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A scanning and transmission electron microscopic study of the embryonic mouse telencephalon

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INTRODUCTION

Ependymoglial, or radial glial, cells are present in the embryonic central nervous system of mammals. They may persist into adult life in the spinal cord, particularly in the region of the dorsal median septum (Sturrock, 1981) but it seems unlikely that they are present in the adult forebrain. Some may degenerate during development but many differentiate into astrocytes (Schmechel & Rakic, 1979; Levitt & Rakic, 1980). It has been suggested by Rakic (1972) that they assist neuroblast migration from the proliferative ventricular surface to the cerebral cortex. In a recent study Levitt & Rakic (1980) have elegantly demonstrated ependymoglial, or radial glial, processes in all parts of the monkey central nervous system and discussed their possible significance in neuronal guidance.

The pattern of ependymoglial guide fibres in the developing mammalian forebrain has been described in coronal sections by Astrom (1967) in the sheep, by Smart (1978), Smart & Sturrock (1979) and Sturrock & Smart (1980) in the mouse and by Levitt & Rakic (1980) in the monkey. Ependymoglial fibres have been tentatively identified electron microscopically (Sturrock & Smart, 1980) in the forebrain. These fibres are similar to those described in the embryonic spinal cord (Henrickson & Vaughn, 1974). A detailed study of ependymal cell development in the mouse (Sturrock, 1981) confirmed the identity of the ependymoglial fibres but seemed to indicate that the spinal cord ependymoglial cells were much richer in organelles than those found in the forebrain.

It was decided to investigate the ependymoglial fibre pattern in the forebrain using a combination of scanning and transmission electron microscopy supplemented by light microscopy, as it was hoped this would give a clearer view of fibre patterns and of the depth of the ventricular layer in regions where interpretation of depth is complicated by fibre bundles (Sturrock & Smart, 1980).

MATERIALS AND METHODS

Mouse embryos aged 11–19 days post-conception were used in this study. Blocks of embryonic forebrains were prepared for semithin (1 μm) light microscopy and electron microscopy as described previously (Sturrock & Smart, 1980). The 6 μm haematoxylin and eosin sections were largely those used in a study of the neostriatum (Sturrock, 1980) but also included a series of 15 day post-conception brains cut at different angles. Horizontal sections were considered to be 180°, coronal sections 90°, and further serial sections were cut at 30°, 60° and 120°. This series proved of particular value in following the scattered fibre bundles of the internal capsule which run throughout the neostriatum of mice (Smart & Sturrock, 1979; Sturrock, 1980).

Brains for scanning electron microscopy were obtained at E11, E12, E13, E14 and E15. These brains were fixed using a variety of fixatives and using either perfusion or immersion fixation in an attempt to find an ideal method of demonstrating the ependymoglial fibre bundles. The primary fixatives used were 2 % glutaraldehyde and 2 % paraformaldehyde in a 0·05 M cacodylate buffer and 1 % glutaraldehyde and 4 % paraformaldehyde in a 0·1 M cacodylate buffer. The brains were post-fixed in a solution of 12 vols of 1 % osmium tetroxide and 1 vol of saturated mercuric chloride in a 0·1 M phosphate buffer. After dehydration in graded alcohol, the brains were taken through graded mixtures of Freon 113 and alcohol to 100 % Freon 113 and critically point dried using liquid carbon dioxide.

The brains were fractured with a razor blade. Fracturing was carried out either before post-fixation or after post-fixation or after critical point drying. The fractured brains were coated with gold and examined in a Jeol scanning electron microscope.

RESULTS

Scanning electron microscopy

The best results were obtained in brains from E11 to E14 which were fractured after post-fixation but before critical point drying. It had previously been observed that the histological structure of the cerebral vesicle is not uniform (Sturrock & Smart, 1980) and may be divided for descriptive purposes into medial roof, medial wall, ventricular roof and ventricular elevations. The areas which were examined were those which had previously been observed to have quite different distribution patterns of ependymoglial fibres, namely the medial roof, the ventricular roof including the caudatopallial angle, and the ventricular elevations.

The caudatopallial angle is particularly rich in ependymoglial fibres and, in Golgi-stained sections, these can be seen as a large bundle initially running superolaterally from the caudatopallial angle and then turning inferiorly to separate the developing neostriatum from the cortical plate (Smart & Sturrock, 1979; Sturrock & Smart, 1980).

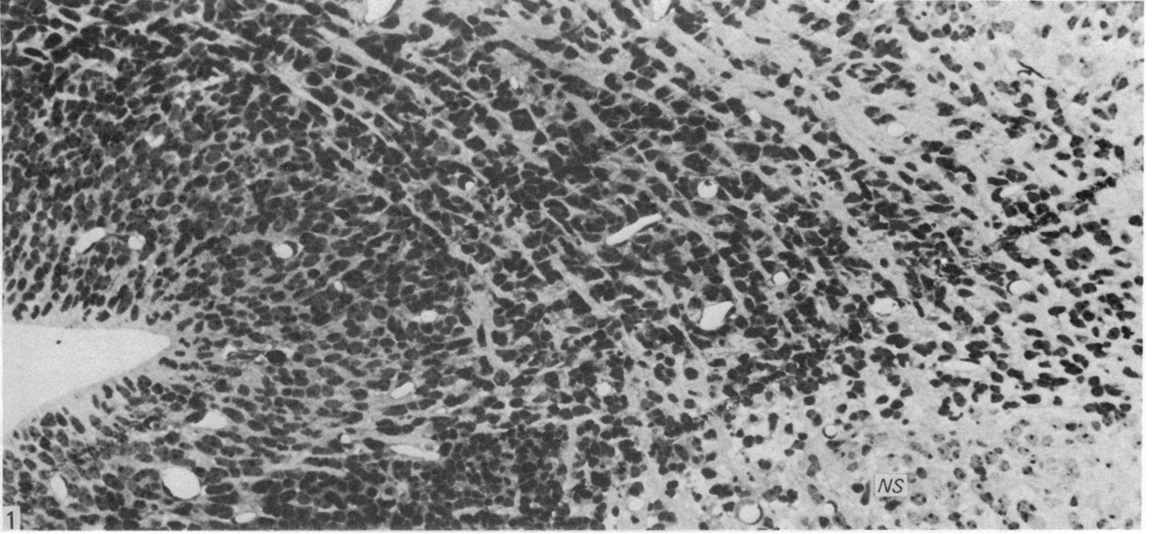
In semithin sections the initial superolateral course of the ependymoglial cells was seen as a paler staining region (Fig. 1) but by E13 discrete bundles of fibres intersected the ependymoglial fibres (Fig. 1). These bundles were fibres of the internal capsule which in mice and rats is made up of fibre bundles scattered throughout the neostriatum. The identity of these bundles was more obvious in obliquely sectioned brains (Fig. 2).

In the region of the ventricular elevations, ependymoglial fibre bundles extended into the subventricular layer, occasionally as far as the junction with the neostriatum (Fig. 3) but never beyond this junction.

The medial roof showed little evidence of ependymoglial fibres extending beyond the ventricular layer (Fig. 4), at least in bundles, but the glia limitans contained a

Fig. 1. One μm coronal section stained with toluidine blue. The bundle of fibres sweeping outwards from the caudatopallial angle (bottom left) is intersected by numerous small fibre bundles, some of which can be seen extending into the neostriatal anlage (NS). E15. ×250.

