

Nervous System
Muscle
Bone
Joints

Systemic Pathology

SECOND EDITION

by THIRTY-EIGHT AUTHORS

VOLUME 5

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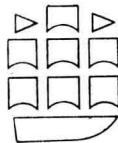
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The caption of each illustration that requires an acknowledgement includes the symbol §, printed after the figure number (for example, Fig. 34.57.§). A footnote on the page on which the first such illustration in each chapter appears refers the reader to the page on which the acknowledgements are made. In the lists of acknowledgements, all the illustrations from each source are grouped together, in numerical sequence.

Some of the authors of the book and some of those who provided them with illustrations for the first volumes of this edition have found this method of acknowledgement to be inadequate. The § footnote, appearing only once in each chapter, is liable to be overlooked: this has led to a mistaken impression that acknowledgements have not been made in all instances requiring them.

The decision not to include acknowledgements in the captions of the illustrations but to collect them at the end of the chapter was made by the editor, who is responsible for the embarrassment caused to the authors and to those who helped to illustrate the book.

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34: *The Central Nervous System*

by W. H. McMENEY

revised by THE AUTHOR and W. THOMAS SMITH

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34: The Central Nervous System

by W. H. McMENEHEY *

* William Henry McMenemy: 16th May 1905–24th November 1977

revised by THE AUTHOR and W. THOMAS SMITH

Note: Except when stated otherwise, the histological preparations illustrated in this chapter are sections of tissues that were embedded in paraffin wax. See also footnote on page 2098.

THE CYTOLOGY OF THE CENTRAL NERVOUS SYSTEM

Introduction

The average weight of the brain is about 1400 g in men and 1250 g in women. In children, it rises steadily from its weight of 250 to 350 g at birth (see Table 34.1); at any age, the weight of a boy's brain is about 10 per cent greater than that of a girl.

The infolding of the brain during development and the resulting multiplicity of sulci accommodate a very large surface area of cortex. The two main divisions of the brain, the cerebrum and the cerebellum, are very different in structure. The two layers of the cortex of the cerebellum—the molecular

abutting on the latter—contrast with the more numerous layers of the cerebral cortex, which are still conventionally described as consisting of six laminae. Each cerebral lamina has a number of synonyms, including the following sequence—outer molecular, outer granular, outer pyramidal cell, inner granular, inner pyramidal cell, and fusiform cell layers. The distinctive lamination of the cerebral cortex is best appreciated in celloidin sections, about 30 μm thick and stained with cresyl violet by Nissl's method. The cells of the cerebral cortex reach their location in these layers during the period of migration of the neuroblasts from the centre of the fetal brain—the so-called 'mantle' (Fig. 34.1): this mainly occurs during the later months of intrauterine life. In children up to the age of 10 years, however, neurons are sometimes present in the white matter, especially of the occipital lobes; this misplacement has no significance. Occasionally, clusters of neuroblasts fail to reach their destination, but develop in abnormal sites (*heterotopia*).

The high metabolic activity of the brain requires a blood flow of about three-quarters of a litre a minute (roughly one-seventh of the cardiac output at rest).^{1, 2} From studies on arteriovenous oxygen differences, it is estimated that the brain extracts rather more than 50 ml of oxygen from this volume of blood. This high oxygen requirement reflects the very large number of cells in the brain: the neurons alone are believed to number at least 26×10^9 , and the glial cells are more numerous. In the cortex beneath every square millimetre of the surface of the cerebrum there lie some 50 000 nerve cells, a concentration of about 10 000 cells in each cubic millimetre.^{3, 4} Cell density studies on the striate cortex of a young man showed 17.5×10^6 neuronal

Table 34.1. Mean Weight of the Brain of Children at Various Ages†

Age	Weight (grams)	Age	Weight (grams)
6 months	660	5 years	1237
12 months	925	7 years	1263
2 years	964	9 years	1275
3 years	1141	12 years	1351

† Coppoletta, J. M., Wolbach, S. B., *Amer. J. Path.*, 1933, 9, 55.

and granular layers, with the cell bodies of the Purkyně cells‡ at the deep aspect of the former,

