Davide Schiffer

Brain Tumors

Pathology and its Biological Correlates

With the collaboration of
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With 274 Figures

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Preface

Neuro-oncology has in the past decade undergone tremendous developments, so much so that it is now a scientific field of vast proportions. Molecular and genetic biology, on the one hand, and the improvements in imaging techniques, therapies, and general management, on the other, have been highly instrumental in effecting this progress. Despite all recent developments, descriptive pathology, however, with its many biological correlates – foremost among them immunohistochemistry – and, therefore, histological diagnosis and prognostic assessment continue to be the reference points for judging all new achievements in neuro-oncology.

Years of experience of patients with brain tumors and collaboration with neurosurgeons, neuro-oncologists, neuro-radiologists, radiotherapists, and neurobiologists have taught us that the pathologist supplying the histological diagnosis may in fact sometimes fail to get across the biological message. Sometimes this failure arises because it is realy impossible for pathology to provide the expected nosographic definition of a tumor. Sometimes, by contrast, it is due to real difficulties in understanding the language of the pathologist. This is particularly true when the prognosis deducible from the diagnostic label is not unequivocal. In attempting to be objective, the pathologist counterbalance the lack of a clear-cut definition with a detailed histological description, which means that everything depends upon his partners' ability to interpret this information properly.

The aim of this book is thus to provide neuroligsts, neurosurgeons, neuro-oncologists and interested students of this subject with a broad knowledge base on the pathology of brain tumors.

The book describes the pathology of brain tumors and its relationship to clinical and biological features, taking particular account of the importance of the various problems from a general neuro-oncological point of view. Such a treatment may risk giving the impression that disproportionate attention is given to some topics, at the expence of others. However, the aim of the book was to describe and discuss the various subjects in the light of their clinical and biological importance during this historic period of development. Accordingly, the initial chapters on ontogenesis and immunohistochemistry must be considered of valuable help. Today, as everybody knows, some diagnoses are overused or even abused and some conditions are frequently overtreated. Such topics have also been given due attention in this book.

I am deeply indebted to many colleagues who helped in preparing the volume: Dr. Humberto Cravioto New York University for supplying pictures: Dr. Antonio Migheli and Dr. Maria Claudia Vigliani of our Institute for their help in electron microscopy and immunohistochemistry, Mrs. Maria Teresa Bertello and Dr. Angelo Attanasio for their help in preparing the manuscript; and Mrs. Annalisa Ferraiolo for histological preparations. I was helped with the English text by Dr. Marco L. Rossi, Charing Cross

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Torino, Januar 1993 Davide Schiffer

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1 Cytogenesis of the Central Nervous System

1.1 Neurogenesis and Gliogenesis

In humans, during embryonal development, at the 18th day of intrauterine (i.u.) life, a thickening of the ectoderm (the neural placode) forms in the midline of the embryo. This thickening, induced by the notochord and by the parachordal mesoderm, subsequently infolds to form the neural groove. This latter closes on the 22nd day, giving rise to the neural tube. Before closure, the edges of the groove proliferate to form the neural crests from which cells of the dorsal roots and sympathetic ganglia, Schwann cells, melanocytes, and cells of the adrenal medulla originate.

The neural tube closes anteriorly at the level of the nasal-frontal groove (anterior neuropore) on the 28th–29th day of i.u. life and posteriorly at the L1–L2 level (posterior neuropore) on the 25th–27th day. Although still a matter of debate, the currently accepted view is that mesenchymal tissue, from which spinal meninges derive, interposes itself between the epiblast and the neural tube.

In the cephalic part, the neural tube is formed from three vesicles (caudal, intermediate, and rostral), respectively called rhomboencephalic, mesencephalic, and prosencephalic. The neural tube gives origin to the spinal cord; the rhomboencephalic vesicle to the medulla oblongata, pons, and cerebellum; the mesencephalic vesicle to mesencephalon; the prosencephalic vesicle to diencephalon and telencephalon. An early groove between the neural tube and the rhomboencephalic vesicle, followed by ventral displacement of the encephalic anlage, gives rise to a cervical flexure which becomes the boundary between the spinal cord and encephalon. When the embryo is 11mm in length, the rhomboencephalic vesicle folds anteriorly, thereby forming a caudal and a cranial part. The former thickens ventrally, forming the myelencephalon from which the medulla oblongata develops. As the latter grows, it forms the metencephalon, from which the pons then develops. The dorsal part of the metencephalon undergoes a remarkable development and becomes the cerebellum.