Fig. 2. Six μm oblique section stained with haematoxylin and eosin. In this section from a E15 mouse the small discrete fibre bundles can be followed from the internal capsule to the intermediate layer between the cortical plate and the ventricular layer. ×100.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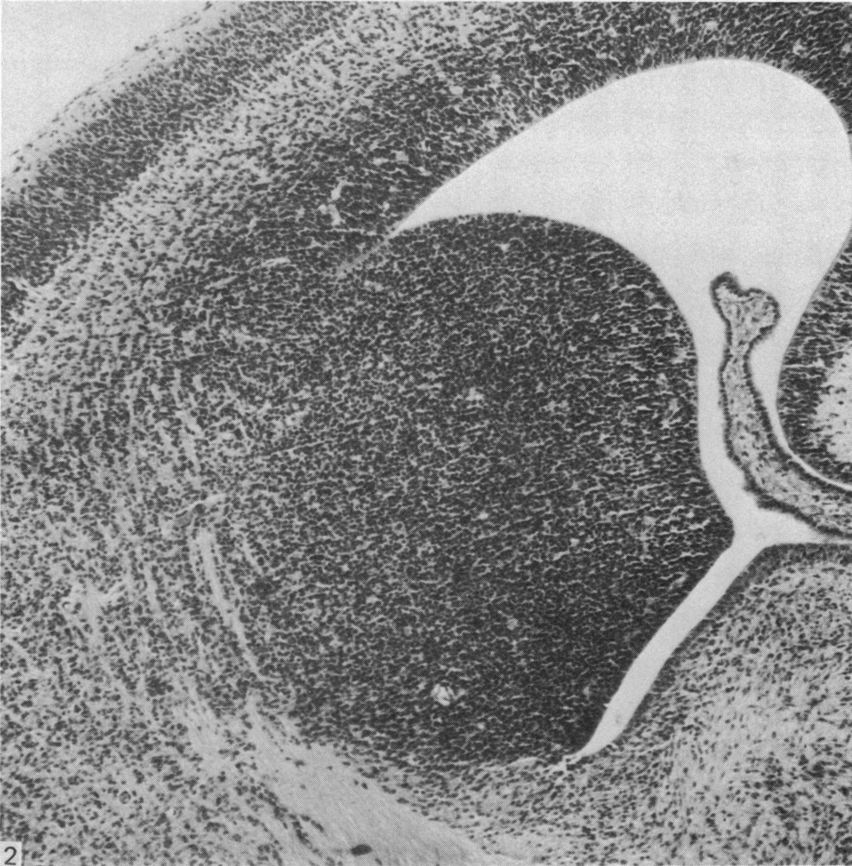
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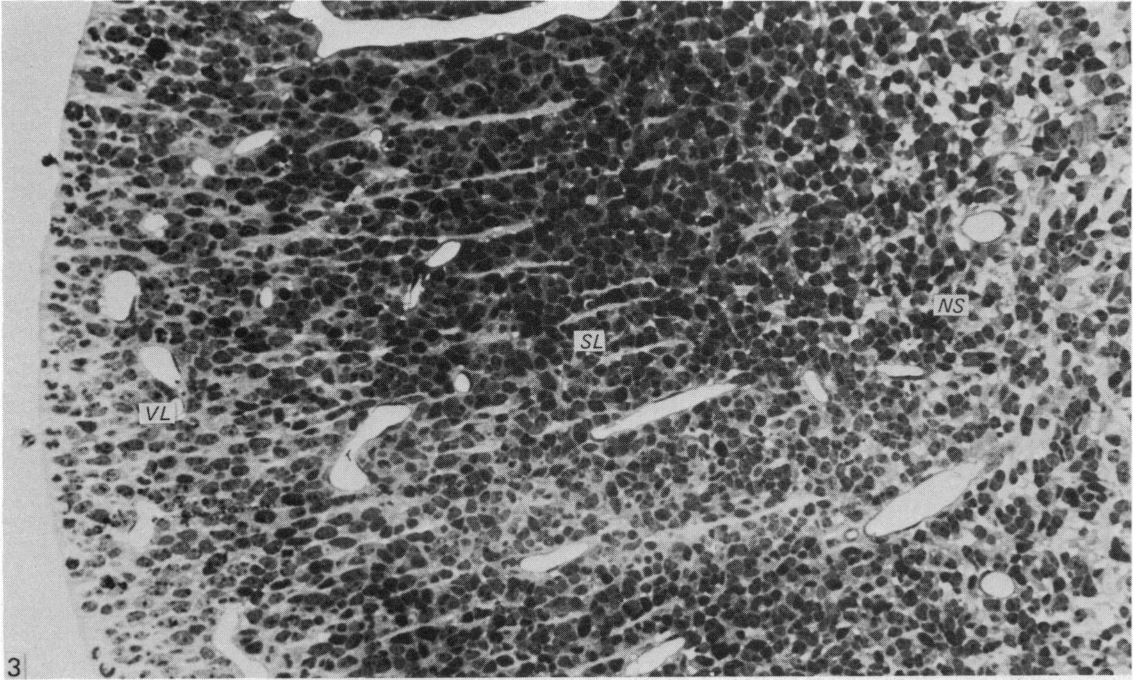

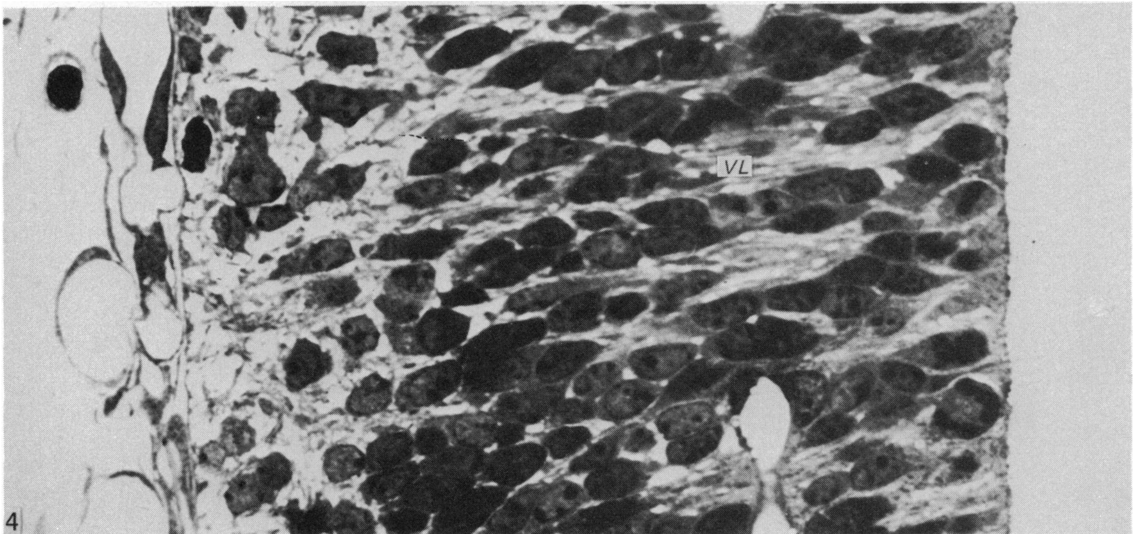

Fig. 3. One μm coronal section stained with toluidine blue. Small fibre bundles can be seen in the ventricular elevation extending from the ventricular layer (*VL*) into the subventricular layer (*SL*) but not into the neostriatal anlage (*NS*). E15. × 250.