‡ Jan Evangelista Purkyně was born in 1787 in Libochovice, in Bohemia. He was professor of physiology in Breslau (Wrocław) from 1832 to 1850 and in Prague from 1850 until his death in 1869. The Czech spelling of his name is less familiar to the reader of English than the German transliteration, Purkinje, which was used in the paper in which he gave the first description, in 1837, of the cells of the cerebellar cortex that are now known as 'Purkyně cells' or 'Purkinje cells' (Purkinje, J. E., *Ber. Versamml. dtsch. Naturf. Aertz.* [Prag 1837], 1838, 179).



Fig. 34.1.§ The human brain at the fourth month of fetal development. The broad band surrounding most of the lateral ventricles is the mantle layer: a few of the migrating cells have already reached the rudimentary cortex, which at this stage is without gyral pattern. *Stern-Weil-Davenport stain*. $\times 3$.

nuclei and 77×10^6 glial nuclei in each gram of fresh brain tissue; the figures are similar in the rhesus monkey and the rat.⁵ It has been calculated that the neurons, although much outnumbered by the glial cells, utilize over half the oxygen supplied to the brain; nearly three-quarters of the oxygen is believed to be consumed in the grey matter and the rest in the white matter.⁶

The whole of the nervous system, with the exception of the blood vessels, their accompanying mesenchymal cells, the leptomeninges and the dura mater, is derived from the ectoderm. The medullary epithelium, which in early embryonic life lines the primitive neural canal, differentiates in two directions, forming the neurons (the excitable cells of the nervous system) and the neuroglia (the supporting and nutritive cells).

The Neuroglia⁷⁻¹⁰

The *neuroglia** is generally taken to comprise the astrocytes and the oligodendrocytes; it is usual to include also the ependymal cells, which retain a

* Virchow believed that the neuroglial cells, of which he could see only the nuclei, constituted the connective tissue or 'glue' (hence the name *glia*) of the brain (Virchow, R., *Virchow's Arch. path. Anat.*, 1854, 6, 135). There seems to be little doubt that he recognized that some of the cells also had a phagocytic function.

§ See *Acknowledgements*, page 2293.

closer resemblance to embryonic medullary epithelium than any other mature cells of the nervous system. The term *glia* is used in a general sense to refer to these cells; the tumours that originate from them are the gliomas. The term *gliosis* is generally used with the restricted meaning of proliferation of the fibrillary processes of the astrocytes.

The Astrocyte*

It is usual, with the light microscope, to distinguish two varieties of astrocyte, the *protoplasmic astrocyte*, found in the grey matter, and the *fibrous astrocyte*, found in the white matter throughout the brain and spinal cord, and less widely in the grey matter. Both varieties have a similar cell body; it is in their cytoplasmic processes that they differ. In paraffin wax sections stained with haematoxylin and eosin, the astrocyte can be identified by its round or ovoid, vesicular nucleus, some 8 to 10 μm in diameter (Fig. 34.2); unlike most neurons the normal astrocyte lacks a prominent nucleolus, and this is helpful in differentiating cells in the grey matter. Its cytoplasm, when visible at all in haematoxylin-eosin preparations, appears to be scanty, and its processes are seldom recognizable, and then only for a fraction of their length. When the processes are seen, they generally project in a radial pattern from the cell body: this arrangement led early neuro-histologists to name the cells 'spider cells' or, alternatively, 'stellate cells' ('astrocytes'). If stained by Holzer's crystal violet or Anderson's Victoria blue methods, the processes of the fibrous astrocytes become more distinct, especially in the white matter, and their tenuous prolongations can be followed for 300 μm or more. To demonstrate astrocytes in grey matter, Mallory's phosphotungstic acid haematoxylin is preferable; in white matter this method is less valuable, largely because