When the embryo is 14 mm in length, the prosencephalic vesicle forms two symmetrical outpouchings anteriorly. These represent the anlage of the cerebral hemispheres. The posterior part of the prosencephalon becomes diencephalon. The median structure which links the two pouches develops into the lamina terminalis. In the ventral part of the diencephalon, two symmetrical outpouchings develop, externalize, and thus give rise to the retinal anlage which remains bound to the diencephalon through peduncles, i.e., the optic nerves. The anlage of the hypophysis is formed in the midline of the diencephalon. Thus, all the anlage of the definitive segments of the central nervous system are present in the 15-mm embryo.

The fundamental parts of the central nervous system (CNS) are visible externally by the fourth month of gestation. The hypothalamus, mammillary bodies, tuber cinereum, and the hypophyseal peduncle develop from the ventral diencephalon; the two optic thalami originate from the dorsal part of the diencephalon. The telencephalon, which together with the diencephalon forms the prosencephalon, increases in volume and thus obscures the diencephalon. Its surface, initially smooth, becomes ever richer in folds, forming the sulci and gyri, including the anlage of the Sylvian fissure (which appears at the end of the third month of gestation).

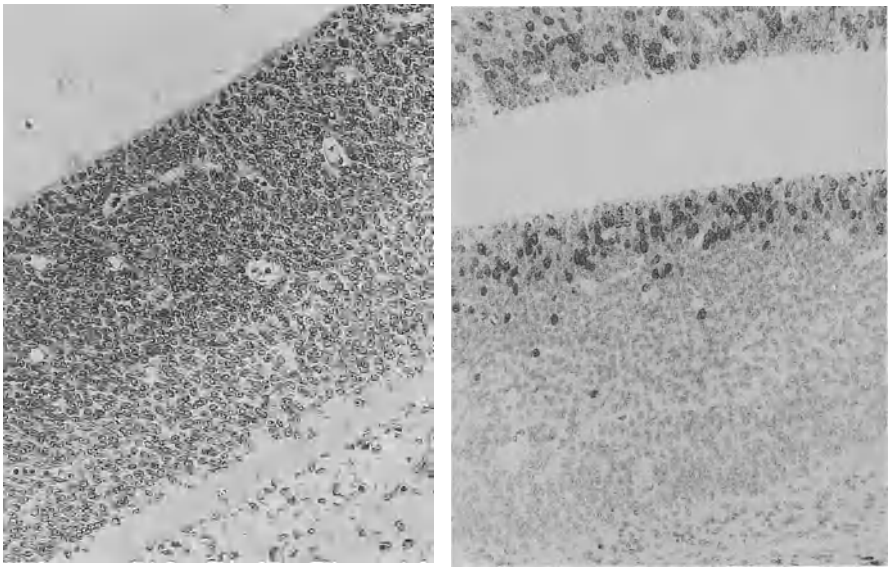


Fig.1.1a,b. Rat embryo on the 14th day of i.u. life. Germinal layer: **a** H&E, ×200; **b** BrdU labeling, PAP-DAB, ×200

The growth of the neural tube and of its derivatives is related to the existence of the ectodermal matrix, which is composed of stem cells capable of multiplication. The development consists initially of an increase in the number of matrix elements. Subsequently, as the differentiation process proceeds, the growth is mostly related to an increase in cell volume.

Most of our knowledge of the early phases of neural cytogenesis is based on studies carried out in rats [2319]. In the rat on the 12th day of i.u. life, the neuroepithelium of the telencephalon consists of pseudostratified epithelium, i.e., the ventricular zone.

In the ventricular zone, the stem cells multiply and subsequently migrate, giving rise to neurons and glial cells. In the first stages of development, the germinal cells of the neural tube are in asynchronous phases of the mitotic cycle, and all become labeled with [^{3}H]thymidine or bromodeoxyuridine (BrdU). The multiplication process of the germinal cells is characteristically accompanied by a mechanism of the to-and-fro movement of the nucleus. Nuclei in S phase are situated in the most external part of the layer while those in G_2–M phase are situated close to the lumen (Fig.1.1a,b). The duration of the cycle is 7–10 h, while that of the S phase alone is 6 h. Later, these values increase to 20 and 10 h, respectively. The mitotic elements may begin to divide before reaching the luminal surface (subsuperficial prophases), where they complete the mitotic cycle, or they may complete division without reaching the luminal surface (nonsuperficial mitoses) [2670].