Fig. 4. One μm coronal section stained with toluidine blue. By E13 the beginning of the cortical plate is present in the medial roof. It is made up of loose fibres and scattered cells and lies superficial to the pseudostratified columnar epithelium of the ventricular layer (*VL*). × 800.

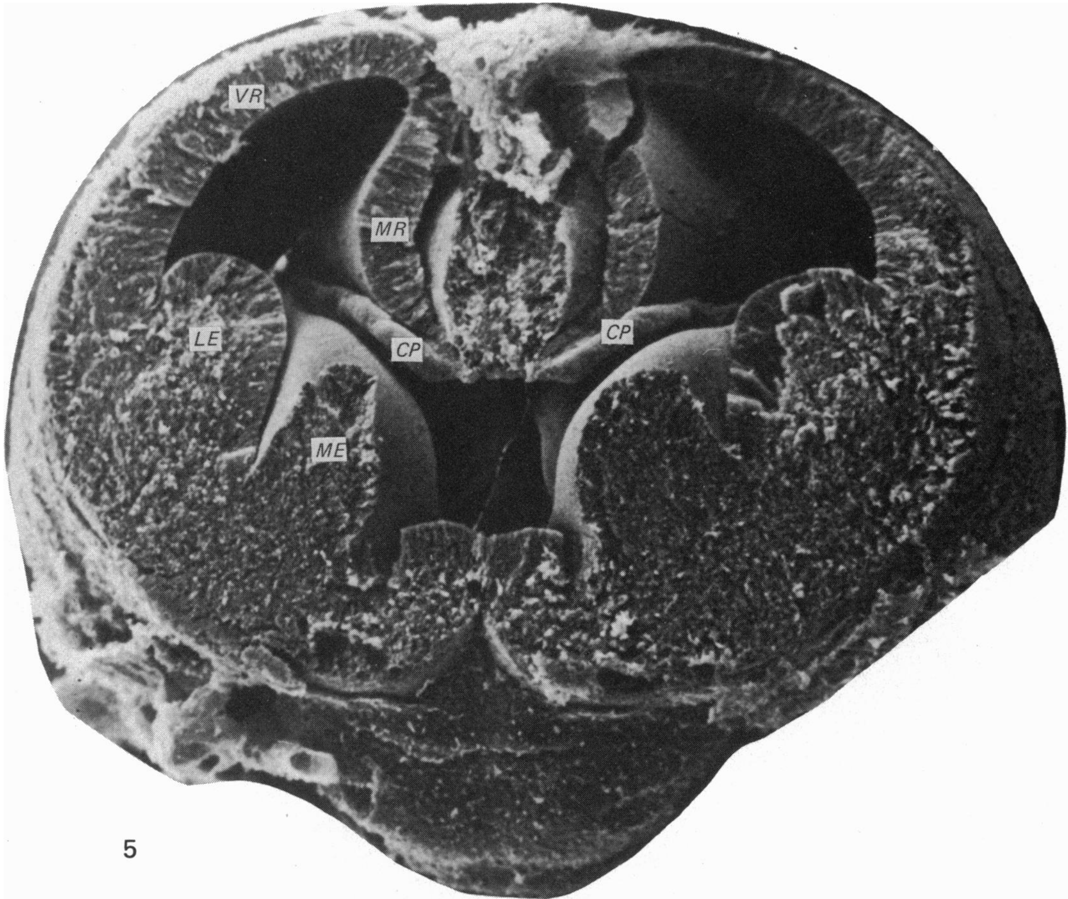

Fig. 5. Scanning electron micrograph of an E13 brain fractured at the level of the intraventricular foramen shows the medial roof (*MR*), ventricular roof (*VR*), lateral (*LE*) and medial (*ME*) ventricular elevations. The developing choroid plexus (*CP*) is visible in both lateral ventricles. ×65.

few scattered glycogen granules in the processes forming it as early as E12. This indicated that the glia limitans was formed by ependymoglial processes, at least initially.

A fractured brain at E13 is illustrated in Figure 5. This brain was fractured at the level of the interventricular foramen and the various subdivisions mentioned above can be seen, as can the developing choroid plexus. By E13 the beginning of the cortical plate was visible in the medial roof. The external limit of the ventricular layer was marked by processes and occasional flattened cells or sheet-like processes running at right angles to the pseudostratified ventricular epithelium (Fig. 6). Some fine processes, probably ependymoglial, extended through the developing cortical plate to the pia-glial surface (Fig. 6). By E14 the cortical plate was thicker and the junction with the ventricular layer was marked by the presence of transversely running fine fibres (Fig. 7). Isolated ependymoglial fibres continued to penetrate the cortical plate.

At the caudatopallial angle the most prominent feature was the very large number of narrow processes at the upper lateral border (Fig. 8). Unlike the adjacent roof

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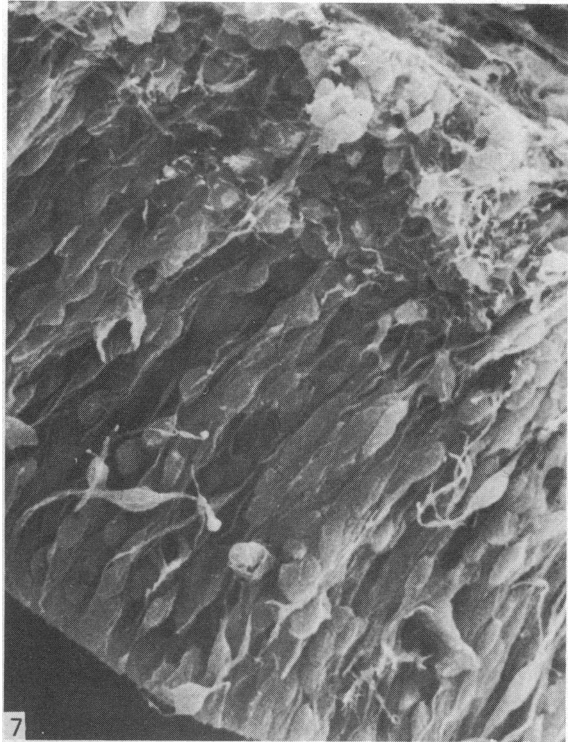
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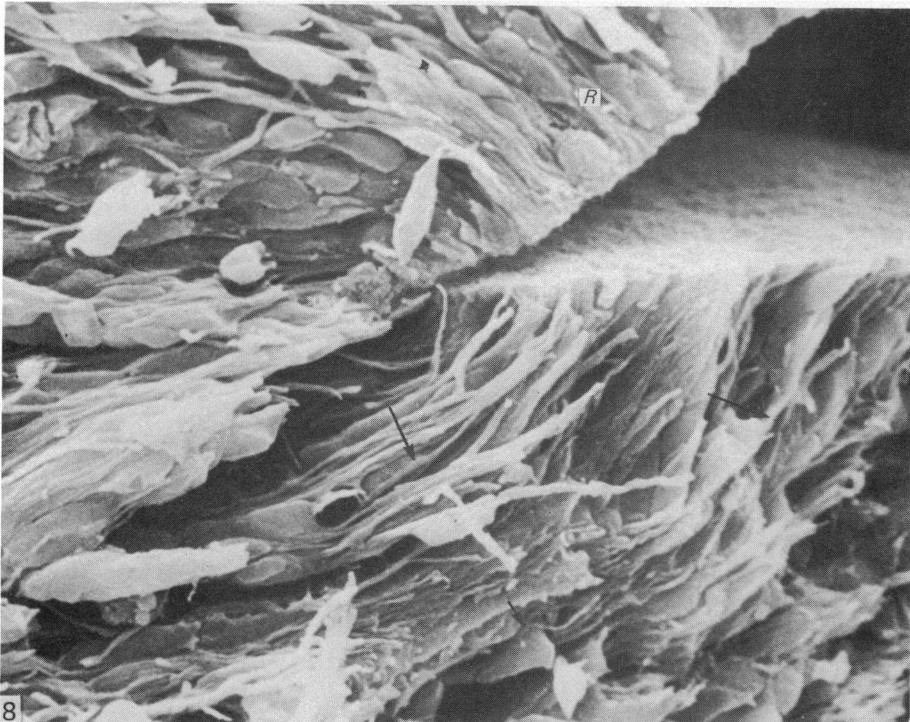
R
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area, surface nuclei were rarely present. Some of the processes were sheet-like in appearance (Fig. 8). Numerous narrow processes were also present at the ventricular surface of the ventricular elevations (Figs. 9, 10). Nuclei were present adjacent to the ventricular surface (Fig. 10) but there were fewer surface nuclei at the ventricular elevations than along the roof (Fig. 13) or medial roof (Figs. 6, 7). Nuclei of the ventricular epithelium were elongated except at the ventricular surface but subventricular cells were more nearly spherical and appeared to lack long processes (Fig. 9). Bundles of processes were seen in the subventricular layer (Figs. 9, 10). Transversely running processes were present in the subventricular layer, and whilst some of these were undoubtedly produced by the fracture process it seems likely that others were not artefactual. Some lightly coloured cells had quite thick processes running in different directions (Figs. 9, 10, 12) and as these were found deep in the subventricular layer and neostriatal anlage it is tempting to suggest that they were differentiating neurons. The presence of similar cells in the developing medial roof cortical plate (Figs. 6, 7) added very tentative support to this, but there is at present no conclusive evidence that these cells are neurons.

