Z. Zellforsch. 128, 42–57 (1972)

The Relation of the Microglia with the Pericytes in the Cat Cerebral Cortex

Margarita Barón and A. Gallego*

Departamento de Fisiologia y Bioquímica, Facultad de Medicina
Universidad Complutense de Madrid

Received February 8, 1971

Summary. Capillaries, pericytes and microglial cells in layer I of the cerebral cortex of normal adult cats have been studied with electron microscopy. The data obtained in this study show that pericytes are cells which are able to transform themselves into microglial cells by virtue of an activation process in which the astrocytic neuroglia appears to play a decisive role. By virtue of its structure, its mesodermic origin and its function the microglia has to be distinguished clearly from the astrocytic neuroglia and the oligodendroglia.

Key words: Microglia — Pericytes — Cerebral cortex (cat) — Transformation — Electron microscopy.

Apart from neurons and neuroglia, Cajal (1913) described in the nervous centers, a cellular "third element", the "tiny adendritic cells" or "non-polar corpuscles". Utilizing his ammoniacal silver carbonate technique, Rio Hortega (1917, 1919, 1920, 1921a, b) identified within the "third element" two cellular types, the *microglia* and the *oligodendroglia*, both types distinct one from the other, both from their morphology as well as from their embryonic origin. The oligodendroglia or "glia with scanty processes" should be, according to Rio Hortega, a type of neuroglia of ectodermic origin, whereas the microglial cells should have an extra-nervous, mesodermic origin, "which penetrate into the nervous tissue by virtue of ameboic movements and of translation, and have as principal function that of scavenging and eliminating products of metabolism and nervous disintegration" (Rio Hortega, 1924).

According to this concept, the microglia would not be a neuroglial component of the central nervous system but rather the nervous division of the reticulo-endothelial system, originating from the meninges or cellular elements of the vascular walls or inclusively, of extravasated blood elements.

Rio Hortega (1919, 1920, 1921a, b, 1924, 1927) studied the microglia by light microscopy in the normal state and in various pathological conditions of the central nervous system. The phagocytic role of the microglia and their transformation into the distinct cellular types which have been described in various pathological processes by diverse names ("Stäbchenzellen", "Abräumzellen", "Körnchenzellen", "corpúsculos granuloadiposos", "Gitterzellen" . . .) was demonstrated by the aforesaid worker, who described the intermediate steps between the microglia at rest, characteristic of normal nervous tissue, and such cellular elements present in various pathological processes.

* This study was partly supported by a grant from the Seguridad Social, Instituto Nacional de Previsión.

Nevertheless, in the modern literature on the microglia, electron microscopic studies appear to raise doubts concerning some problems which appeared resolved by the studies of Rio Hortega. The microglial cells so difficult to were identify with the electron microscope that various authors doubted their existence in normal nervous tissue in face of the results of their own investigations (Maxwell and Kruger, 1965; Eager and Eager, 1966; King, 1968) and the ambiguous descriptions of other authors (Herdorn, 1964; Bodian, 1964; Stensaas and Stensaas, 1968).

On the other hand, disregarding the above-cited work of Rio Hortega, the microglia continue to be considered as more of a type of neuroglia (Mori and Leblond, 1969; Robain, 1970) or even as simple forms of oligodendroglia without relation to the phagocytic elements present in pathological processes, in that "a subdivision of glia which includes the 'microglia' involved in repair of brain injury remains open to question" (Maxwell and Kruger, 1965). Some authors consider that the participation of blood cells is more important in the formation of macrophages, particularly in cases of intracerebral hemorrhages (Schultz and Pease, 1959; Russel, 1962; Konigsmark and Sidman, 1963); the hematogenic origin of the latter is deduced simply at times from the perivascular location of many of the pathological cells encountered in lesions of the nervous tissue (Hills, 1964).

Such confusion may be attributed to the exclusive use of electron microscopic techniques, since for those accustomed to employ the techniques of Rio Hortega, the existence of the microglia as a normal component in the central nervous system is obvious. Thus, Mori and Leblond (1969) who studied the cerebral cortex by a combination of light and electron microscopic techniques identify the microglia with extreme clarity, describing two cellular types, "pericytal" and "interstitial".

The relation of the microglia to the cerebral blood vessels had been already established by Rio Hortega (1920) who described a "vascular satellite" microglia which accompanies the blood vessels forming lengthwise series with them and oriented in the same direction, and at other times perpendicular or obliquely directed with relation to the vascular wall. The description by Rio Hortega (1920) of microglia "intimately backed-up against the wall of the blood vessels" appears to correspond to the microglia that Mori and Leblond call "pericytal" in that for Rio Hortega his "vascular satellite" "extends its protoplasm in the form of irregular sheets over the wall of the vessels" "and appears at times as corpuscles somewhat distant from the capillary but in relation with it through laminar extensions".

Apart from perivascular fibrous neuroglia, perivascular cellular elements have been described which could be related with the origin of microglia: the "pericytes" (Zimmermann, 1923); the satellite cell of vascular neuroglia described by Moya Rodríguez (1970); and intermediary precursor cells of neuroglia of mesodermic origin according to the interpretation of Valenzuela (1970).

In the present work the relation which may exist between the said perivascular elements and the microglia of the gray cortical matter is studied in the cerebral cortex of the adult cat.

Material and Methods

Adult cats of both sexes were anesthetized intraperitoneally with sodium nembutal (30 mg/kg). The exposition of the cerebral surface was undertaken with conservation of the dura mater "in situ". The dura mater is excised and separated carefully leaving the cerebral convolutions covered by the pia mater,

Several samples approximately 1–2 cubic millimeters in size were then extracted from the anterior lateral cortical area of association (Thompson *et al.*, 1963).

The tissue was fixed by immediate immersion in 2% osmium tetroxide in phosphate buffer at pH 7.2 at 4° C for 2 hours and cut into smaller pieces to facilitate its further orientation. The tissue pieces were washed rapidly in distilled water and then immersed in a saturated solution of uranyl acetate in distilled water. Dehydratation was completed in progressively concentrated ethanol. Embedding in epoxy resin (method of Luft, 1961). An ultramicrotome (Porter-Blum MT-2) was used for preparing the sections which were treated with Reynolds lead solution. In all cases 0.5–1.0 micron thick sections were obtained which were examined by phase-contrast microscopy to control the orientation of the sample. Electron microscope: Philips EM 200.

The observations of the present investigation arose in the course of a study on the general organization of layer I of the cerebral cortex. For this reason, the descriptions of the results obtained refer principally to the microglia of the said layer and were obtained by the study of slices sectioned according to two mutually perpendicular sectional planes:

a) Sections perpendicular to the cerebral surface following the vertical plane of organization of the gray cortical matter.

b) Sections tangential to the cerebral surface following the horizontal plane of organization of the gray cortical matter.