Still later, some cells no longer take up label. They enter a postmitotic phase and constitute young neurons which migrate to the marginal zone. This zone appears on the 13th day (in the rat) and progressively increases in thickness. On the 16th day, it divides into a superficial part, which will become the anlage of laminae I–VI (cortical plate), and a deep part, the subcortical zone, which will become the subventricular and inter-

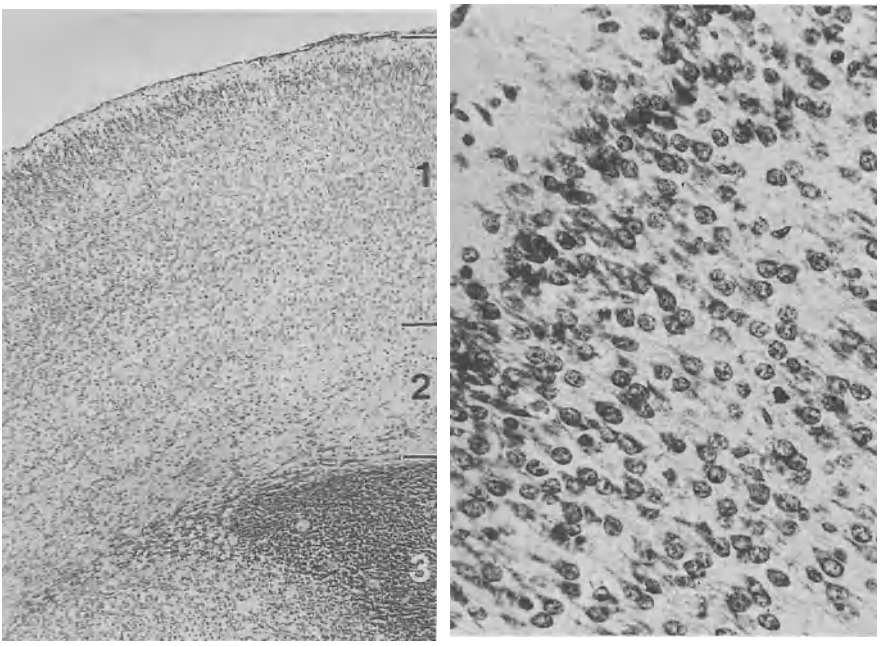


Fig.1.2a,b. Rat embryo on the 18th day of i.u. life: **a** *1*, cortical plate; *2*, intermediate zone; *3*, subventricular zone; H&E, ×200; **b** mitoses in the cortical plate, H&E, ×400

mediate zones (Fig.1.2a). In these zones, the number of mitoses decreases from inside outwards (Fig.1.2b). Between the 17th and 21st days of i.u. life, the neurons continue to migrate towards the cortical plate. In this plate there are initially no mitoses because neurons migrate after the cessation of mitotic activity. Later, mitoses appear in glial cells. The cells in contact with the pia in the marginal zone are glial in nature, a fact confirmed by their ability to express specific antigens such as glial fibrillary acidic protein (GFAP) and C1 [2319]. The subventricular and intermediate zones become the white matter. They contain astrocytic cells in mitosis. Generally, glial cells form; they also migrate after neuronogenesis is completed.

There is a relationship between the time of migration of neurons and their subsequent localization in the cortex. Neurons which arrive first in the superficial part of the marginal zone are displaced downwards by neurons arriving later, so that the pyramidal cells of the deep layers are those which matured earlier. However, this rule does not apply to the cells of Cajal–Retzius, the first cells to mature and place themselves in the marginal zone, where they subsequently form neurons with an as yet unknown function. In man, the Cajal–Retzius cells develop and mature before the neurons of the cortical plate arrive [433].

It is not known whether neurons and glial cells are produced by the same germinal cells, or whether they originate from different cells, even though they are histologically indistinguishable from one another [847, 2998, 2761]. The exact timing of divergence of the glial and neuronal cellular elements remains a matter of debate. According to