In fractured brains it was not possible to follow ependymoglial fibres from the roof or caudatopallial angle to the cortical plate (Figs. 11, 13). The boundary between the ventricular layer and the intermediate layer showed up clearly (Fig. 13) but there was no very obvious fibre pattern in the intermediate layer. The intersecting fibre pattern at the caudatopallial angle, which was clearly shown in 1 μm sections (Fig. 1), was not obvious in fractured brains (Fig. 11). Cells in the intermediate layer of the roof tended to be spherical in shape, unlike the elongated cells of the ventricular layer (Fig. 13).

In the transmission electron microscope, bundles of pale, glycogen-containing processes, probably ependymoglial, were seen from E13 (Fig. 14). Rarely, what seemed to be junctions between ependymoglial processes were observed (Fig. 15). These were associated with dense core vesicles. Bundles of axons were also present in the intermediate layer and one such bundle, passing from the intermediate layer/corpus callosum anlage into the neostriatal anlage, is shown in Figure 16. Fibre bundles of the internal capsule in the neostriatal anlage often contained processes with scattered glycogen granules in them (Fig. 17) and, rarely, bundles were observed in which the majority of processes contained glycogen granules (Fig. 18).

In the stages examined, a subventricular layer was obvious only in the ventricular

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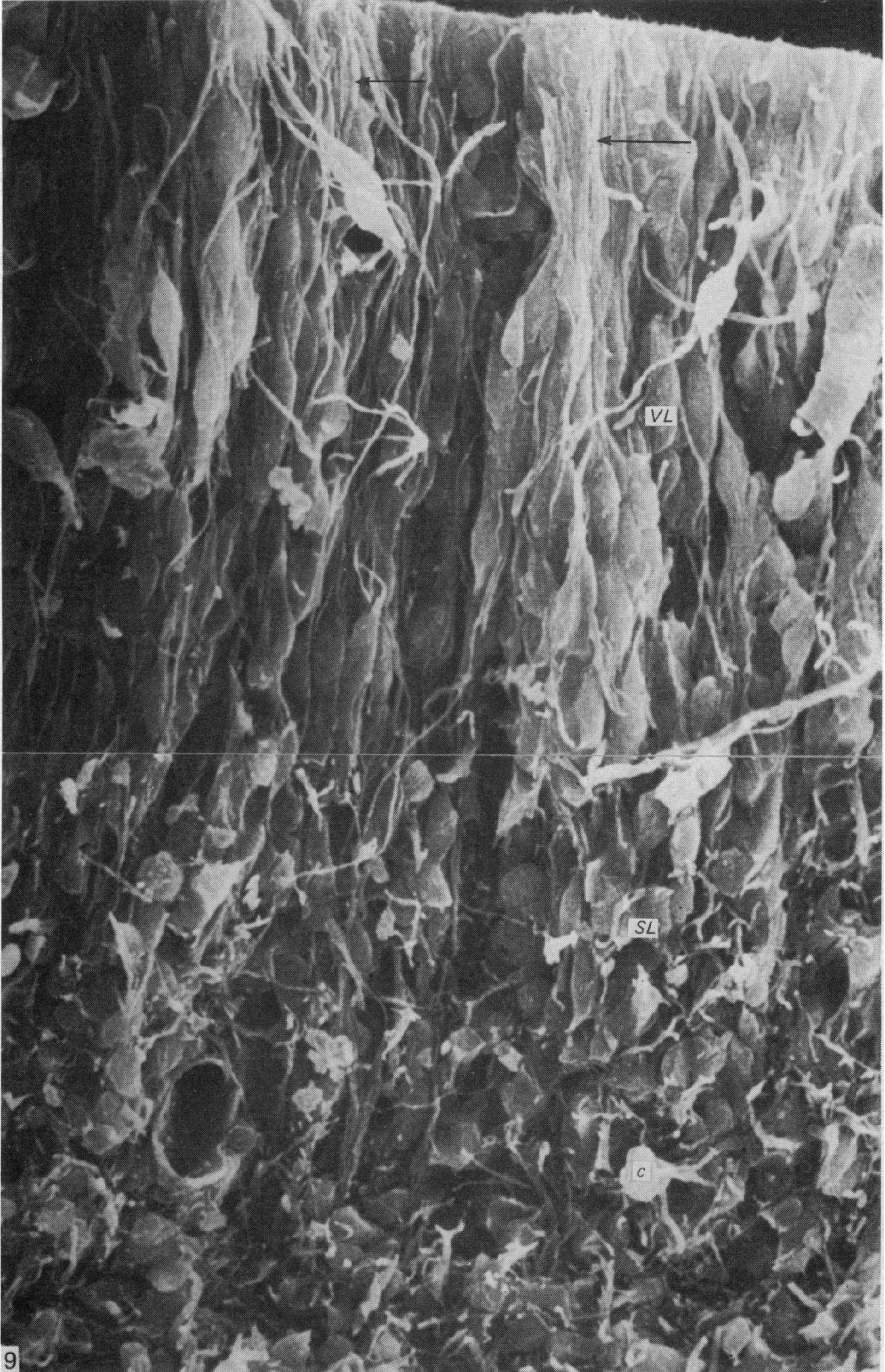
Fig. 6. Scanning electron micrograph. At E13 a layer of cells and fibres begins to appear superficial to the columnar ventricular layer. The outer surface of the ventricular layer is marked by transversely running fibres and flattened processes (vertical arrow). Some fibres (arrows) appear to extend from the ventricular layer to the surface of the brain through the outer layer. ×860.

