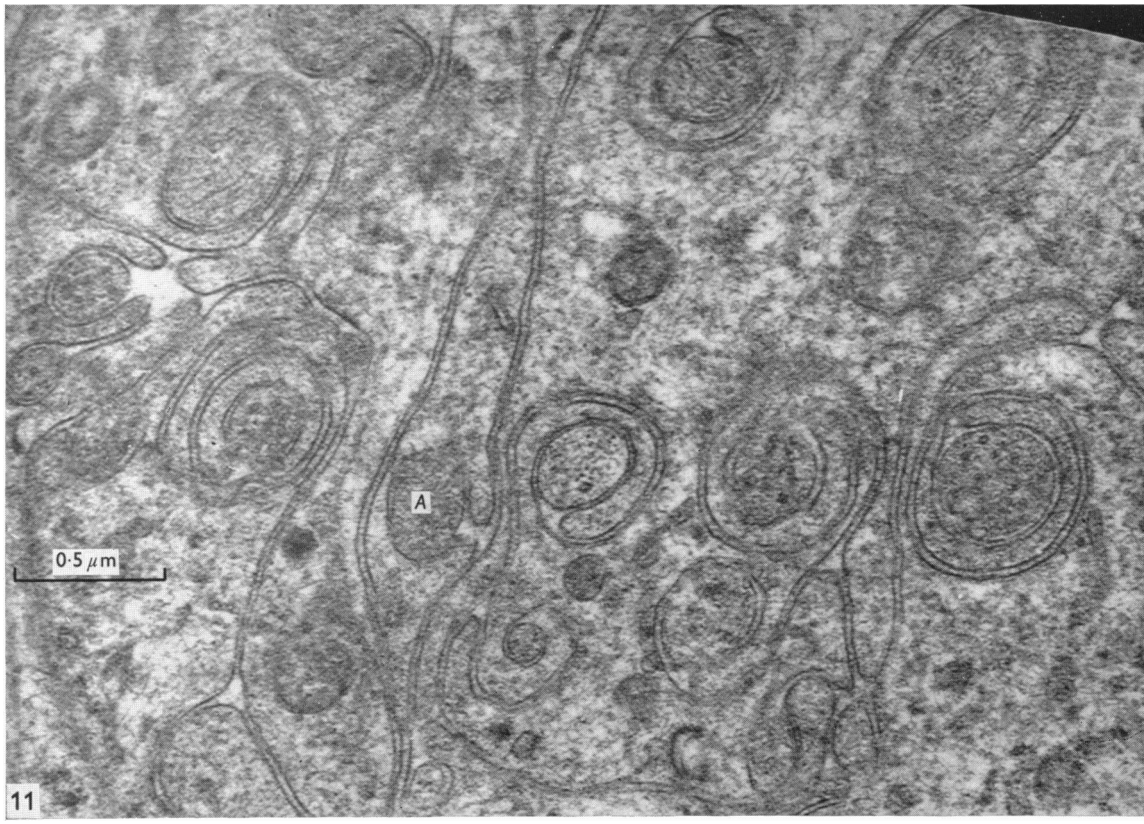
corresponds with the deepest part of the anterior intersegmental tract but there is no evidence that it becomes this latter tract by later myelination of its axons.

Identification of detached cytoplasmic processes in neuropil and in the marginal layer was often difficult or impossible in the smaller specimens. In the older specimens, as in peripheral nerves, much of the difficulty disappeared when a smaller process was seen to be invaginated into a larger process and an axon/satellite cell relationship could be assumed. In the smaller specimens few invaginations were seen and, indeed, the glial cells identified in the marginal zone bear only a few short cytoplasmic processes. Most of the many rounded profiles present, then, would seem most likely to be axonal despite the failure to demonstrate their origin from a nerve cell body in the mantle layer or to recognize characteristic features in their structure.

Where glial invagination of unmyelinated axons was seen in the 12 cm specimen the axon/satellite cell relationship was markedly similar to that seen in human foetal peripheral nerves (Figs. 5 and 6 may be compared with Fig. 3 in Gamble, 1966). Glial cell of central nervous system or Schwann cell of peripheral nerve may at the same time provide separate ensheathing processes of cytoplasm for each of several large unmyelinated axons, and a common investment for a bundle of smaller unmyelinated axons. The difference in the two situations is that the glial cell lies in close contact with its fellows and with unwrapped axons while the Schwann cell is always invested by basement membrane and separated from its fellows by a collagen-containing endoneurial space.