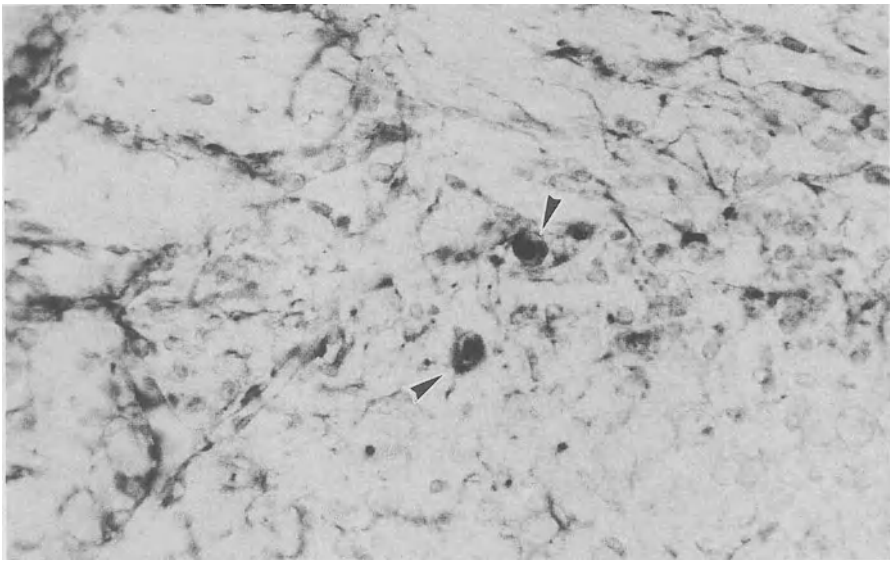


Fig.1.3. Rat embryo on the 1st day of e.u. life. GFAP-positive dividing cells. PAP-DAB, ×1000

His (1889) [1145], the germinal zone is composed of two cell lines: the "Keimzellen" or "germinal cells," which will give rise to neurons, and the "spongioblasts," which will give rise to the glia. Schaper (1897) [2467] was of the opinion that a single, mitotically active cell population produces "indifferent" cells. Upon migrating into the marginal zone, these give rise to neurons and glial cells. More recently, autoradiographic studies have demonstrated that in the germinal zone there is a homogeneous population of dividing cells, and that glial cells of a given structure are generated only after the production of neurons has ceased [848, 849]. The general concept is, therefore, that the matrix produces neurons first and later glia.

These concepts have been shaken by the observation that in rodents there are two cell populations with different generation times [2953]. Moreover, in monkeys the radial glia, or ependymoglia, and Bergmann's glia already exist during the latest stages of neuronogenesis [2261, 2263, 2531]. The radial glia is situated in the ependymal layer and gives off long processes which reach the pia mater and the capillaries. This glia functions as a guide for the migration of neurons. The precursors of neurons and glial cells, therefore, coexist in the first stages of development. In *Macaca mulatta* it has been demonstrated that, by the 80th day of i.u. life, which corresponds to the peak of neuronogenesis, the germinal matrix contains a large number of proliferating GFAP-positive cells mixed with proliferating negative cells [1632]. Two mitotically active cell populations are, therefore, present at the same time. This has been confirmed by electron microscopy.

The localization of GFAP in cells that are actively dividing demonstrates that the acquisition of glial differentiation features by matrix elements is not incompatible with mitotic activity (Fig.1.3). The coexistence of differently committed precursor cells in

the fetal rat brain is supported by the observation that single embryonal cells, taken from the septal forebrain region of rat on the 14th day of gestation, give in microcultures clones of neurons, glial cells, or both cytotypes. The heterogeneity of the clones probably depends on intrinsic properties of the precursor cells [2822].

Glial cells which have migrated into the intermediate zone, the commissures, and the fiber tracts continue to proliferate, whereas neurons do not. This finding is of great importance from the point of view of carcinogenesis.

Another still debated problem is the histogenetic relationship between astrocytes and oligodendrocytes, taking into account that, in broad terms, the latter do not appear in the neocortex before birth [579, 2757]. It has yet to be established whether the two glial types appear simultaneously or consecutively, and whether they derive from the same or from different precursors. In the corpus callosum of the mouse, oligodendrocytes have been observed to appear before astrocytes. They could have either originated from different precursors or subsequently transformed into astrocytes [2671]. On the other hand, others have suggested that astrocytes arise before the oligodendrocytes [2920]. Less likely is the possibility that the two types of glia originate from different precursors [1274].

The differentiated oligodendrocytes are of three varieties: with a clear, an intermediate, or a dark nucleus [1935]. It is possible that these represent three stages of maturation, the first type deriving from oligodendroblasts which, in turn, arise from glioblasts. However, it is not known whether these glioblasts are identical to those which give rise to astrocytes [2757, 2658, 1246]. The differentiation of the oligodendrocytes is a postnatal process, but it has not been established whether it occurs in an identical fashion at all sites. Differentiation is connected with myelination, and, for example, it occurs earlier in the spinal cord than in the optic nerve. The period of rapid proliferation of the interfascicular oligodendrocytes in the first stages of development has been called myelination-gliosis [1274] and accompanies or precedes myelin formation. The optic nerve, which originates from the optic peduncle, an extension of the neural tube, represents an ideal site for the study of this problem. In fact, only astrocytes and oligodendrocytes (and no other type of glia or neurons) arise from the optic peduncle.