Observations

a) Structure of the Cortical Capillaries. The study of the perivascular region, as much pericytal as glial, led us to the ultrastructural study of the capillaries of the cerebral cortex. Our data (Figs. 1–3) coincide with those found by other workers in different species of animals and at various stages of development (Maynard *et al.*, 1957; Donahue and Pappas, 1961; Caley and Maxwell, 1970).

The vascular lumen may be occupied by a blood cell or simply filled with plasma (non-perfused animals) which appears as granular material (Figs. 1, 2). In those cases in which the cleavage plane of the tissue section coincides with the cytoplasm and nucleus of an endothelial cell this latter appears protruding in the vascular lumen.

The endothelial cell appears with an electron dense cytoplasm which completely surrounds the capillary lumen. The chromatin in the nucleus is arranged so as to form a border of increased density next to the nucleoplasmic membrane throughout its extension. At times, irregular masses of chromatin are observed dispersed throughout the nucleoplasm (Fig. 2). The nucleus can be kidney-shaped, more or less rounded, and sometimes very irregular, depending on the plane of section.

The cytoplasm, very scarce in the perinuclear zone, is mainly arranged in the form of processes which thin themselves out distally from the nucleus and surround the vascular lumen which appears rounded or stretched out according to the plane of section. Its boundary is irregular or undulating on account of the protrusion of the endothelial cell nucleus and the folds and invaginations of the endothelial cytoplasmic processes on its margin. The processes of the nearby endothelial cells establish junctional complexes. The cytoplasm of the endothelial cell contains dispersed ribosomes, a scanty endoplasmic reticulum, and at times

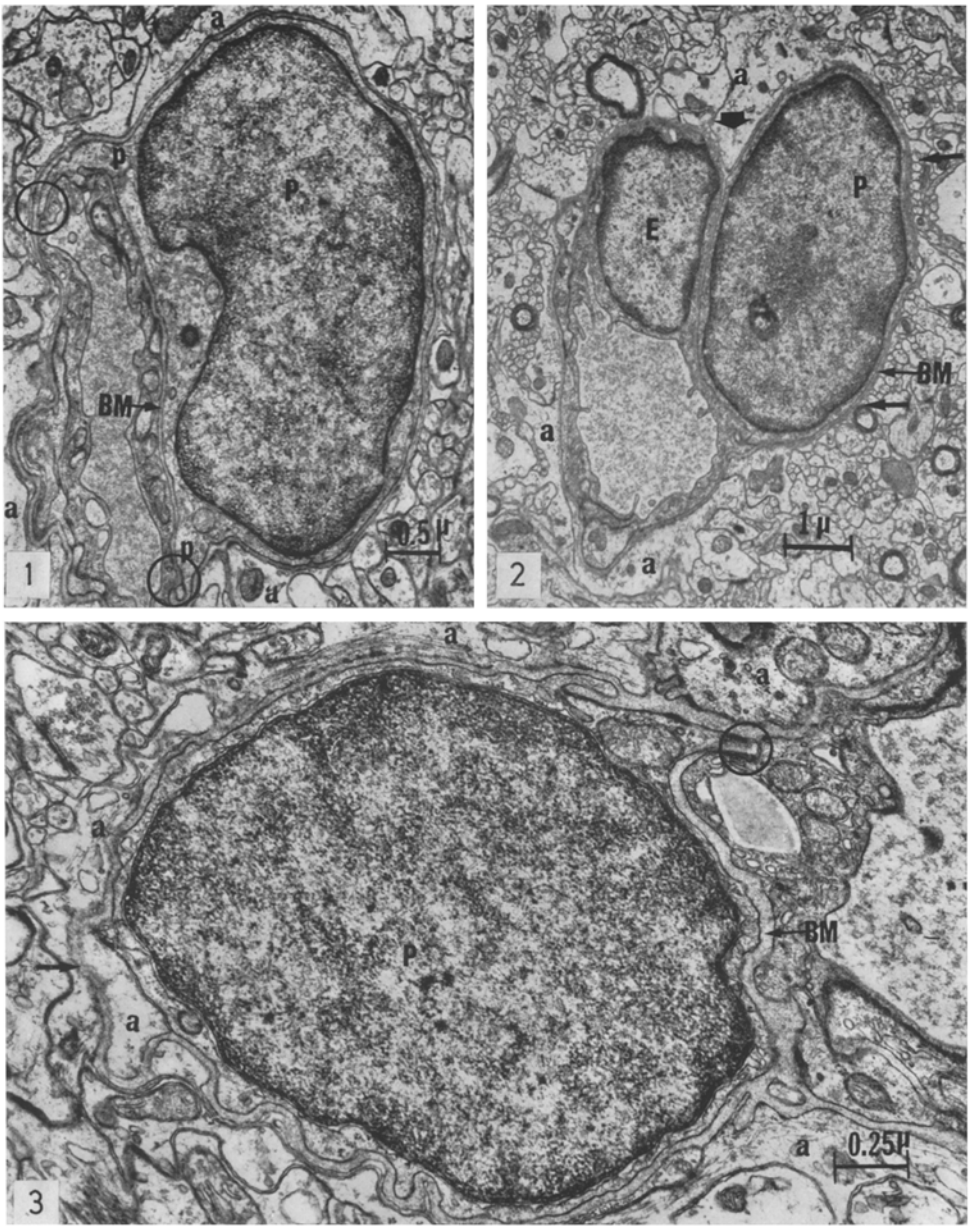
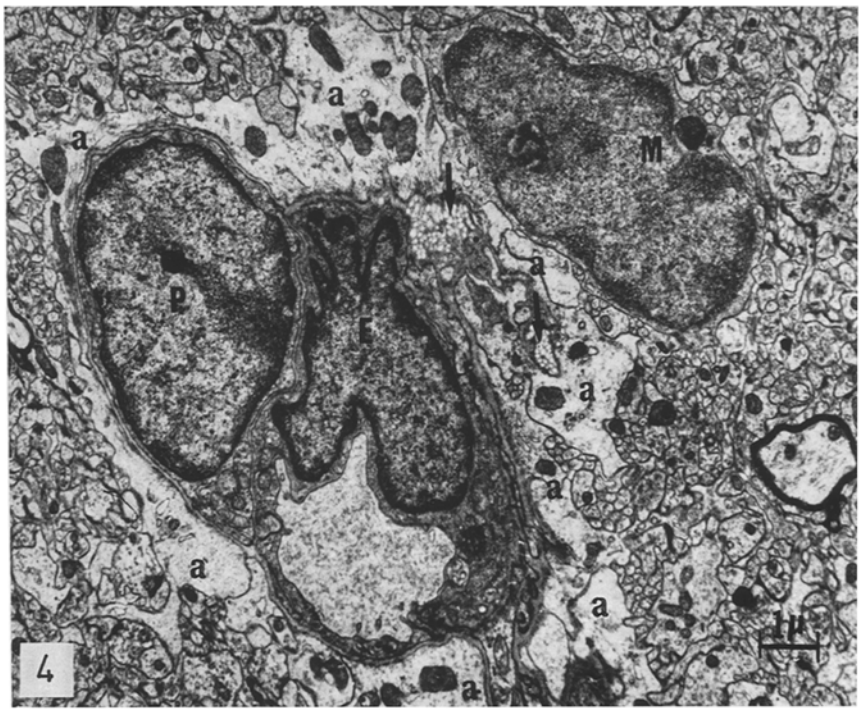
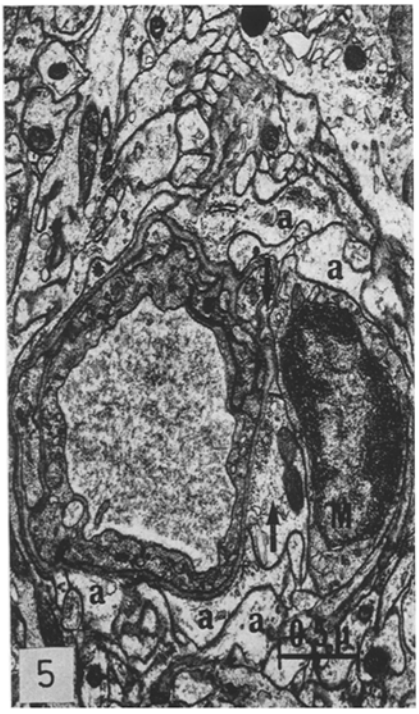