Fig. 7. Scanning electron micrograph of medial roof at E14. The developing cortical plate is thicker than at E13. A number of light cells are present in it. Fibres from the ventricular layer continue to penetrate the developing cortical plate. The boundary of the ventricular layer is marked by small, transversely running fibres. ×650.

Fig. 8. Scanning electron micrograph of the caudatopallial angle at E14. This demonstrates the very large number of fibres present at the caudatopallial angle. Some flat sheets (small arrows) are present but the majority of processes are cylindrical and vary in size. Few nuclei are visible near the surface of the caudatopallial angle in contrast to the adjacent roof (*R*). Fibre bundles can be seen splitting into individual fibres which appear to enmesh cells (left arrow). ×1080.


VL
SL
c
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elevations (Figs. 9, 10). The ventricular layer extended almost to the incipient cortical plate in the medial roof (Figs. 6, 7) and to the intermediate layer over the ventricular roof (Fig. 13).

It was not possible in the scanning electron microscope to distinguish axons or other neuronal processes from ependymoglial processes. Transmission electron microscopy, however, indicated that fibres arising from the ventricular layer and extending beyond the boundaries of the ventricular layer had the ultrastructural characteristics of ependymoglial fibres. In the intermediate layer, cortical plate and neostriated anlage there were, of course, neuronal processes intermingled with ependymoglial fibres. Comparison of similar regions, using scanning and transmission electron microscopy, assisted in identifying the relative contribution of ependymoglial and other processes to fibre bundles. The densest accumulation of ependymoglial fibres appeared to occur at the caudatopallial angle.

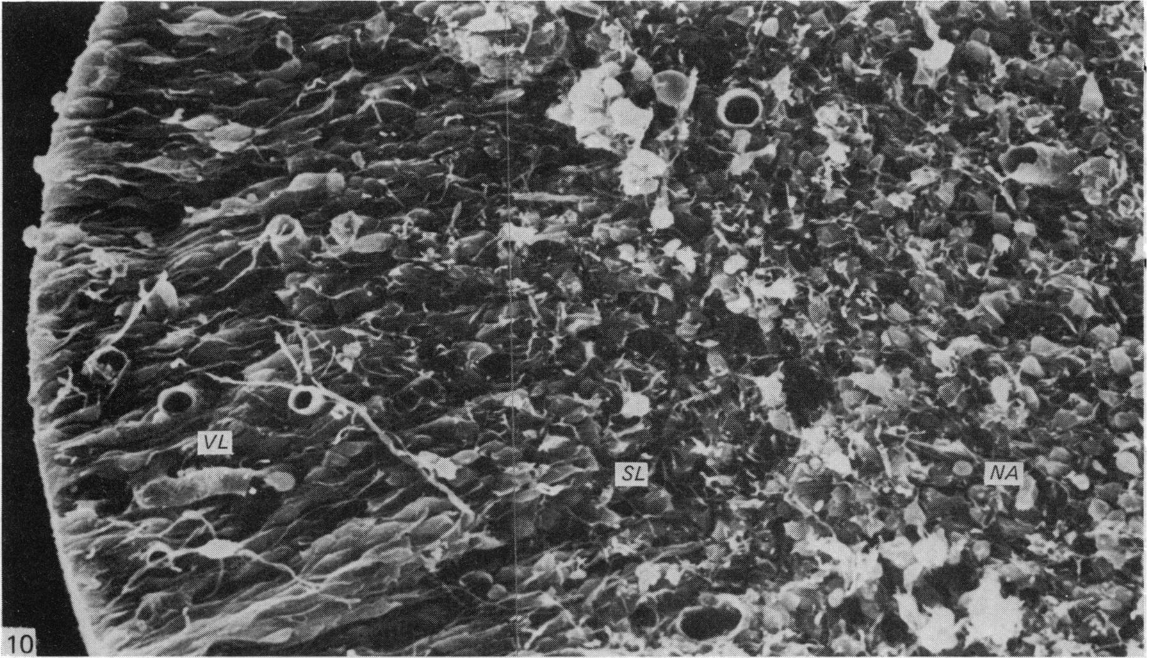
DISCUSSION

The scanning electron microscope gives an indication of the very large number of fine processes which are present in the developing mouse brain. Ideally one would hope to identify these processes using a method such as that used by Levitt & Rakic (1980), but unfortunately glial fibrillary acidic protein does not appear to be present in sufficient amounts in rodent ependymoglial cells to be detected immunocytochemically. Bignami & Dahl (1974) were unable to detect it in prenatal rat brain until 18 days post-conception, although it can be demonstrated in human embryonic glial cells at 10 weeks post-conception (Antanitus, Choi & Lapham, 1976; Choi & Lapham, 1978) and in monkey central nervous system at E41 (Levitt & Rakic, 1980).

The ependymoglial fibre system which shows up clearly in Golgi material (Astrom, 1967; Schmeckel & Rakic, 1979; Smart & Sturrock, 1979; Sturrock & Smart, 1980) is not at all obvious in fractured brains examined in the scanning electron microscope. This is probably due to the fact that the Golgi stain selectively impregnates only a small proportion of the cells and their processes which are present. In the scanning electron microscope all processes passing in all directions are visible and present a picture of apparent chaos, more so, even, than semithin light microscopy.

The course of the very densely packed fibres from the caudatopallial angle is no longer obvious once they become enmeshed with the intersecting fibres in the intermediate layer. Examination of semithin and haematoxylin and eosin-stained sections indicates very strongly that many fibre bundles in the intermediate layer of the ventricular roof, passing laterally around the superolateral part of the lateral ventricle to pass in discrete bundles into the neostriatum, eventually forming the internal capsule. It is not possible, at present, to identify the origin of these fibres but a substantial number seem to be axons and are either projections from the cortical plate to lower centres or projections from the thalamus to the cortical plate. The deepest layers of the cortex, V and VI, are the first to be formed and give rise