In short-term cultures, GFAP-positive astrocytes and galactocerebroside-positive oligodendrocytes are identifiable. In turn, the astrocytes are subdivided into two populations: types 1 and 2. These are different morphologically, antigenically, and in response to growth factors [141]. Astrocytes of type 2 are labeled by the monoclonal antibody A2B5. In the rat optic nerve, astrocytes of type 1 appear on the 16th day of gestation, oligodendrocytes on the first day after birth, and type 2 astrocytes between the 8th and 10th day after birth [2251]. It has been observed in vitro [2251] that glial cells in the optic nerve develop along two distinct lines, one giving rise to type 1 and the other (O-2A) to type 2 astrocytes and to oligodendrocytes. The two lines diverge on the 17th day of gestation. The existence of two subpopulations of astrocytes, A2B5-positive and A2B5-negative, has been confirmed in optic nerve sections [1895]. Type 1 astrocytes give off processes towards blood vessels, and type 2 astrocytes to the nodes of Ranvier [141].

Oligodendrocytes originate from the A2B5-positive precursor called O-2A, as do type 2 astrocytes [141]. This precursor also expresses NG2 (the proteoglycan chondroitin sulfate) (Fig.1.4a), but when reactivity for galactocerebroside appears, the former

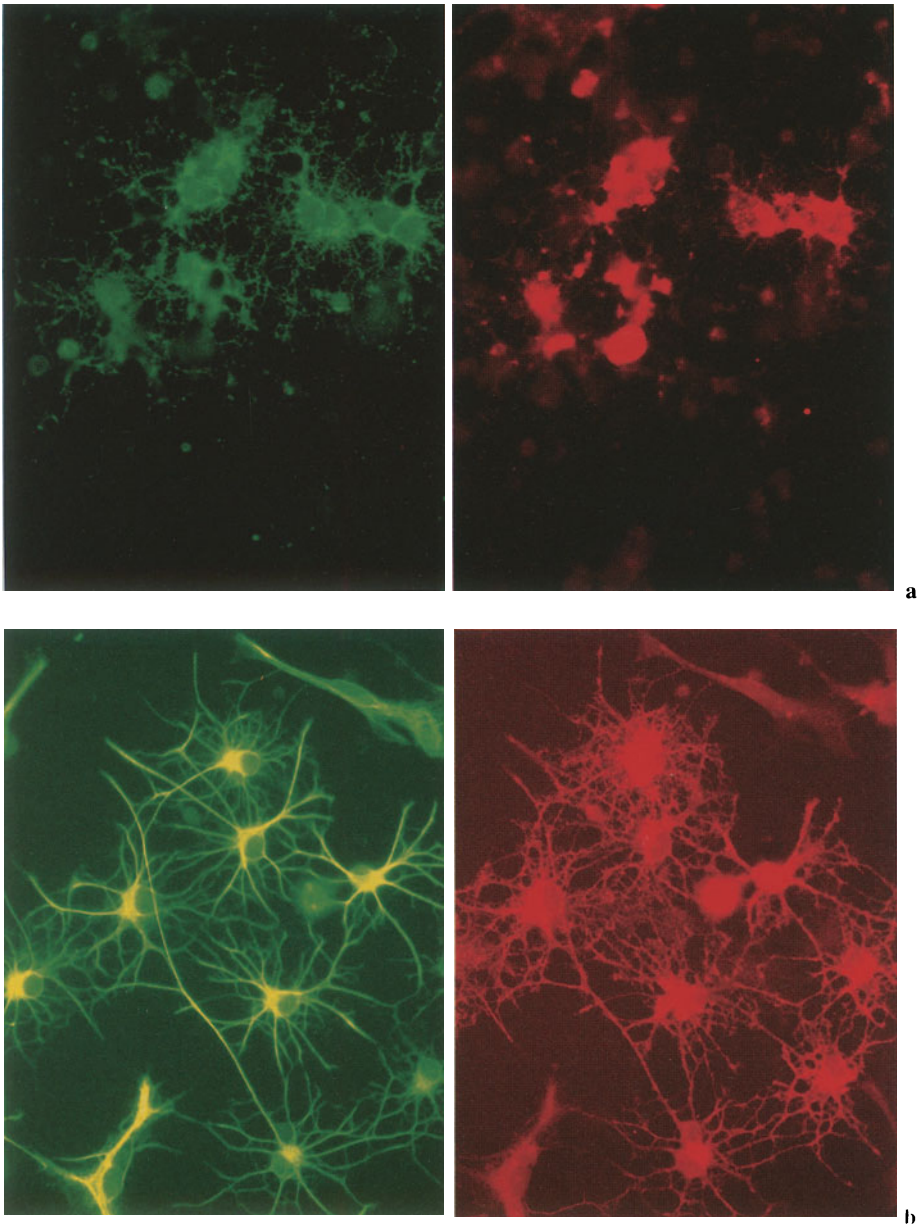


Fig.1.4. a Culture of neonatal rat cerebellum; the same cells are positive for A2B5 (green fluorescence) and chondroitin sulfate proteoglycan (red fluorescence), ×1000; **b** stellate astrocytes cultured from neonatal rat cerebellum are positive for chondroitin sulfate proteoglycan (red fluorescence) and GFAP positive (green fluorescence), ×1000

disappears [2711]. The same phenomenon has been observed in cultures of neonatal rat cerebellum; in the same model differentiated stellate astrocytes are positive simultaneously for GFAP and chondroitin sulfate proteoglycan (Fig.1.4b) [868]. NG2 has been shown to be a surface marker for a class of protoplasmic astrocytes in adults [1627].

Cultured precursor cells from the rat optic nerve differentiate into type 2 astrocytes only in the presence of fetal calf serum and, on the contrary, precociously into oligodendrocytes in its absence [2251]. PDGF (platelet-derived growth factor) regulates the proliferation of the precursor cell before differentiation takes place [2042, 2252] (see also Sect. 2.1). In fetal serum, factors are present which induce differentiation towards type 2 astrocytes. One of these is CNTF (ciliary neurotrophic factor) [141]. Type 1 astrocytes produce the A chain of PDGF [2316] and probably CNTF [141].