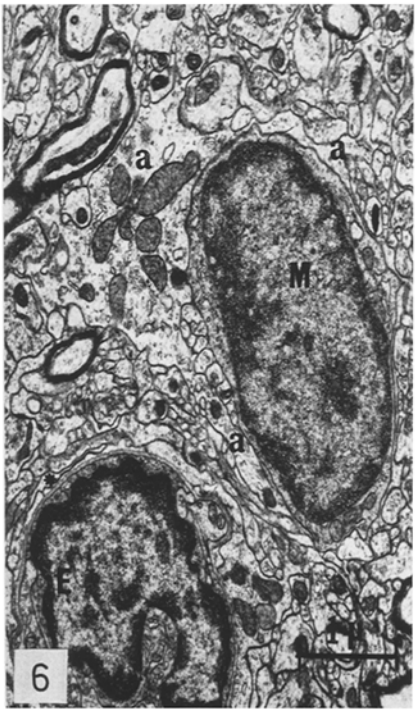
Fig. 1. Pericyte (*P*) resting on the capillary wall and separated from it by the basement membrane (*BM*). The terminal pericytic processes (*p*) are in direct contact with the endothelial cell expansions (circles). Astrocytic end-feet (*a*)

Fig. 2. Endothelial cell (*E*) of a capillary and pericyte (*P*) resting on its wall. Note the pronounced deflection (thick arrow) between the pericyte and the capillary wall marked by the penetration of an astrocytic process (*a*). The astrocytic "atmosphere" around the pericyte is incomplete; its basement membrane (*BM*) is partially in direct contact with the neuropile (thin arrows)

Fig. 3. Pericyte (*P*) resting on the capillary wall and separated from it by the basement membrane (*BM*) except at the point where its process is in contact with the endothelial cell expansions (circle). One astrocytic process (*a*), separates the basement membrane (arrow) from the pericytic surface







Figs. 4–6

cisternae with adherent ribosomes. The Golgi apparatus appears occasionally lodged in the narrow cytoplasmic space limited by the nuclear lobule. The most notable feature of the endothelial cytoplasm is its vesicular appearance brought about by the dissemination throughout it of numerous vesicles of different size. The mitochondria are small, and of medium density. Occasionally pinocytotic vesicles are observed at the side of contact with the basement membrane (Fig. 11). From the luminal side vacuoles are observed which are in the process of being enclosed by the vascular endothelium.

The endothelium is surrounded throughout its length by a well-defined homogeneous basal membrane of 300–400 Å thickness. The covering of the endothelium by the basal lamina is interrupted solely at those places in which a fine pericytic process enters into direct contact with the vascular endothelium (Figs. 1, 3).

External to the basement membrane but in intimate contact with it are found the vascular end-feet of the astrocytic glia. The astrocytic end-feet appear in the form of large plates (sucker feet) which surround the capillary (Figs. 1, 2, 4), or in the form of fine astrocytic lamellae which follow closely along the capillary contours and surround it in the form of a casting (Figs. 5, 6). Among the astrocytic end-feet, complexes of the "gap junction" type described by Brightman and Reese (1969) can be observed; in its cytoplasm are found the usual astrocytic structures, especially gliofilaments cut in all directions. The astrocytic expansions create a closed glial ambient around the capillary. The astrocytic ambient is only interrupted by the relatively frequent presence of pericytes. The basement membrane around the pericyte ceases to be exclusively surrounded by the glia in that the pericyte may or may not be enveloped by a total astrocytic environment.

b) The Pericytes and their Processes. The pericytes are small ovoid cells whose maximal diameter is usually not greater than that exhibited by the vascular lumen outlined by its wall. They rest directly on the basal lamina of the capillary separated from the glia and neuropile by a sheet of basement membrane continuous with that of the capillary. In this manner the basement membrane covers the endothelial cells which form the wall of the vessel and the satellite element, the pericyte (Figs. 1–4).

The pericytes are cells with electron dense cytoplasm. They are easily distinguished from the neuropile and more especially from the astrocytic expansions

Fig. 4. Capillary with endothelial cell nucleus (*E*) and pericyte (*P*) surrounded by a complete astrocytic "atmosphere" (*a*). A perivascular microglial cell (*M*) rests with one of its long surfaces on the astroglial ambient of the vessel in which fragments of apparently disorganized basement membrane can be observed (arrows)

Fig. 5. A perivascular microglial cell (*M*) separated from the capillary wall by a wedge of astrocytic expansion (lower arrow), and a very thin astrocytic lamina (upper arrow). Note the astroglial ambient of the vessel made up by astrocytic end-feet (*a*) and some very thin glial lamellae (asterisks)

Fig. 6. Perivascular microglial cell (*M*) separated from the capillary by astroglial expansions and neuropil; the surface of the microglial cell is mainly surrounded by a large astrocytic process (*a*), similar to the vascular end-feet. Note the very thin astroglial lamellae (asterisk) around the capillary. Endothelial cell nucleus (*E*)