In the smaller specimens studied there was no sign of myelination in the marginal zone, nor, except in the special case of the floor plate, any sign of individual ensheathing of unmyelinated axons. Even in the largest specimen, of an age estimated at 13–16 weeks of intra-uterine life, myelination had not proceeded far upon any axon, and not at all upon the vast majority. A few of the myelinated fibres were just large enough (1–2 μm) to allow their recognition by light microscopy but most were considerably smaller and invested only by a very thin sheath of myelin so that their presence would not be detectable except by electron microscopy. This finding is to be compared with Keene & Hewer's (1931) report of definite staining for myelin in the anterior ground bundle, near the base of the posterior funiculus and in the antero-lateral region of the cord in human foetuses of 14–16 weeks gestation. The present material shows myelination too scattered to allow any attempt at identification of particular fibre tracts. It is true that myelinated axons are sometimes seen in little groups of three to five but it seems likely that these sheaths are the product of a precociously active glial cell in their immediate neighbourhood. There is no evidence that any axon is myelinated over long lengths of its course; only very fortunately cut longitudinal sections could show whether nodes are present, implying an orderly progression of myelination along an axon.

Malinský & Brichová (1967) studied the outer limits of the ependymal layer in human foetal thoracic spinal cord and felt able to identify a variety of glial cells (e.g. glioblasts at 6–7 weeks, tanycytes and primitive astrocytes at 12 weeks). Their illustrations of tanycyte processes are not wholly convincing (their Figs. 15, 16) and, indeed, are taken from a 7-week specimen described in the text (p. 70) as containing only 'glioblasts' which could not be classified more precisely. The present material has been no easier to analyse into its component cells. Except in the largest specimen,



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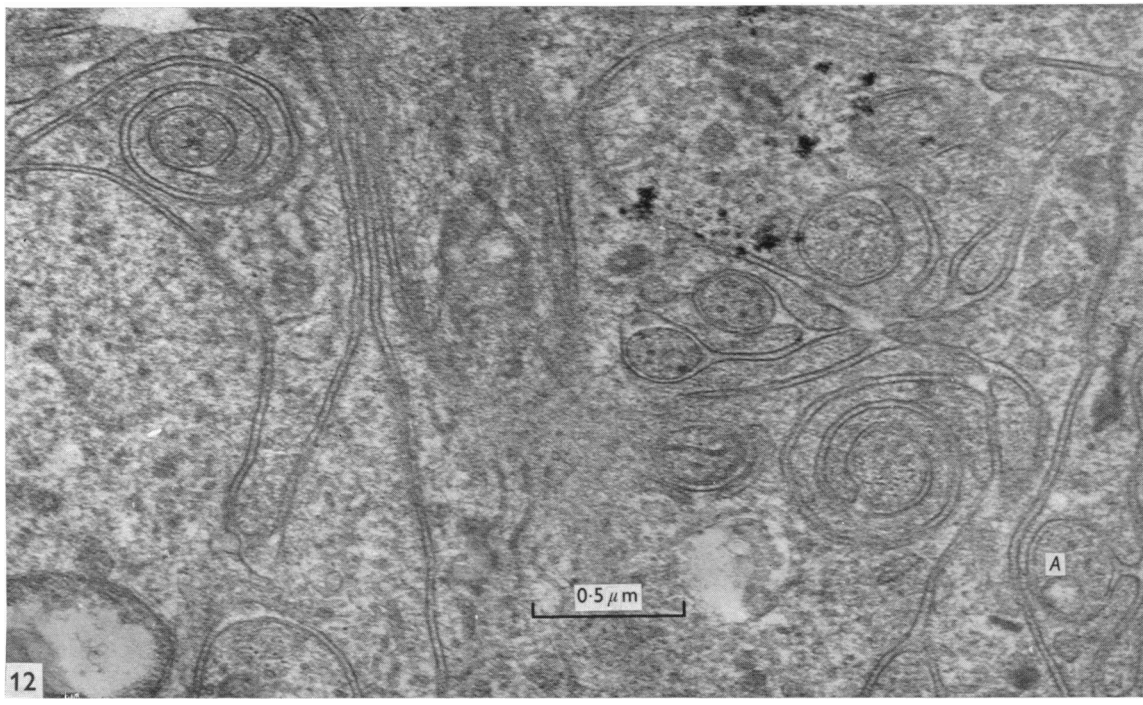

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ependyma was not clearly demarcated from the mantle layer. While neurons may be identified in the 3, 4 and 12 cm specimens the great majority of the cells present in the mantle layer and all of those present in the marginal layer could be identified merely as glial. In the floor plate of the 1·5 cm specimen the external limiting membrane was almost certainly formed by expanded peripheral processes of ependymal cells but in the larger specimens the processes forming the membrane appeared identical with those associated with blood vessels and the latter may be assumed to belong to astrocytes or their precursors. Recent studies (Wendell-Smith, Blunt & Baldwin (1966); Kruger & Maxwell (1966)) have thrown doubt upon the identification of myelin-forming macroglial cells of the central nervous system so that not even this property of a glial cell suffices fully to identify it. It seems clear that myelin formation, and even the segregation of axons is a late developing property of glia. It had begun but not proceeded far in the 12 cm specimen. The segregation of nervous tissues from the basement membrane limited connective tissue spaces, however, is a property developed by glial or ependymal cells even in the 1·5 cm specimen.