Under certain culture conditions, the cells may acquire intermediate phenotypes. This is a further demonstration that astrocytes and oligodendrocytes have a common progenitor and that environmental influences and developmental plasticity characterize their differentiation. Not only do astrocytes and oligodendrocytes have a common origin, but transitional forms may exist. In culture, if CNTF is lacking, precursors which had already acquired GFAP expression lose it and become oligodendrocytes [2249]. In the human fetus, at the 15th–16th week of gestation, cells with ultrastructural and immunocytochemical characteristics of oligodendrocytes have been described. These cells are, in fact, positive for myelin basic protein but also for GFAP [434]. This positivity is transient and disappears by the 17th–18th week of gestation.

The existence of "transitional" or "bipotential" forms of glial cells has been confirmed in cultures of human oligodendrocytes. After 2 weeks in culture, the cells express both GFAP and galactocerebroside. If, however, cyclic adenosine monophosphate (cAMP) and substances able to increase its level are added, the majority of cells become positive only for galactocerebroside [1417]. In the subpial astrocytes in the mouse spinal cord, an increased mitotic activity before myelination has, furthermore, been observed, and immediately thereafter oligodendrocytes appear. Finally, "transitional" cells with ultrastructural characteristics of oligodendrocytes may express GFAP [434].

1.2 Gliogenesis in Adult Animals

Our knowledge regarding gliogenesis in the adult is incomplete. It is known that new glial cells may substitute those which degenerate; however, there is no evidence that death of glial cells occurs in the adult. On the other hand, in pathological conditions there may be hypertrophy and hyperplasia of astrocytes. It is not easy to understand how an increase in the number of astrocytes could take place in the adult. It was thought that this occurred by amitosis [2170], but this has not been confirmed. Glial cells are mainly, diploid. However, polyploidy due to duplication of DNA without division of cytoplasm has been observed [1574]. It is not known whether the new glial cells originate from "stem cells" which remain quiescent under normal conditions, or if DNA synthesis may also occur in completely differentiated glial cells. In adults of different species, a glial turnover has been demonstrated.