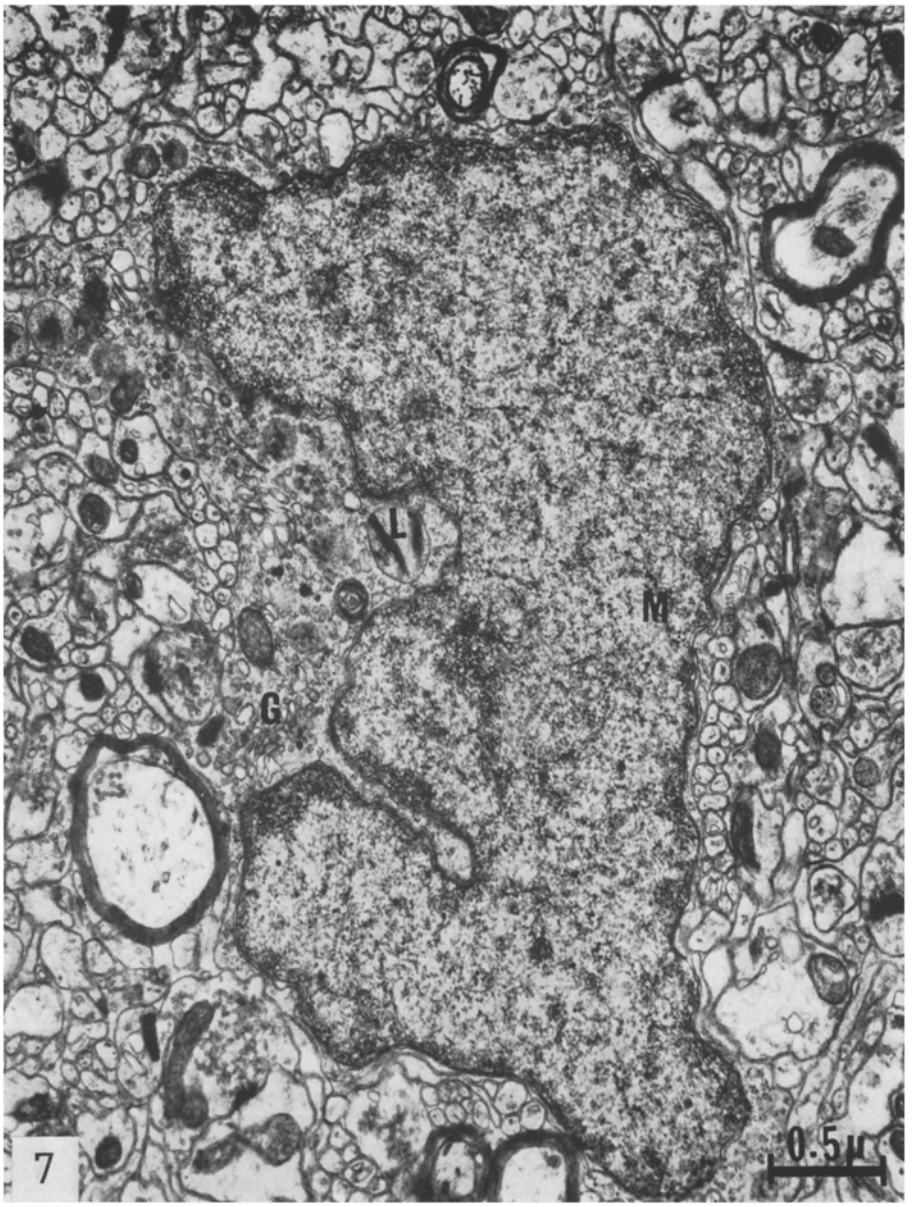


Fig. 7. Interstitial microglial cell (*M*) without intracytoplasmic inclusions. The Golgi apparatus (*G*) is located in the nuclear invagination. Lysosome-like bodies (*L*)

of less electron density which surround them. Nevertheless, if it were not for the definite separation established by the basement membrane, it would be difficult to distinguish them from endothelial cells. The nucleus, as happens in the endothelial cells, occupies almost all of the cellular soma. The darker chromatin

is disposed evenly to form a border below the nuclear membrane. There are also occasionally irregular masses of chromatin dispersed throughout the nucleoplasm and at times a semblance of nucleolar organization (Figs. 2, 4). The remainder of the nucleoplasm is dense and granular. The nuclear shape is controlled by that of the cell, according to the circumstances which affect the membrane. At times, a slight invagination of the nucleoplasm occurs in which cytoplasmic organellae (Golgi apparatus, centriole, mitochondria or reticulo-endoplasmic cisternae) are lodged (Fig. 1). The scarcity of cytoplasm makes its structural study difficult although it is very similar to the endothelial cytoplasm in its characteristics.

Apart from little endoplasmic reticulum, free ribosomes, some osmiophilic granules, dilated cisternae and mitochondria of slight density are found.

In optimal sections the cellular processes of the pericyte can be seen: those close to the cell body are thick and completely wrapped arround with basal membrane (Fig. 1). The processes further away from the cell body are thinner and their end portions appear to be in direct contact with the cellular processes of the endothelial cell in areas where the basal lamina is lacking.

The basal lamina which covers the endothelial cells, is completely surrounded by astrocytic end-feet, generally of ample size. However, the basement membrane of the pericyte at its boundary with the nervous tissue may be surrounded completely by astrocytic expansions (Figs. 3, 4), though very frequently only a few glial lamellae enter into contact with it in that the remainder of the basement membrane is in direct contact with thin processes of the neuropile, either dendrites or axons, which in some instances are myelinated (Fig. 2).

c) Microglial Cells. The study of the cerebral cortex at the level of layer I reveals the existence of microglial cells which by their situation with respect to the blood vessels can be divided into perivascular and interstitial.

The perivascular microglia (Figs. 4–6) are formed of small elongated cells whose nuclei and cytoplasm are practically identical with those of the pericytes just described. In Fig. 4 the microglial cell appears as resting with its proximal surface at the capillary on the astrocytic end-feet which compose the glial ambient of the vessel. The surface of the soma of the microglial cell which is not in contact with the perivascular glia is encompassed by a multitude of processes of different nature (glial and neuronal). In this electron micrograph a basement membrane is noted situated between the capillary and the microglial cell of anomalous appearance and interspersed with astrocytic expansion. Vacuolization, hypertrophia and heterogeneous aspect of the basement membrane are evident. In Fig. 5 the microglial cell appears separated at one of its poles by an astrocytic wedge and at the other by a tenuous glial plate (arrows) which is interposed between the basement membrane of the capillary and the cytoplasmic membrane of the microglial cell. In Fig. 6 a typical perivascular microglial cell is observed relatively distant from the capillary. This cell is accompanied and partially enveloped by an astrocytic prolongation as frequently is encountered in the interstitial microglia. The perivascular microglial cells do not usually show intracytoplasmatic inclusions, and when they exist, they are small and dense (Fig. 4).