* Deiters in 1865 was the first to recognize the astrocyte (Deiters, O., *Untersuchungen über Gehirn und Rückenmark des Menschen und der Säugethiere*; Braunschweig, 1865), but it was not until the introduction of the carmine wash method that its manifold cytoplasmic processes could be identified with any certainty. The method of metallic impregnation, apparently first tried by Krause in 1844, helped to disclose the many ramifying processes possessed by these cells, and the early silver and gold techniques of Ranvier (Ranvier, L. A., *Leçons sur l'histologie du système nerveux*; Paris, 1878) and Golgi (reference 13a on page 2227) were later modified by Ford Robertson (Robertson, W. F., *Scot. med. J.*, 1899, 4, 23), Ramón y Cajal (Ramón y Cajal, S., *Rev. Cienc. méd. [Madr.]*, 1892, 18, 457; and many subsequent publications) and del Río Hortega (reference 34 on page 2227).

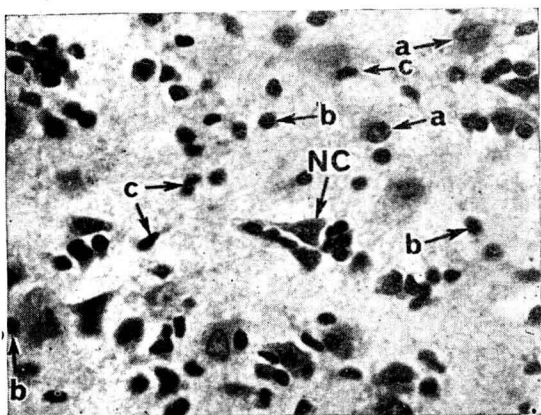


Fig. 34.2. The cells in diseased cerebral cortex. The nuclei of astrocytes (a) are of moderate size and roundish, with palely-stained contents: surrounding the nucleus a rim of pale cytoplasm can often be discerned together with the beginnings of the processes, but the cell outline is always indistinct, tending to fade imperceptibly into the background; the cytoplasm is more prominent and the nucleus often lies eccentrically when, as in the present instance, these cells are reacting. The nuclei of oligodendrocytes are small, round and pyknotic (b) and are usually surrounded by a fine unstained halo or, less often, by a thin rim of palely-stained cytoplasm. Intermediate in size and in their ability to hold the haematoxylin are the nuclei of Hortega cells (microglia): they are often reniform (c) but in cross section are round and so may resemble oligodendrocytes; they have to be distinguished from the endothelial cells of capillaries. The degenerating nerve cell in the centre (NC) is adjoined by Hortega cells, but the cluster of round cells to its right could be oligodendrocytes. *Celloidin. Haematoxylin-eosin.* $\times 300$.

the cell processes are obscured by the presence of myelin, which also takes up the haematoxylin.

While most of the astrocytes in the cerebral cortex are of the protoplasmic variety, fibrous astrocytes are present in the outer cellular layer and also round the penetrating arterioles. The distinction between protoplasmic and fibrous astrocytes can be shown microscopically by various methods of metallic impregnation of histological sections. The processes of the protoplasmic astrocytes are short and stout (Fig. 34.3), and they branch oftener than the long, fine, fibrillary processes of the fibrous astrocytes (Fig. 34.4); these differences in structure may reflect differences in the functions of the two varieties of cell. When the protoplasmic astrocytes react—for instance in lesions in which cortical neurons have been lost—their processes become fibrous, fibrils developing in them that are clearly revealed by the methods of Anderson and of Holzer. The glial fibrils were shown by del Río Hortega to be within the cytoplasmic processes and not extracellular structures,¹¹

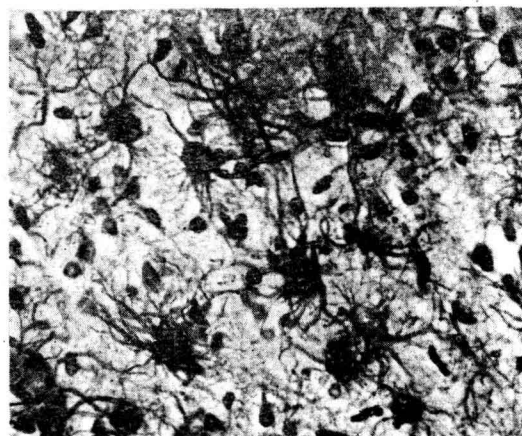


Fig. 34.3. Proliferating protoplasmic astrocytes in cerebral cortex. Frozen section. *Hortega silver method for astrocytes.* $\times 360$.

a finding that has since been confirmed with the electron microscope. In fact, on the evidence of electron microscopy, the distinction between protoplasmic and fibrous astrocytes is not always possible. The fibrils that are seen with the light microscope probably consist of compact bundles of the intracellular filaments that are disclosed by the electron microscope (Figs 34.5 and 34.6).