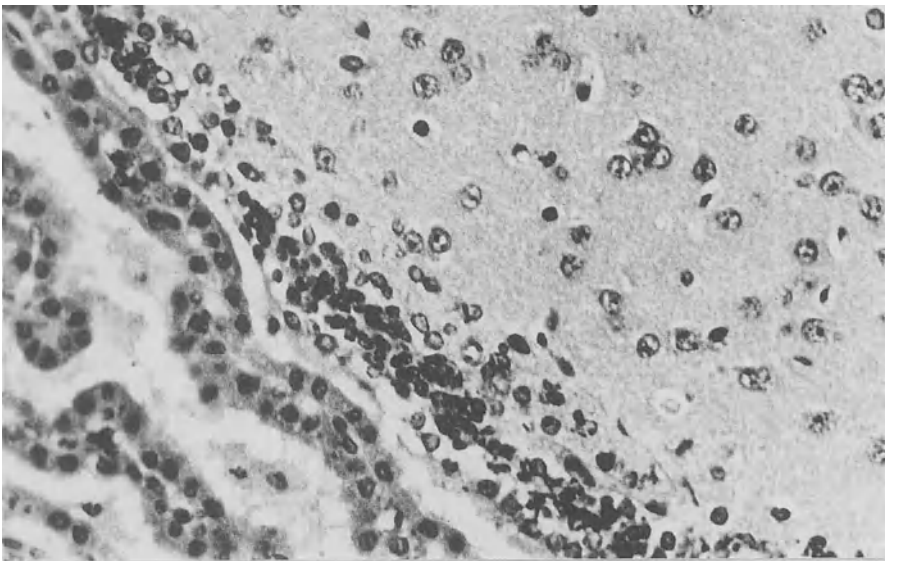


Fig.1.5. Rat, subependymal plate, H&E, ×400

In contrast to what occurs for neurons which rapidly become postmitotic, glial cells may continue to divide over time. A series of experiments has demonstrated that glial cells can proliferate postnatally [1220]. In the spinal cord of the rat, between 3 and 7 months there is an increase in the number of oligodendrocytes of about 15% per month, while the number of astrocytes remains at a constant level. The labeling index of glial cells in the white matter with [^{3}H]thymidine is 12% after 4 weeks. After a month of continuous labeling starting from the age of 4 weeks, the oligodendrocytes in the spinal cord and in the cerebellum have an index of 20%, while in the same regions astrocytes have an index of only 10%.

In the final stages of embryonal development, a second layer of proliferating cells, localized between the ventricular germinal layer and the intermediate or mantle zone, is formed. This has been called the "subependymal zone" [1407], or "subependymal cell plate" [943, 2669]. It progressively decreases with time and persists vestigially in the lateral ventricles of adult mammals (mouse, rat, dog, primates, and so forth). It is, however, limited to those parts of the lateral ventricles underneath the neo- and paleocortex and not the archicortex. In the subependymal plate, mitoses are found (Fig.1.5) but without movement of the nuclei in the interkinetic phase, and the generation time is 18 h [1636].

The subependymal plate in postnatal life may produce, for a short time, small neurons and glial cells in the adult. Its role may well be that of replacing glial cells in adult life.

Stem cells may be found in adult brains apart from the subependymal plate, in the myelination glia, in the external granular layer of the cerebellum, in the fascia dentata, and in the subpial molecular layer of the cerebellum [1637]. The following scheme of

differentiation of the subependymal layer has been proposed [1221]: The "stem cells" which migrate in the brain have a small, dark nucleus and give rise to glial precursors with small and clear nuclei. Twenty percent of these cells may transform into young astrocytes with a large and clear nucleus. The cells with a small and dark nucleus, however, may also be oligodendrocytes.

There is no general agreement that the subependymal layer is the continuous source of glial cells [2043, 1492, 1493]. In the mouse, labeled glial cells have been demonstrated within 1 h from the administration of [^{3}H]thymidine in all cerebral areas. Pairs of labeled cells have also been found. These findings demonstrate that, as stated above, proliferation may also occur in situ.

Though the glial turnover in the cerebral cortex, as compared to that of the white matter, is minimal [1492], the population is not static: 0.07% of glial cells are labeled 1 month after administration of [^{3}H]thymidine in the rat visual cortex. This implies that cell turnover is present, although slow and with a very long cycle [1352]. From double labeling experiments with [^{3}H]- and [^{14}C]thymidine, it has been found that the cycle time is 20 h. In the subependymal layer, around 30% of cells are in cycle, while in other parts of the brain no more than 1% of these cells are.

It would be of great importance to know not only if glial cells undergo mitosis, but also which type. Autoradiography cannot provide this answer, so great caution is necessary in drawing conclusions [2760]. Furthermore, the difficulty in demonstrating mitoses, which are very sensitive to anoxia [398] and require particular fixation techniques for visualization, has to be taken into account. The fundamental fact remains that in the adult, outside the subependymal layer mitoses are very rare [2758].