In the gray matter, far from the vessels, appear the *interstitial* microglial cells (Figs. 7–9) sometimes surrounded by an extensive astrocytic ambient

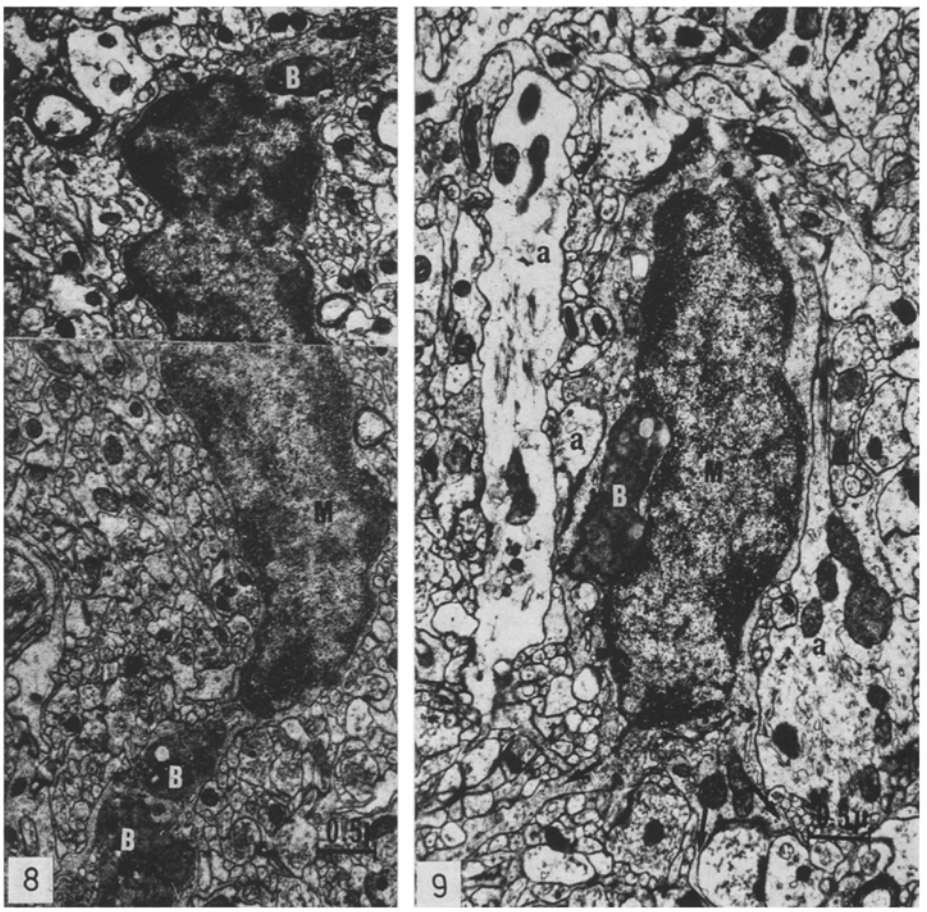
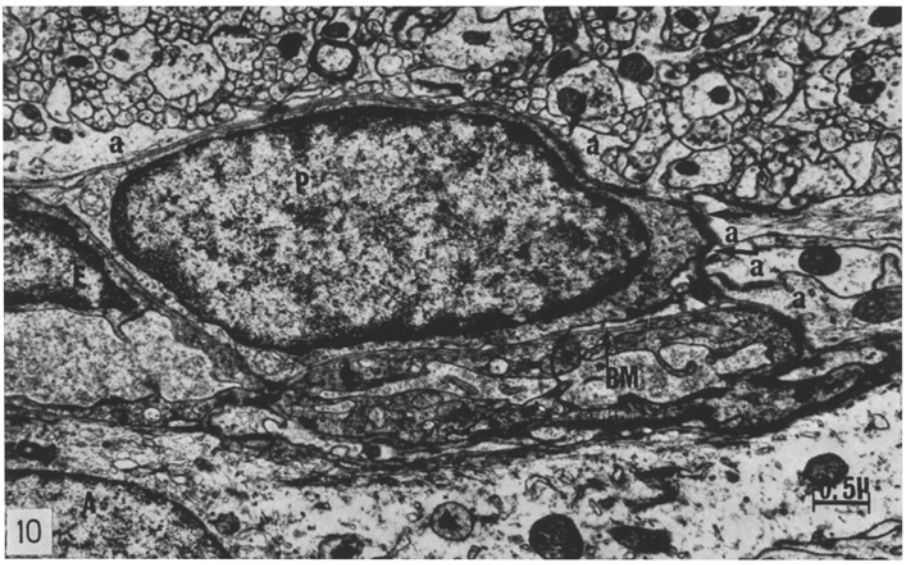


Fig. 8. Elongated and irregular interstitial microglial cell (*M*) with two polar prolongations filled with inclusion bodies (*B*). The indifferent astrocytic ambient around the cell and the thickness of the activated processes are to be noticed

Fig. 9. Interstitial microglial cell (*M*) with intracytoplasmic inclusion body (*B*). The cell is accompanied by large astrocytic processes (*a*). Three slender microglial prolongations (arrows) insinuate themselves in the tissue interstices

(Fig. 9) and at others without apparent astrocytic "atmosphere" (Figs. 7, 8). The interstitial microglial cells have an ultrastructural aspect similar to that of the perivascular microglia but differing from the latter by their greater size, marked elongation, the presence of large and less dense intracytoplasmatic inclusions, and the presence of some slender processes which interpenetrate the contiguous neuropile (Fig. 9). Their nuclei have a very irregular shape, corresponding to the accidental form of the cytoplasmic membrane, and having its bends marked by the lodgement of cytoplasmatic inclusions. Masses of nuclear chromatin are found dispersed in the nucleoplasm forming a rim on the nuclear periphery. The astrocytic expansions which in some cases accompany this



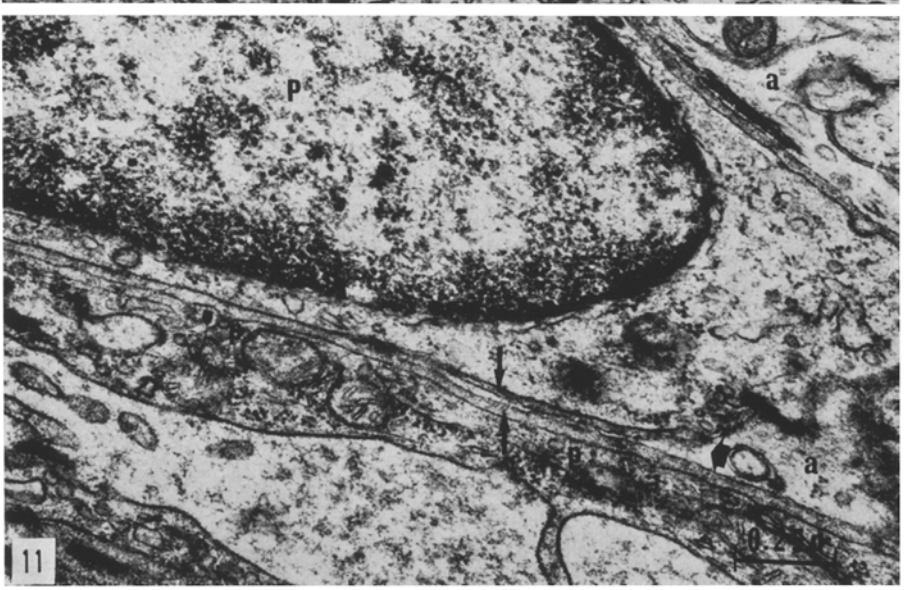


Fig. 10. Penetration of a thin astrocytic lamina (thick arrow) separating the pericyte (*P*) and the vascular wall. The astrocytic "atmosphere" of the pericyte is limited at its poles. The basement membrane of the pericyte in contact with the astrocytic end-feet (*a*) appears diffuse at the side of separation of the cell from the vascular wall (thin arrows). The basement membrane which remains over the vascular wall is normal (*BM*); the one limiting the cytoplasmic membrane of the pericyte tends to disappear at some points (curved arrow)

Fig. 11. Detail of Fig. 10 in another serial section. The astrocytic lamina (thick arrow) appears very thin and separates into two parts the basement membrane of the vascular wall (thin arrows). Pinocytotic vesicles (*p*).

cellular type are large and numerous, some of them parallel to the surface of elongation of the microglial cell and in direct contact with it (Fig. 9).