Electron microscopy shows that the cytoplasm of astrocytes contains—in addition to the filaments noted above—rough endoplasmic reticulum, Golgi complexes, mitochondria and lipid droplets (Fig. 34.5). The foot processes (see below) are also easily recognized in electron micrographs (Fig. 34.6); they are separated from the capillary endothelial cells by their basal lamina.

Protoplasmic astrocytes are present in the

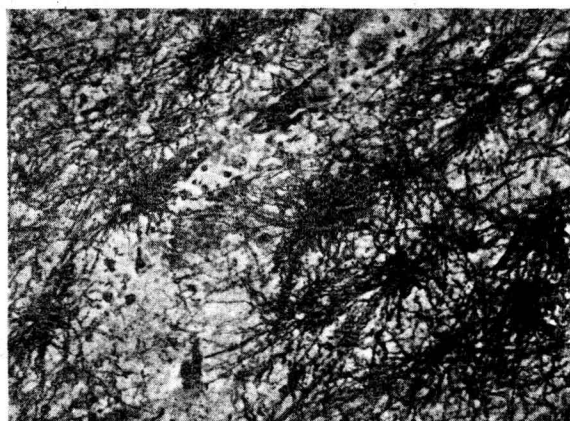


Fig. 34.4. Proliferating fibrous astrocytes in white matter. Frozen section. *Golgi-Cox stain.* $\times 200$.