Fig. 9. Scanning electron micrograph of the ventricular elevation at E14. The ventricular layer (*VL*) is much deeper at the elevations than along the roof. The nuclear region of the ventricular layer cells is elongated. Bundles containing numerous fine fibres can be seen (arrows) and bundles of fibres and individual fibres penetrate the subventricular layer (*SL*) in which most cells are spherical. A light cell (*c*) with a number of short processes is present at the area where the neostriated anlage appears. × 1080.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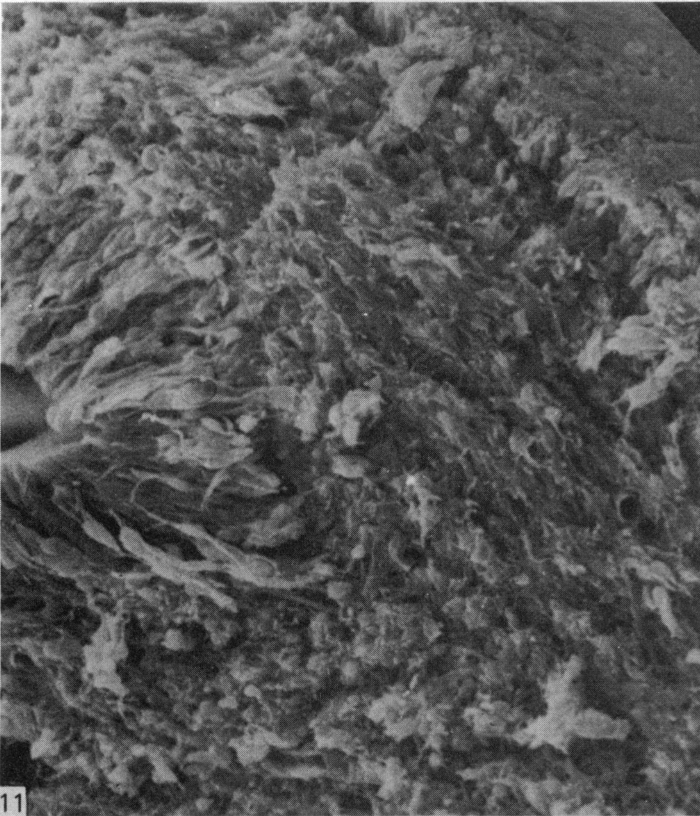
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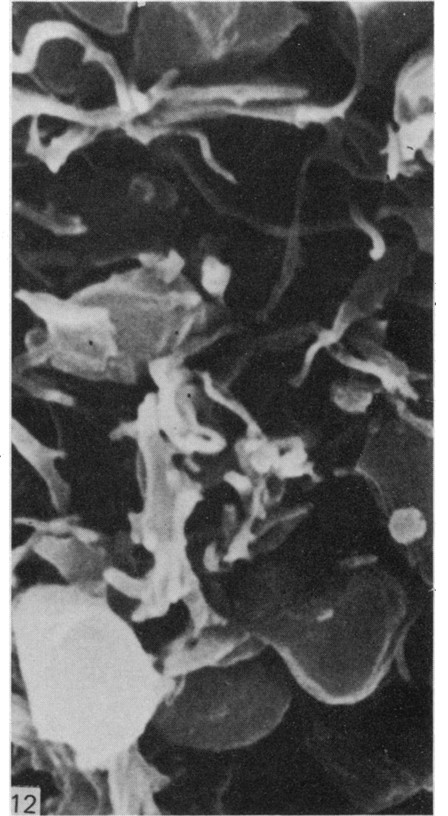
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to the longest projections. Thalamic neurons in the mouse are formed between E11 and E17 (Angevine, 1970) with the peak of production between E13 and E15. The first signs of the cortical plate in the regions studied was at E12 so that by E13–E14, when the internal capsule fibres were first observed, it is possible that both corticofugal and thalamocortical axons are present in the internal capsule.

Some fibres in the internal capsule are pale staining and contain glycogen granules. Either these fibres are ependymoglial or the ultrastructural criteria for the identification of ependymoglial processes are unreliable. A third possibility is that ependymoglial cells are capable of differentiating into neurons, but this seems unlikely as Golgi (Schmechel & Rakic, 1979), immunocytochemical (Levitt & Rakic, 1980) and ultrastructural evidence (Sturrock, 1981) all indicate that ependymoglial cells differentiate into astrocytes.

Ependymoglial or radial glial fibres have been identified in the fetal mouse spinal cord (Henrikson & Vaughn, 1974) and their gradual differentiation into astrocytes has been followed electron microscopically in fetal and postnatal mice (Sturrock, 1981). The ependymoglial processes in the forebrain are identical to those in the spinal cord and are different ultrastructurally from axons. A recent study of the monkey brain by Levitt & Rakic (1980) using immunocytochemical techniques demonstrated radial glial fibres in the fetal monkey and showed that they are immunologically distinct from axons and that radial glial cells eventually differentiate into astrocytes. In spinal cord, no glycogen-containing axons were observed and glycogen was present in ependymoglial cells but not in the mitotically highly active neural epithelial cells (Sturrock, 1981). Shoukimas & Hinds (1978) found no glycogen in any of the axons in their reconstruction study of the developing mouse cerebral cortex. Thus, the available evidence seems to indicate that it is unlikely that the pale glycogen-containing processes are axons or that they differentiate into axons at a later stage of development.

Singer, Nordlander & Egar (1979) proposed a 'blueprint' hypothesis of neuronal pathway patterning, whereby ependymoglial cell processes formed channels for developing axons. They suggested that the cell surface of ependymoglial processes contained mechanical–chemical trace pathways which neurites followed depending on their particular chemical affinities. Whilst ependymoglial fibres do not form channels in the neostriatal anlage, it is possible that they form a 'skeleton' of the internal capsule along which axons grow. It has previously been noted that the guide fibre system arising from the roof and caudatopallial angle marks the site of the future corpus callosum (Smart & Sturrock, 1979; Sturrock & Smart, 1980). If

Fig. 10. Scanning electron micrograph of the ventricular elevation at E14. This low power montage shows the area demonstrated in Fig. 9 and its surroundings. The transition from the regular columnar ventricular layer (*VL*) to the subventricular layer (*SL*) and neostriatal anlage (*NA*) is apparent. The neostriatal anlage contains numerous light coloured cells (cf. Fig. 3). ×480.

Fig. 11. Scanning electron micrograph of the caudatopallial angle, intermediate layer, cortical plate and neostriatal anlage at E13. The intersecting fibre bundles shown in Fig. 1 are not evident in this fractured brain. The caudatopallial angle fibres disappear into the mass of surrounding tissue. ×360.

Fig. 12. Scanning electron micrograph of the neostriatal analge at E14. The lightly coloured cell (upper left) has a thick cylindrical process on the left side with a broad sheet-like process above it. On the right, a long process can be seen extending sideways and upwards before it bifurcates. ×2400.