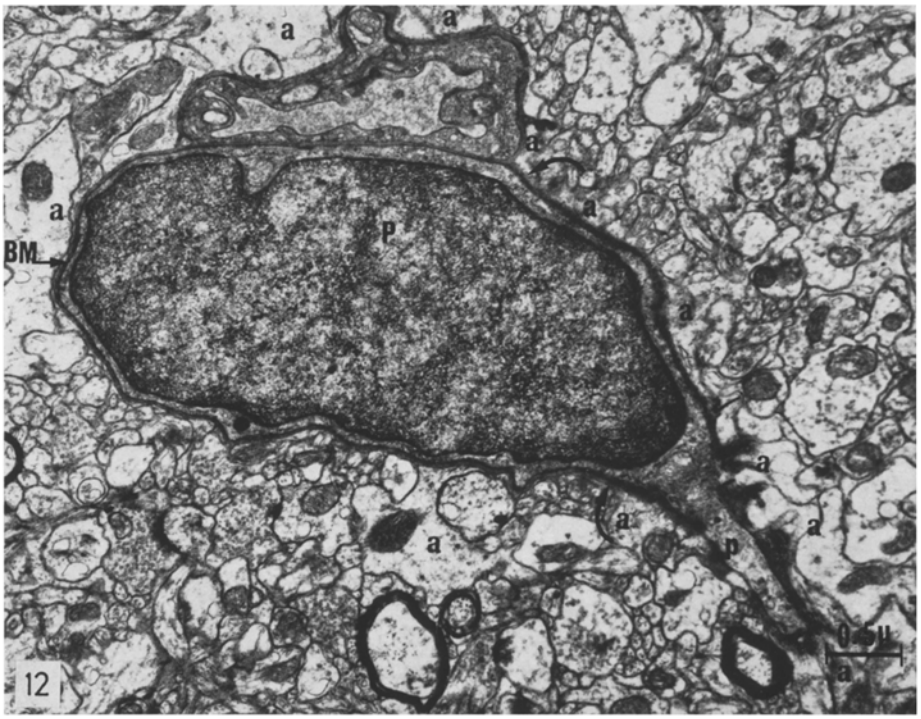
Other microglial interstitial cells are completely deprived of astrocytic "atmosphere" but their structural characteristics are identical with those previously described. The microglial prolongations are slender when they have no cytoplasmatic inclusions (Fig. 9), but appear enlarged when charged with them (Fig. 8). When interstitial microglial cells are encountered free from cytoplasmatic inclusions (Fig. 7) there are found in it the organellae characteristic of the cytoplasm, a vesicular and cisternal Golgi apparatus generally located in a nuclear invagination, lysosomes, osmiophilic vesicles, free ribosomes and some reticuloendoplasmic cisternae of the rough type. In relation to the nucleus the cytoplasmic mass is small. In the cells lacking cytoplasmatic inclusions the nuclear chromatin usually is less dense, the chromatin edging is less apparent, and the dispersed intranucleoplasmatic masses are quantitatively and qualitatively less conspicuous.

By its location in the cerebral cortex there exists another type of microglia, the *sub-pial* microglia. It is situated near to the cerebral surface and separated from it by the astrocytic expansions and the basement membrane which bound it. This type of microglia is comparable in every way to the perivascular microglia. One of its elongated surfaces is usually in contact with or in proximity with the astrocytic subpial end-feet of the cortex. It can contain small and dark inclusions or be free from them.

In the structure of layer I it is possible to differentiate the cellular process of the microglia when the cellular soma does not appear in the section. It is dense in appearance and the ultrastructural characteristics of its content are typical; coated vesicles, dilated cisternae, free ribosomes, and especially, the presence in some of them of inclusions equal in all respects to those present in the soma of the microglia, make them easily identifiable.

d) Transition Images between Pericytes and Microglia. Frequently end-feet of the astrocytes can be observed which rest on the capillary surrounding the pericyte at its base of contact with the vascular wall (Figs. 1, 2, 10). Slender prolongations of the astrocytic cell introduce themselves between the pericyte and the basement membrane which covers the endothelial cell on which the former rests, commencing to separate the two cells. In Figs. 10 and 11 is shown a detail of this phenomenon. In Fig. 11 the basement membrane appears to be left separated into two parts by the interposition of the very fine astrocytic lamina. In Fig. 10 the glial lamina separates a pericytic surface practically bare of basement membrane. It is also observed that the basement membrane of the pericytic surface in contact with the astrocytic covering presents occasionally a discoloured and heterogeneous appearance, differing also in density as in thickness from the rest of the basement membrane (Figs. 10, 11). The same phenomenon is apparent in Fig. 3 over the pericytic pole distal to the vessel; an astrocytic expansion of medium caliber (arrow) is interspersed separating the basement membrane from the pericytic surface, the detached segment of the basement membrane appearing less distinct and homogeneous than the remainder.

Fig. 12 reproduces a pericyte in the process of liberation from the capillary wall with various characteristic details. The soma has a long axis much larger



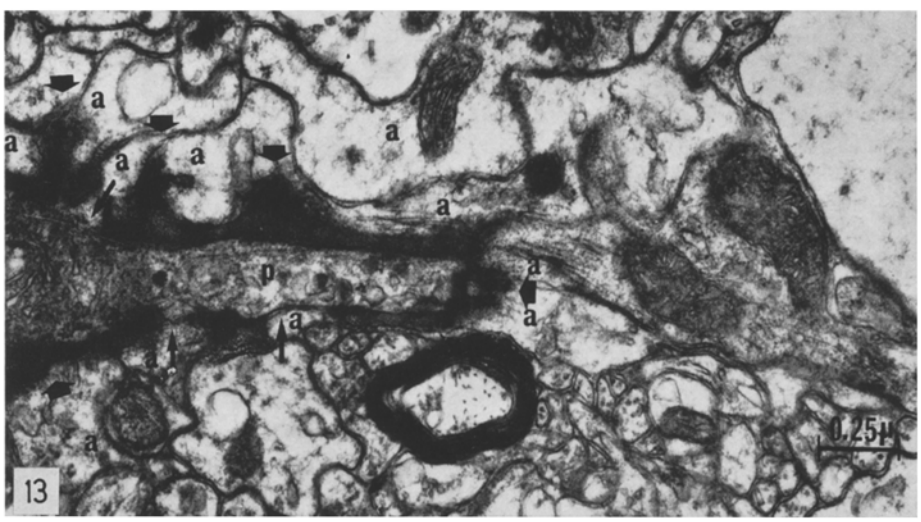


Fig. 12. Pericyte (*P*) exceeding much in diameter that of the capillary. The basement membrane (*BM*) which surrounds the pericyte appears normal up to the points indicated by the curved arrows. From here to the end of the pericytic process (*p*), the basement membrane turns diffuse and disorganized in appearance. Astrocytic expansions (*a*)