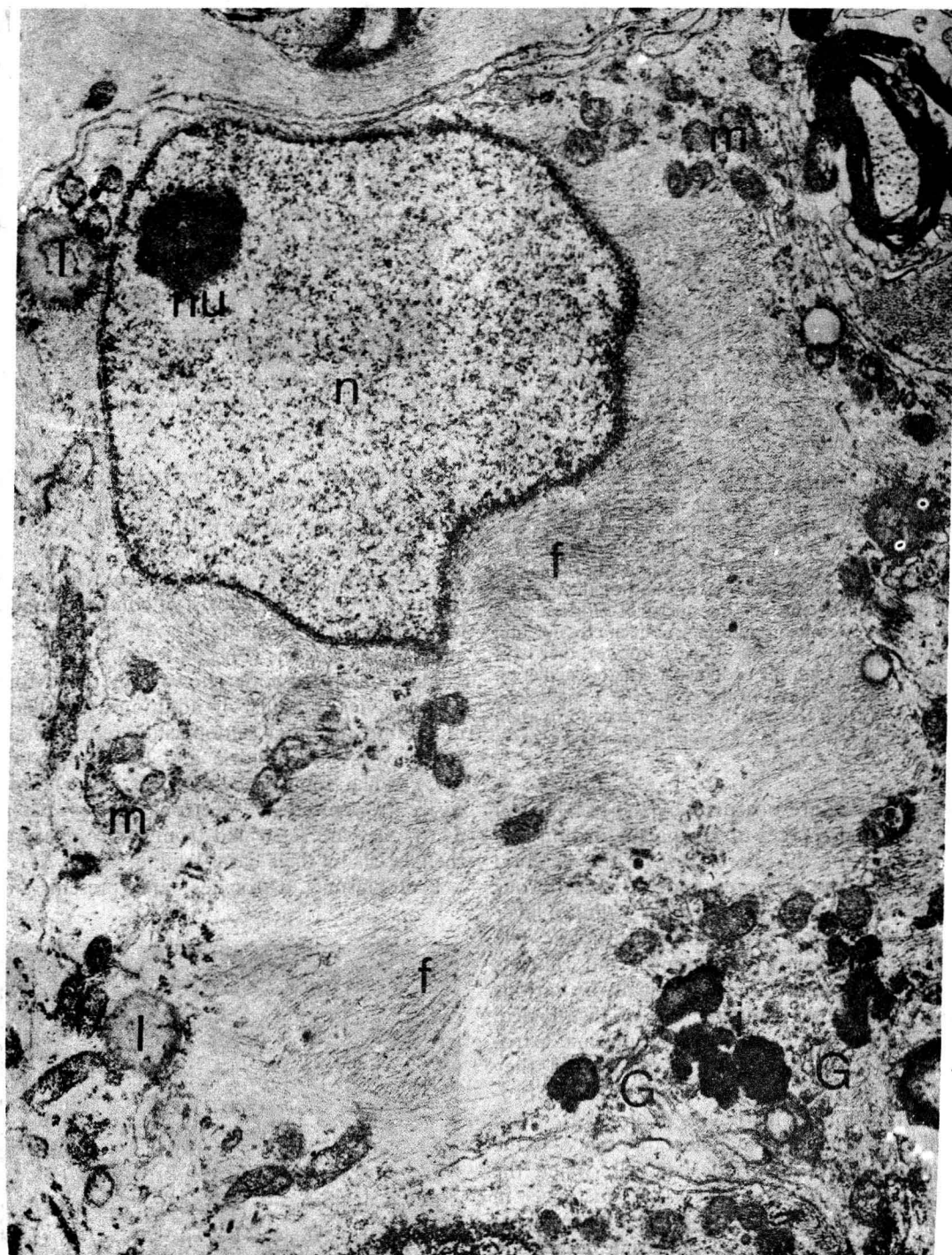


Fig. 34.5.8 Electron micrograph of a reacting astrocyte. The nucleus (n) is eccentrically placed and contains a prominent nucleolus (nu). The abundant cytoplasm contains large numbers of filaments (f); there are also Golgi complexes (G), mitochondria (m), lipid droplets (l) and electron-dense inclusions (i). $\times 16\,400$.



Fig. 34.6. § Electron micrograph of a reacting astrocyte surrounding an oligodendrocyte (O). The nucleus of the oligodendrocyte has a regular outline; its electron-dense cytoplasm contains closely-packed ribosomes, rough endoplasmic reticulum and organelles. The outline of the nucleus of the astrocyte (n) is very irregular; its chromatin is evenly distributed. The abundant cytoplasm of the astrocyte contains: cisternae of rough endoplasmic reticulum (rer), Golgi complexes (G), filaments (f), mitochondria (m) and lipid droplets (l). A capillary (c) is seen: its endothelial cells (E) are separated from the clear foot processes of the astrocytes (P) by a basal lamina. $\times 9200$.

caudate nuclei and putamina, and in the granular layer of the cerebellum. Elsewhere in the central nervous system most astrocytes are of the fibrous type, although variations among them have been observed. Some, the *Bergmann cells*, found in the granular layer of the cerebellum near the Purkyně cells, have a well-developed fibrous process that extends to the pial surface, while others, the *Fañanás cells*,^{11a} lying more superficially in the cerebellar cortex, have processes that are shorter and stouter than usual, somewhat resembling those of the protoplasmic astrocytes.

Astrocytes have been compared with the fibroblasts of other tissues of the body, for one of their functions is to close, by means of glial scar formation, any gaps caused by the destruction of neurons or of the myelin that surrounds the axons.¹² The analogy should not be carried too far, for fibroblasts are of mesodermal origin, and the collagen fibres that they produce are extracellular structures,¹³ whereas astrocytes are of ectodermal origin and the glial fibres are part of their cytoplasm. Moreover, the astrocyte by no means completely replaces the fibroblast within the central nervous system, for under certain circumstances collagenous scars can develop, as, for instance, in the wall of abscesses, round foreign bodies, and in post-trau-

matic meningocortical adhesions; these collagenous scars are stronger, and more rapidly produced, than astroglial scars. Nevertheless, the ability of astrocytes to form dense masses of glial fibrils is at times remarkable, notably in multiple sclerosis, in which an abundance of fibrils may soon obscure the cells that have produced them. When gliosis develops along the course of demyelinated axons, the fibrils assume a regular and parallel arrangement (*isomorphic gliosis*) (Fig. 34.7).