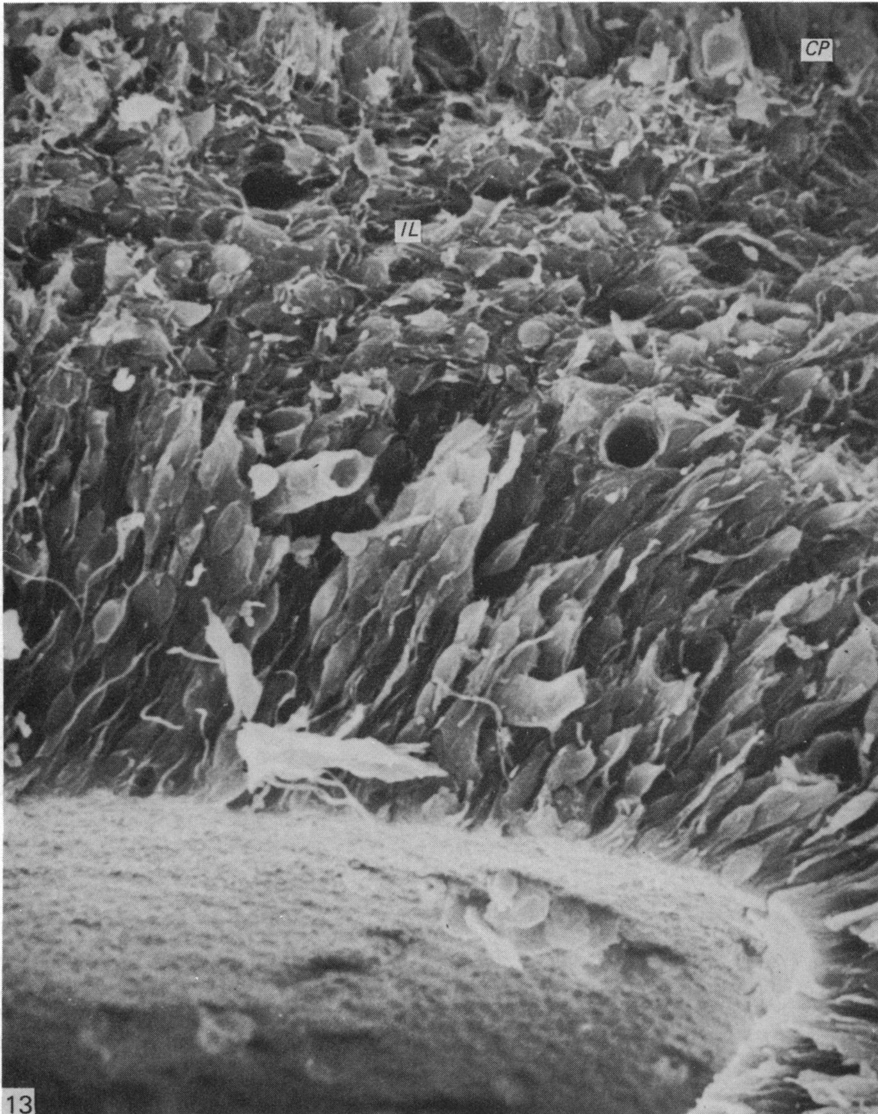


Fig. 13. Scanning electron micrograph of the ventricular roof at E14. The depth of the ventricular layer can be clearly seen. Most of the cells in the intermediate layer (*IL*) are roughly spherical in shape. Numerous short processes are visible in the intermediate layer, mostly running transversely. A few diagonal processes arising from the cortical plate (*CP*) are present at the top right hand corner of the micrograph. × 790.

ependymoglial fibres act as guides to axons in this fashion, there must be a very specific affinity between groups of axons and groups of guide fibres.

If one considers the case of the axons forming the internal capsule, these axons arise in layers V and VI of the cortex and then pass diagonally through masses of ependymoglial fibres which are running from the ventricular roof and the caudato-pallial angle to the pia-glial surface. The internal capsule axons would then have to select the correct group of guide fibres which run in the 'skeleton' of the internal capsule. Similarly, axons which go to form the corpus callosum must find their way

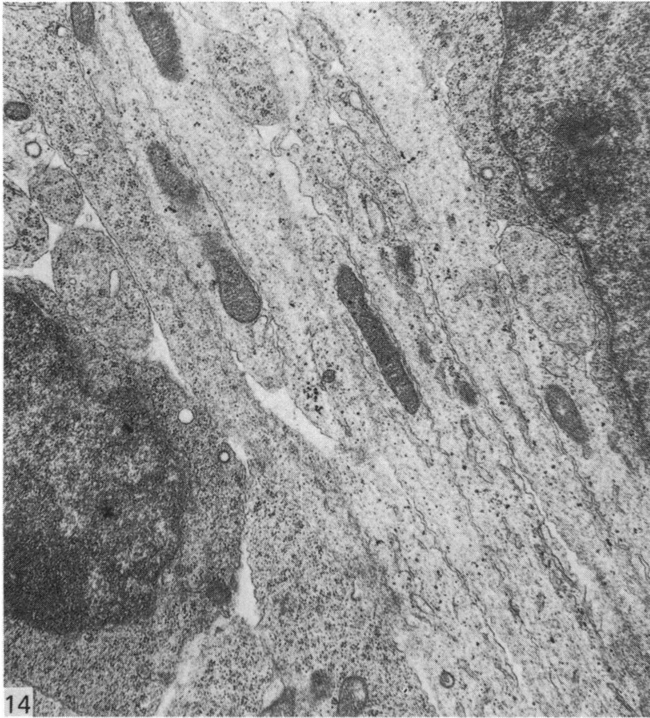
in the opposite direction through both internal capsule axons and ependymoglial fibres to the contralateral cortex. In view of the complexity of cortical connections, one can understand Cajal's view that His's theory that epithelial cells orientated the development of axis-cylinders, while possibly applicable in the spinal cord, was not applicable to the brain (Cajal, 1929). Nevertheless, one cannot at present reject the blueprint hypothesis of Singer *et al.* (1974) out of hand if one accepts the concept of ependymoglial fibres guiding neurons to their final destination.

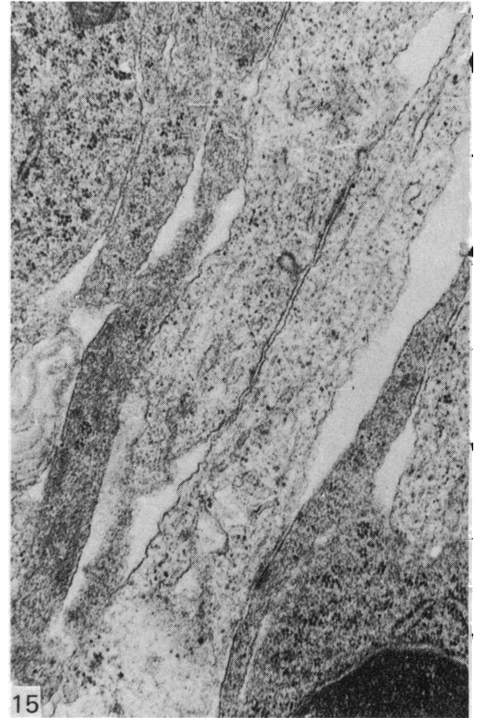
If ependymoglial fibres act as guides to neurons, there must be a mechanism whereby neurons 'recognise' guide fibres, otherwise later produced neurons could migrate in the wrong direction along axons, particularly in regions where numerous intersections exist. At the caudatopallial angle there are numerous guide fibres but few mitotic cells, therefore the neurons guided by these fibres must be produced elsewhere, almost certainly along the mitotically active ventricular roof. If neurons being produced along the roof simply followed the nearest guide fibre, they would all end up travelling to the part of the cortical plate immediately above the ventricular roof. As this does not happen, some recognition system must exist to prevent it occurring. A similar recognition mechanism may exist between guide fibres and axons: thus, guide fibres may not only guide neurons to their destination but may also, as Singer *et al.* (1979) have suggested, form a blueprint to guide their axons to their appropriate synaptic site.

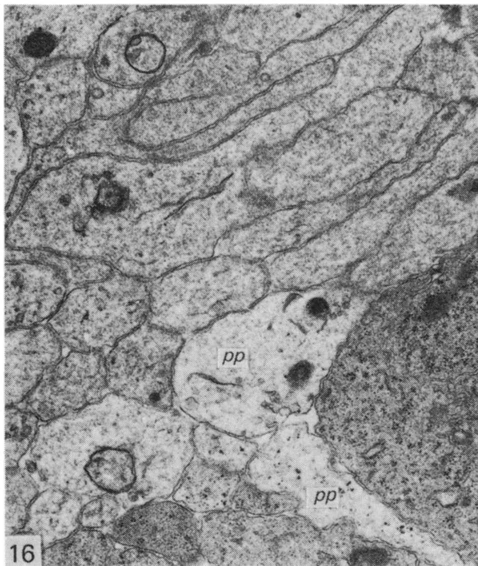
Ependymoglial processes may play an important role in supplying energy for neuron migration and axon growth. In E11–E15 embryos, the ventricular and subventricular layers have a relatively rich blood supply, compared with the rest of the forebrain, and it is possible that the glycogen-containing ependymoglial cells which maintain their attachments in these regions supply energy to the migrating neurons and growing axons which no longer have processes in the vascular ventricular layer. Neurons which have only relatively short distances to migrate may place less reliance on ependymoglial fibres and this may explain why Shoukimas & Hinds (1978) were unable to demonstrate ependymoglial fibres in the medial roof region, although glycogen-containing processes forming the pia-glial boundary were observed in the present study and in the SEM fibres were observed passing to the cortical plate.