Fig. 13. The pericytic process (*p*) in Fig. 12 at a greater magnification. The disorganization of the basement membrane is manifest. Zones of reabsorption of it by the astrocytic end-feet are observed (thick arrows). There are some zones (thin arrows) in which the disappearance of the basement membrane is complete and the astrocytic expansions (*a*) are in contact with the membrane of the pericytic process

than the maximal diameter of the capillary and the basement membrane surrounding one of the poles of the cell in contact with astrocytic expansions or plates appears diffuse, dense and as if it was in dissolution (arrows), in contrast with the remainder of the basement membrane of normal aspect.

Fig. 13 illustrates in detail the lacerated, hypertrophic and abnormal aspect of the basement membrane which covers the pericytic process directed towards the nervous parenchyma, a prolongation which is partially denuded of basement membrane.

Discussion

In agreement with Mori and Leblond (1969), the results obtained in the present investigation permit the unequivocal identification with the electron microscope of microglial cells in the gray matter of the cerebral cortex. The presence of microglia in the cerebral cortex of normal animals and their special abundance in layer I of the same had been demonstrated already with the light microscope by Rio Hortega (1919, 1920, 1921 b).

In our preparations the identification of microglial cells presented no difficulties. There was no possibility of confusion either with the astrocytic glia or with the neurons of the gray matter. Nevertheless it may be worthwhile to discuss their characteristic differences with the oligodendroglial cells which have been object of confusion on the part of workers in this field. Mori and Leblond note the ambiguity of the descriptions that had been made previous to their work in that the microglia described by Herdorn (1964) and Bodian (1964) were completely different from those which figure in the study of Stensaas and Stensaas (1968). Maxwell and Kruger (1965) arrived at the suggestion that the microglia are nothing more than the cells described by Rio Hortega as oligodendrocytes.

In their extensive study on the cerebral cortex of the cat, Jones and Powell (1970) did not detect the presence of oligodendroglia in layer I of the cerebral cortex. However, in our preparations the existence of oligocytes is constant, even though in small quantity. We have been able to differenciate the microglia from the oligodendroglial cells by the general morphological characteristics of their nucleus and cytoplasm.

The oligodendroglial cells appear rounded with very evident cytoplasm whereas the microglial cells have large nuclei, lobulated at times and in comparison to the soma, a minimum quantity of cytoplasm. The beginning of the microglial prolongations is frequently seen, a more difficult matter in the case of the oligodendroglia.

The nucleus of the oligodendroglial cells is also electron dense but its chromatin masses are more defined and darker and it is always round or ovoid in shape. Moreover, no type of inclusions are met within the cytoplasm of the oligodendroglia which could be confused with the frequent inclusions that appear in the soma and processes of the microglial cells. In mature animals the presence of microglial cells appears to be greater than in young adults, and particularly of cells with inclusions in the cytoplasm, thus permitting differentiation of the microglial cellular processes with relative facility in the neuropile content.

The general morphology of the microglial cells may vary according to their perivascular or definitely interstitial localization. The perivascular microglia

consists of less irregular shaped cells without or lesser amounts of inclusions than are present in the interstitial microglia which ramify, finally emitting prolongations which insinuate themselves within the interstices of the neuropile.

The morphological modifications of the microglia according to the tissue structure have been already indicated by Rio Hortegal (1920) in defining their migratory character. When considering the microglial cell as an element which traverses the interstices of the nervous tissue dynamically, its morphology may vary in adapting itself to the interstices of the tissue into which it penetrates.

The presence of pericytes in the capillaries of layer I of the cerebral cortex is constant. These cells, described by K. W. Zimmermann (1923) at the capillary level in general can be made evident clearly by the Rio Hortega variant of the Golgi method, as was demonstrated by Aguirre (1971). The pericytes originate from the mesodermic cords which give birth to the cerebral vessels. Caley and Maxwell (1970) demonstrated by electron microscopy the presence in the mass of nervous tissue of mesodermic cellular cords, demonstrable four days after birth. The cells of which they are formed originate on the one hand the cells of the vascular endothelium and on the other the pericytes. According to the description of Caley and Maxwell the basement membrane commences to form as a more electron dense condensation at those points at which the glia enter into contact with the cellular elements of the said mesodermic cords. The capillary becomes finally constituted towards the tenth day after birth.

In our preparations it is observed that the perivascular neuroglia penetrates and insinuates itself between the pericyte and the perivascular basement membrane separating and producing an alteration in it which tends to produce its disappearance. At times there is observed an alteration of the basement membrane at the points contacting the astrocytic end-feet more particularly towards the neural pole of the pericyte.

The basement membrane which surrounds the pericyte ends up by progressively disappearing and liberating the microglial cell. It has yet a more rounded appearance than the forms of microglia which on displacement towards the neural tissue insinuate themselves into the neuropile acquiring a morphological character with slender processes and enlarged soma and nucleus, characteristics of the interstitial microglia.

The separation phase of the pericyte in its transformation into microglial cells gives cellular images when studied with light microscope which have been described by various names. Moya Rodríguez (1970) recently describes an intermediate cell (satellite) of the vascular neuroglia which, in our opinion, is the image in the optical microscope of a pericyte in the course of separation from the vascular wall, surrounded by the end-feet of the vascular glia.

The images of perivascular elements presented by Valenzuela (1970) as proof of the mesodermic origin of the neuroglia, a hazardous interpretation made with insufficient basis, can be interpreted in the same manner.

The mesodermic origin of the microglia, starting from cells of the vascular wall or blood elements, had been postulated already by Rio Hortega who suggested for the microglia based on this reason the name of "mesoglia". This term had been used previously by Robertson (1900) in a little known work and which had relevance thanks to the studies of Rio Hortega and in that Cajal (1920)

initially used the same term "mesoglia" to denominate the cells of Rio Hortega. Possibly, if the term "mesoglia" had been generalized to designate the microglia there would have been evaded the confusion shown by present day workers who consider the microglia as more of a form of the glia of nerve tissue. By its structure, origin and function, the microglia should be distinguished clearly from the astrocytic glia and the oligodendroglia.