Gliosis is not always pathological. It may be found to some extent in the normal brain, for instance in the olivary nuclei, the floor of the fourth ventricle and round the aqueduct and the central canal of the spinal cord.

Astrocytes possess one or more terminal protoplasmic expansions that embrace the adjacent capillaries; these 'sucker feet', which were first noted by Golgi,^{13a} are especially well seen in Cajal preparations of the white matter. They are so numerous that it has been suggested that they constitute an anatomical blood-brain barrier (Held's limiting membrane). Electron microscopy, however, has indicated that there may be gaps in this investment round some capillaries.¹⁴ In addition to their attachment to blood vessels, astrocytes that are near the surface of the cortex—for instance,

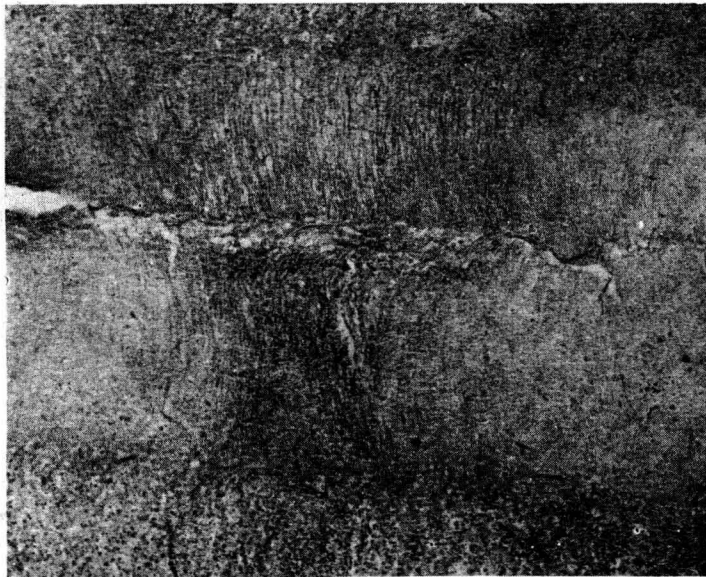


Fig. 34.7: Isomorphic gliosis in the molecular layer of the cerebellum, a not infrequent finding indicative of local ischaemia. These glial fibrils have developed in the processes of the Bergmann astrocytes (in the Purkyně cell layer) and extend to the pial surface. The distended venule near the right of the centre of the picture lies at the bottom of a sulcus. *Celloidin section. Holzer stain. × 90.*

the Fañanás cells—often have a process that is secured to the pial membrane. Studies on the ultrastructure of astrocytes indicate that their processes ramify very widely and are much more voluminous than other histological techniques suggest: within the substance of the central nervous system they are believed to fill all the available space between the other cells and their processes.¹⁵⁻¹⁷

In tissue culture, chick embryo astrocytes grow best when the oxygen tension is reduced to 2 per cent and the carbon dioxide tension is 4 per cent.¹⁸ In human pathology, the stimulus to the proliferation of the cortical astrocytes appears to be death of nearby neurons. For example, within 48 hours of a hypoxic or hypoglycaemic episode in which neurons have been lost, the astrocytes in the vicinity of the dead cells swell and begin to proliferate. The nuclei of the dividing astrocytes can be seen lying in pairs, and the cytoplasmic processes become grouped into two sets, one associated with each nucleus. If many neurons have been destroyed, and the patient survives, further proliferation of astrocytes takes place, with the formation of cell clusters (*astrocytosis*) (Fig. 34.8). In grey matter, the presence of astrocytic nuclei paired or clustered in this way is presumptive evidence of neuronal loss. Sometimes nuclear division takes place without separation of the swollen cytoplasm, the formation of a multinucleate giant astrocyte resulting. Under other conditions, the cell body of the astrocyte swells considerably, its nucleus enlarges and assumes an eccentric position, and its cytoplasm and nucleolus usually become clearly visible, even in haematoxylin-eosin preparations. The German

word *gemästet* ('fattened', 'plump') was applied to this type of cell, and has been 'anglicized' in the names *gemistocytic astrocyte* and *gemistocyte*. Such swollen forms are to be seen in oedematous white matter and near rapidly expanding inflammatory, ischaemic or neoplastic lesions. They may also be found in the white matter within as little as six hours after the onset of acute oedema.