One feature which was clearly demonstrated by scanning electron microscopy was the variation in depth of the ventricular layer in different regions. The ventricular layer was thinnest over the ventricular roof and thickest at the ventricular elevations. This may be related to the rate of cell division. Mitotic counts show that the ventricular roof is mitotically more active than the ventricular elevations (Smart, 1976). The cells of the neural epithelium undergo mitotis at the ventricular surface and then the daughter cells migrate to the opposite surface of the layer (F. C. Sauer, 1935*a*, *b*, 1936, 1937; M. E. Sauer & Chittenden, 1959; M. E. Sauer & Walker, 1959; Hinds & Ruffett, 1971; Seymour & Berry, 1975). It seems likely that this elevator movement would occur more rapidly in regions where the distance travelled by dividing cells is least and the differences in mitotic rate are probably related to the depth of the neural epithelium or vice versa.

The apparent absence of a subventricular layer except in the ventricular elevations was surprising, since scattered remnants of this layer are present all round the lateral ventricle of adult mice (Sturrock & Smart, 1980). It is possible that the subventricular layer only appears in the ventricular and medial roof areas once the ventricular layer begins to regress, and that most of the glial precursors are produced in the ventricular elevations. This would explain the differences in subventricular cell types at different







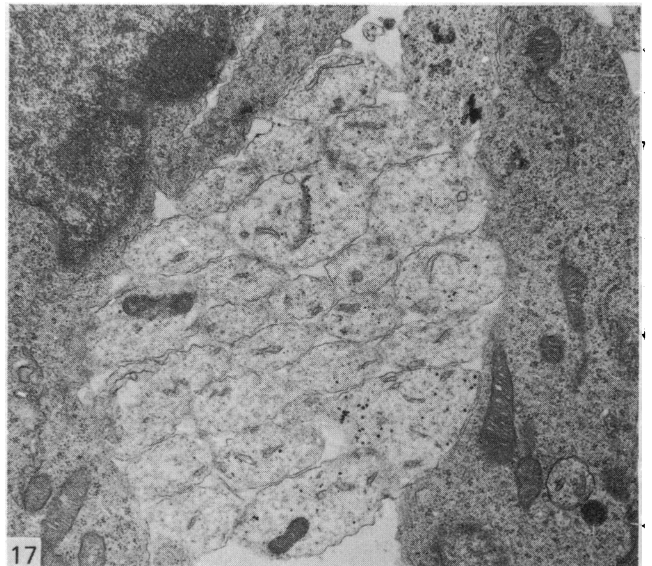


Fig. 14. Transmission electron micrograph. The bundle of pale, glycogen-containing processes running diagonally across the micrograph was present in the intermediate layer above the ventricular roof at E15. As well as glycogen, the processes contain mitochondria and strands of endoplasmic reticulum. × 12600.

Fig. 15. Transmission electron micrograph. The two pale, glycogen-containing processes are joined together by a punctate junction. A coated vesicle is visible on either side of the junction. × 18900.

Fig. 16. Transmission electron micrograph. A bundle of axons at the neostriatal–intermediate layer boundary. The axons are dark and contain no glycogen, unlike the adjacent pale processes (*pp*). E15. × 12600.

Fig. 17. Transmission electron micrograph. A bundle of axons and pale, glycogen-containing processes in neostriatum at E15. The majority of processes do not contain glycogen. × 12600.

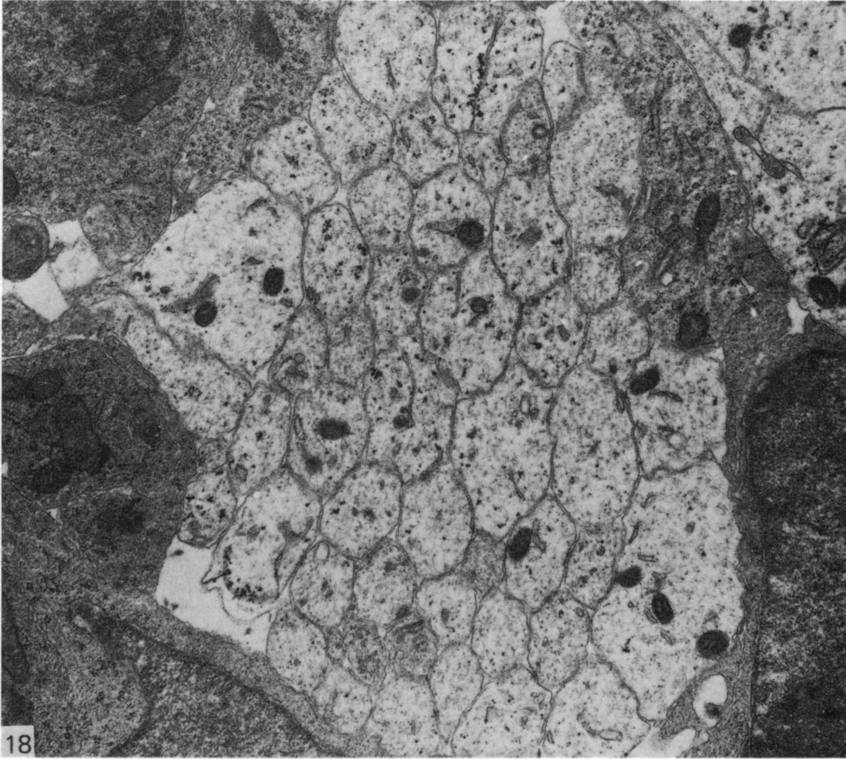


Fig. 18. Transmission electron micrograph. Unlike the fibre bundle shown in Fig. 17, the majority of processes in this bundle are pale and do contain glycogen granules. Neostriatum E15. ×12600.

parts of the ventricle (Sturrock & Smart, 1980) and would confirm the importance of the ventricular elevations as the major site of forebrain glial production.

SUMMARY

The fibre systems of the developing mouse forebrain were examined by a combination of scanning and transmission electron microscopy. No clear pattern of ependymoglial fibre distribution emerged, due to the numerous intersecting fibre pathways. Scanning electron microscopy did show the presence of numerous fine fibres, particularly in regions rich in ependymoglial processes, such as the caudopallial angle; but definite identification of processes as ependymoglial or neuronal was not possible.

Transmission electron microscopy confirmed the presence of numerous intersecting fibre bundles, particularly in the intermediate layer. In the neostriatum, scattered fibre bundles of the internal capsule frequently contained ependymoglial fibres which may act as a skeleton for guiding developing axons to their appropriate destinations.

The difference in depth of the ventricular layer at different parts of the ventricle was clearly shown in the scanning electron microscope and, at the stages examined, a subventricular layer was apparent only in the region of the ventricular elevations.

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