Our results firmly support the thesis of the mesodermic origin of microglia in showing that the parent cells are the vascular pericytes. In this they are in agreement with the results and conclusions of Mori and Leblond, though we ought to make it clear that the concept of pericytal microglia defended by these authors does not appear adequate to us in that it does not reveal well the origin and functional mobility of the microglial cells; pericytes when found "in repose" on the vascular wall are not microglia in the strict sense of the word but rather cells which are able to transform themselves into microglia by virtue of an activation process in which the astrocytic glia appears to play a decisive role.

The participation of vascular or blood elements other than the pericytes in pathological processes of the nervous system in the formation of microglia and of the cells variously described in the same processes ("Stäbchenzellen", "Abräumzellen", "Gitterzellen", "Körnchenzellen"), as well as the demonstration by electron microscopy of the transformation or not of the microglia into the said cellular elements should be the object of further investigations.

References

Aguirre, C.: Personal Communication (1971).

Bodian, D.: An electron microscopic study of the monkey spinal cord. Johns Hopk. med. J. **114**, 13–119 (1964).

Brightman, M. W., Reese, T. S.: Junctions between intimately apposed cell membranes in the vertebrate brain. J. Cell Biol. **40**, 648–677 (1969).

Caley, D. W., Maxwell, D. S.: Development of the blood vessels and extracellular spaces during postnatal maturation of rat cerebral cortex. J. comp. Neurol. **138**, 31–48 (1970).

Donahue, S., Pappas, G. D.: The fine structure of capillaries in the cerebral cortex of the rat at various stages of development. Amer. J. Anat. **108**, 331–347 (1961).

Eager, R., Eager, P.: Glial responses to degenerating cerebellar cortico-nuclear pathways in the cat. Science **153**, 553–554 (1966).

Herdorn, R. M.: The fine structure of the rat cerebellum. II. The stellate neurons, granule cells and glia. J. Cell Biol. **23**, 277–293 (1964).

Hills, C. P.: Ultrastructural changes in the capillary bed of the rat cerebral cortex in anoxic ischemic brain lesions. Amer. J. Path. **44**, 531–551 (1964).

Jones, E. G., Powell, T. P. S.: Electron microscopy of the somatic sensory cortex of the cat. II. The fine structure of layers I and II. Phil. Trans. B **257**, 13–21 (1970).

King, J. S.: A light and electron microscopy study of perineuronal glial cells and processes in the rabbit neocortex. Anat. Rec. **161**, 111–124 (1968).

Konigsmark, B. W., Sidman, R. L.: Origin of brain macrophages in the mouse. J. Neuropath. expt. Neurol. **22**, 643–676 (1963).

Luft, J. H.: Improvements in epoxy resin embedding methods. J. biophys. biochem. Cytol. **9**, 409–414 (1961).

Maxwell, D. S., Kruger, L.: Small blood vessels and the origin of phagocytes in the rat cerebral cortex following heavy particle irradiation. Exp. Neurol. **12**, 33–54 (1965).

Maynard, E. A., Schultz, R. L., Pease, D. C.: Electron microscopy of the vascular bed of the rat cerebral cortex. Amer. J. Anat. **100**, 409–433 (1957).

Mori, S., Leblond, C. P.: Identification of microglia in light and electron microscopy. J. comp. Neurol. **135**, 57–79 (1969).

Moya Rodríguez, J.: Beitrag zur Kenntnis einer besonderen Endformation der perivasculären Glia. Z. mikr.-anat. Forsch. **82**, 341–348 (1970).

Ramón y Cajal, S.: Contribución al conocimiento de la neuroglia del cerebro humano. Trab. Lab. Invest. Biol. Univ. Madrid **11**, 255–315 (1913).

Ramón y Cajal, S.: Algunas consideraciones sobre la mesoglia de Robertson y Rio Hortega. Trab. Lab. Invest. Biol. Univ. Madrid **18**, 109–127 (1920).

Rio Hortega, P. del: Noticia de un nuevo y fácil método para la coloración de la neuroglia y del tejido conectivo. Trab. Lab. Invest. Biol. Univ. Madrid **15**, 367–368 (1917).

Rio Hortega, P. del: El tercer elemento de los centros nerviosos. I. La microglía en estado normal. II. Intervención de la microglía en los procesos patológicos. III. Naturaleza probable de la microglía. Bol. Soc. esp. Biol. **9**, 69–120 (1919).

Rio Hortega, P. del: La microglía y su transformación en células en bastoncito y en cuerpos gránuloadiposos. Trab. Lab. Invest. Biol. Univ. Madrid **18**, 37–82 (1920).

Rio Hortega, P. del: Estudios sobre la neuroglia. La glía de escasas radiaciones (oligodendroglia). Bol. Real Soc. Esp. Hist. Nat. **21**, 64–92 (1921a).

Rio Hortega, P. del: El tercer elemento de los centros nerviosos: histogénesis y evolución normal; éxodo y distribución regional de la microglia. Mem. Real Soc. Esp. Hist. Nat. **11**, 213–268 (1921b).

Rio Hortega, P. del: Lo que debe entenderse por tercer elemento de los centros nerviosos. Bol. Soc. esp. Biol. **11**, 33–35 (1924).

Rio Hortega, P. del, Penfield, W.: Cerebral cicatrix. The reaction of neuroglia and microglia to brain wounds. Bull. Johns Hopk. Hosp. **41**, 278–303 (1927).

Robain, O.: Gliogenèse postnatale chez le lapin. J. Neurol. Sci. **11** 445–461 (1970).

Robertson: A microscopic demonstration of the normal and pathological histology of mesoglia-cells. J. ment. Sci. (Citado por Ramón y Cajal, 1920) (1900).

Russel, G. V.: The compound granular corpuscle or gitter cell: A review, together with notes on the origin of this phagocyte. Tex. Rep. Biol. Med. **20**, 338–351 (1962).

Schultz, R. L., Pease, D. C.: Cicatrix formation in rat cerebral cortex as revealed by electron microscopy. Amer. J. Path. **35**, 1017–1041 (1959).

Stensaas, L. J., Stensaas, S. S.: Astrocytic neuroglial cells oligodendrocytes and microgliacytes in the spinal cord of the toad. II. Electron microscopy. Z. Zellforsch. **86**, 184–213 (1968).

Thompson, R. F., Johnson, R. H., Hoopes, J. J.: Organization of auditory, somatic sensory, and visual projection to association fields of cerebral cortex in the cat. J. Neurophysiol. **26**, 333–378 (1963).

Valenzuela, J.: Névroglie Mésodermique. Etude histologique et histochimique de la névroglie du cerveau. Acta histochem. (Jena) **36**, 129–144 (1970).

Zimmermann, K. W.: Der feinere Bau der Blutkapillaren. Z. Anat. Entwickl.-Gesch. **68**, 29–109 (1923).

Drs. M. Barón and A. Gallego
Departamento de Fisiología y Bioquímica
Facultad de Medicina
Ciudad Universitaria
Madrid-3, Spain