Under normal circumstances astrocytes seldom, if ever, undergo division. There has been much debate whether astrocytes in pathological states divide by mitosis or in some other way: that they proliferate round focal lesions is not in doubt, for experimental studies, using perfusion fixation, mitotic inhibitors and autoradiography, have shown that division does occur.¹⁹

There is no evidence that astrocytes are capable of phagocytosis. Like other cells, they may undergo fatty degeneration, and, in old age, their cytoplasm, like that of neurons, may contain granules of lipochrome. Like other cells, too, they are susceptible to bacterial toxins and other poisons, undergoing a form of degeneration in which the cell and its processes swell ('cloudy swelling'); in the severer, irreversible forms of degeneration, the nucleus disappears (*karyolysis*), and the processes fragment (*clasmatodendrosis*) (Fig. 34.9) and are ingested by phagocytic cells (*dendrophagocytosis*).

The Oligodendrocyte

In sections stained with haematoxylin and eosin or by Nissl's method, the oligodendrocyte is recognized

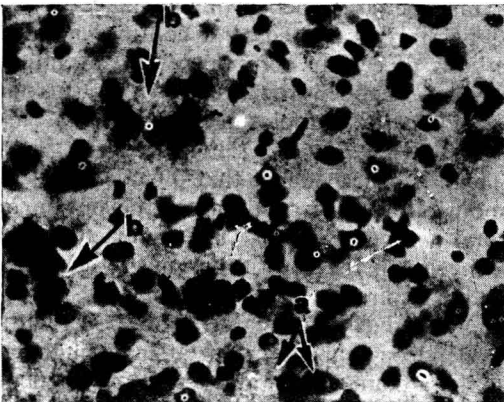


Fig. 34.8. Cerebral cortex showing an unusual degree of astrocytosis. The pale-staining nuclei of astrocytes can be seen in pairs (a) and in clusters (b), lying eccentrically in ill-defined cytoplasm. *Celloidin section. Haematoxylin-eosin. × 360.*

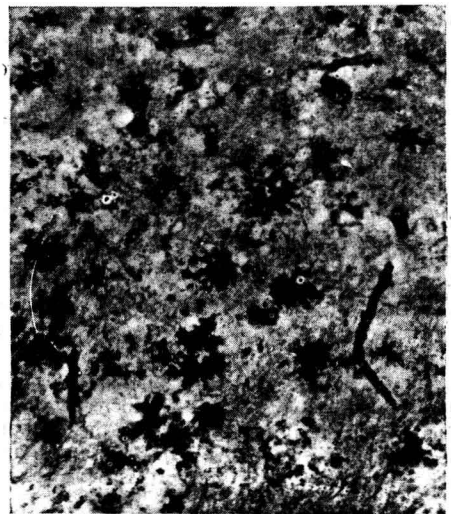


Fig. 34.9. Astrocytes, some in pairs, showing clasmatodendrosis: fragments of processes can be seen adjacent to the contracted proximal stumps. *Frozen section. Cajal's gold sublimate method. × 120.*

by its small, dense nucleus, which is about 7 μm in diameter (Fig. 34.2). The cytoplasm seldom takes these stains but is often recognizable in the form of a clear halo round the nucleus. In the immediate vicinity of a blood vessel it may prove impossible, with ordinary stains, to distinguish the oligodendrocyte from a lymphocyte, but with Golgi's rapid method the nucleus of the former stains selectively as an orange sphere some 6 to 9 μm in diameter.²⁰