It is difficult to compare present observations upon the ependyma with those described by Malinský & Brichová (1967) for they gave only ages for their specimens. Moreover, the present material is lumbar spinal cord, and theirs was thoracic cord, and considerable regional differences have been reported, e.g. Tennyson & Pappas (1962).

The differentiation of the luminal surface of the ependymal cells in Malinský & Brichová's material may be summarized as follows: at 4 weeks there were only irregular projections into the lumen; at 6 and 7 weeks microvilli, flat folds and cilia (one only per cell) were present; at 12 weeks pseudopodia had appeared and at 14 weeks, although individual cells differed, microvilli might occur in penicillate clumps, pseudopodia were often club-shaped and as many as four to five cilia might arise from a single cell. Even in the smallest of the present specimens (estimated age 4–6 weeks) all the features of Malinský and Brichová's 14-week specimen were present (Fig. 9) excepting only the multiple cilia arising from a single cell.

In most other respects cytoplasmic inclusions of ependymal cells described by Malinský and Brichová were similar to those described here. The conspicuous stacks of vesicles of granular endoplasmic reticulum in the present 1·5, 3 and 4 cm C.R. length specimens seem to correspond with their 'ergastoplasm with parallel small sacs of endoplasmic reticulum', described in the 4 weeks specimen only. The function of these organelles is obscure but they were apparently absent from their older specimens, as from the largest foetus of the present series, so that the function may itself be transient, and associated with the proliferative phase of the ependymal cell's existence.

Fig. 11. Part of Fig. 10 shown at higher magnification. To the right an axon is suspended by an ependymal cell mesaxon which makes a little more than one spiralling turn. To the left of this another ependymal cell is invaginated by six axons each with its own short, spiralling mesaxon. Further to the left axons (e.g. that marked *A*) merely indent the sides of ependymal cells.

Fig. 12. This section was a near-serial to that shown in Figs. 10 and 11. The axon marked *A* is the same as that so marked in Fig. 11. Immediately to the left of this, and also to the far left of the field are seen ependymal mesaxons making 1½ spiral turns before their layers separate to enclose small axons.

SUMMARY

1. Segments of lumbar spinal cord from four human foetuses have been examined by light and electron microscopy. The foetuses were of 1·5, 3, 4 and 12 cm C.R. length.

2. Ependymal cells in all specimens had conspicuous junctional complexes close to the lumen of the central canal into which bleb-like structures, microvilli and kinocilia projected. Except in the 12 cm specimen, ependymal cells contained extensive stacks of flattened cisternae of granular endoplasmic reticulum.

3. Floor-plate ependymal cells of the three smaller specimens provided individual sheaths for longitudinally coursing axons; the plasma membrane of the cell was invaginated and sometimes spiralled to form mesaxons resembling those formed by macroglia elsewhere in the central nervous system and by Schwann cells in the peripheral nervous system.

4. Neurons were identifiable by their size and content of Nissl bodies in the 12 cm specimen and, less certainly, in the 4 and 3 cm specimens. Other cells of the mantle layer could be identified only as glial, or as glioblastic. In the 1·5 cm specimen mantle cells generally defied identification.

5. In the three smaller specimens the marginal layer consisted very largely of longitudinally coursing unmyelinated axons. The few, small cells scattered through the marginal layer were assumed to be glial although few processes were seen arising from their perikaryonal cytoplasm.

6. In the 12 cm specimen the marginal layer contained myelinated axons occurring singly or in small groups, together with unmyelinated axons very complexly related to macroglial cell processes.

7. In all specimens the outer aspect of the marginal layer was formed by a mosaic of cytoplasmic processes, in turn covered by a continuous basement membrane. In the floor plate of the smaller specimens these limiting cytoplasmic processes have been taken to be expansions of the floor plate ependymal cells: elsewhere in these specimens, and generally in the 12 cm specimen, a glial origin seems more probable. The cytoplasmic processes are similar to those surrounding small blood vessels which suggests that they may be astrocytic.

8. Axo-dendritic synapses were present in the grey matter of the 12 cm specimen. In the 3 and 4 cm specimens local accumulations of vesicles sometimes coincided with increased density of plasma membrane in tiny processes of mantle layer neuropil, but although 'synapse-like', such structures could not be more accurately identified. In the 1·5 cm specimen nothing resembling synapses was seen.

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