Oligodendrocytes possess processes, as del Río Hortega showed,²¹ but these are difficult to demonstrate and few in number—hence the name of the cell. Although the nucleus of the oligodendrocyte appears round in haematoxylin–eosin preparations, giving an impression that the cell itself is round, the cytoplasm appears angulate when impregnated with silver; silver preparations show that most of the processes are long, and they tend to originate from four corners of the cell. In tissue cultures, the oligodendrocyte and the astrocyte are not dissimilar, and it has even been suggested that they are different forms of a single cell type,^{22, 23} a view in keeping with Hortega's schema, which groups them together as the neuroglia. Although the nuclei of oligodendrocytes and astrocytes are generally easy to identify correctly, it may prove impossible at times to distinguish between them; in fact, in pathological states of the white matter, a gradation may sometimes be recognized between the typical forms of these two cells.

Oligodendrocytes outnumber all other cells in the central nervous system.* They are frequently seen in attendance on the larger neurons, often lying close to the cell body and wedged between dendrites. The accumulation of oligodendrocytes round a neuron is known as *satellitosis*, and the arrangement of the clustered nuclei led Spielmeyer to name the cells *Traubenzellen* ('bunch-of-grapes cells').† *Satellitosis* is specially noticeable round the large and medium-sized pyramidal cells of the frontal cortex and the large neurons of the basal ganglia. It is not so apparent round Betz cells of the motor cortex and cells of the anterior grey columns of the spinal cord. When white matter is sectioned in the long axis of the axons, oligodendrocytes are visible in

long regular rows: these are the periaxonal or interfascicular oligodendrocytes, and they are particularly well seen in the corpus callosum. Oligodendrocytes are also to be found in close relation to small blood vessels (perivascular oligodendrocytes), and it has been suggested that they control the opening and closing of the vessels.²⁴

It has been supposed that the flat, delicate processes of these cells are wrapped round the neuron, including its axon and dendrites.^{25, 26} The views of electron microscopists on this matter are still divided, for some believe that the processes are numerous and extensive while others find them scanty. This difference of opinion may depend, in part, on the existence of more than one form of the oligodendrocyte.

The oligodendrocyte is a sensitive cell and there are many pathological conditions—among them hypoxia, ischaemia, acute infections and trauma—in which it undergoes acute swelling. The pathologist must recognize that some degree of acute swelling is inevitable in tissues fixed by immersion and in biopsy specimens obtained under anaesthesia. In experimental studies perfusion fixation is always desirable.

The cytoplasm of the normal oligodendrocyte is more electron-dense than that of the astrocyte (Fig. 34.6), because of the close packing of the ribosomes, which are often arranged in rosettes or associated with rough endoplasmic reticulum. The usual organelles are present. There are no cytoplasmic filaments in oligodendrocytes, in contrast to astrocytes, but microtubules have been recognized. Electron microscopy and histochemical and biochemical findings together indicate that there is considerable metabolic activity in oligodendrocytes: this may be concerned in maintenance of myelin, and possibly is related to a continuous need for synthesis of certain components of myelin. Interfascicular oligodendrocytes are often surrounded by the clearer cytoplasmic processes of fibrous astrocytes (Fig. 34.6).

There is firm evidence that oligodendrocytes are responsible for the synthesis of the myelin in the central nervous system.²⁷ The compacted layers of the myelin in the central nervous system are disposed in a spiral and have a cytoplasmic component that is derived from and continuous with the oligodendrocytic perikaryon. A single oligodendrocyte, by a connecting process that may be lengthy, may contribute to several internodes and to internodes of more than one axon.

Oligodendrocytes are morphologically heterogeneous, comprising four types, of which three

* As implied above, the word oligodendrocyte means—literally—cell with few dendrites. The increasing tendency to abbreviate the term to oligocyte ignores this derivation and is objectionable also as implying that these cells are few in number, which, as noted in the text, is the opposite of the case.

† The corresponding observation of perineuronal satellite cells in the ganglia of the dorsal roots of the spinal nerves is mentioned on page 2298. The satellite cells in these ganglia are modified neurolemmal cells.