1.3 Development of the Cerebellar Cortex

The development of the cerebellar cortex is a complex event because of the presence of two germinal zones. One is situated in the roof of the fourth ventricle and gives rise to Purkinje cells, to type II Golgi cells, and glial cells. These migrate towards the pia mater to form the mantle layer. The other germinal layer, the external granular layer, is subsequently formed below the pia mater (Fig.1.6). From it originate granule cells, stellate and basket cells, and glial cells of the cerebellar cortex. This layer thickens in time, changing from one to six layers of cells because of cellular proliferation, and persists after birth, even if smaller, in many animals. In man, it only disappears 600 days after birth. At the beginning, 100% of cells of this layer become labeled with [^{3}H]thymidine, while subsequently an area devoid of mitoses is formed adjacent to the molecular layer.

One of the unsolved problems is represented by the migration of the granule cells. Since it occurs late, it meets difficulties because other cellular elements are already fixed in place. The migration is guided by Bergmann's glia [2262]. It entails a complex adaptation of cellular shape. The more deeply situated cells in the layer are those which are generated first.

Glial cells seem to originate from the periventricular germinal matrix. In the mouse, glioblasts from this matrix have already invaded the cerebellum when the migration

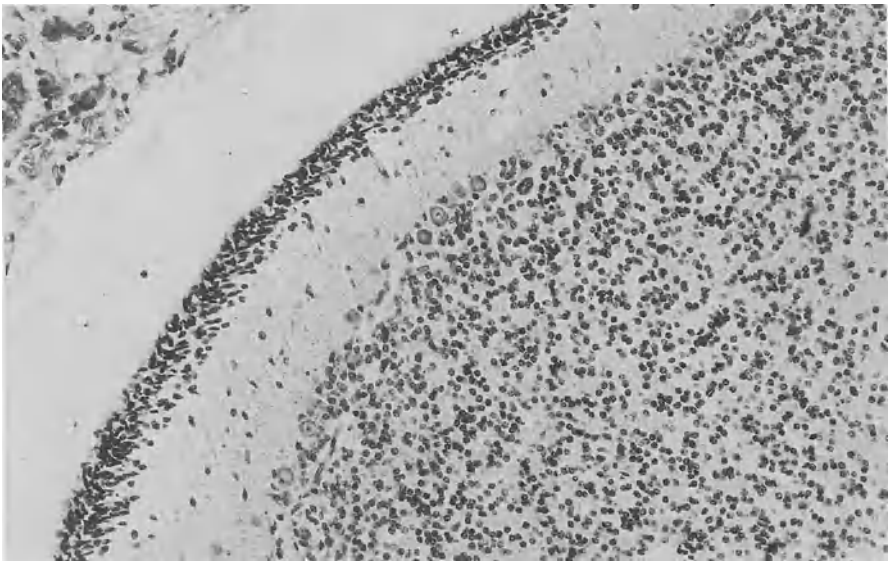


Fig.1.6. Neonatal rat cerebellum; external granular layer, H&E, ×200

from the external granular layer begins [850]. It is possible that glioblasts derive from the external granular layer, from which astrocytes and oligodendrocytes of the molecular layer originate, but that this occurs only after the production of neurons has ceased and, therefore, very late [613, 871]. The same rule applies to the basket cells and to the small star-shaped cells.

1.4 Radial Glia and Ependyma

Long, radially oriented fibers which span the whole thickness of the developing neural tube are present in the embryonal encephalon in very early stages of development. They have been demonstrated with the Golgi technique in many vertebrate species, including man, and have been variously called epithelial cells of Golgi [361], spongioblasts [2734, 2186, 2917], matrix cells [1081], ependymal cells [362, 1880, 2651], ependymoglia [830, 2759], ependymal spongioblasts [2826], and radial glia [2262, 2263, 2531, 2893, 689, 1731]. According to recent observations, the cells of the radial glia demonstrate mitotic activity at least at E13–E15 in the mouse [1907].

The presence of cells of the radial glia during the early phases of neurogenesis in man has been confirmed in studies combining silver and ultrastructural techniques with the demonstration of GFAP [63, 435]. In the human fetus, radial glia fibers have been identified from the 12th week of gestation by means of Golgi techniques, from the 10th week with the demonstration of GFAP, and from the 7th week with ultrastructural stu-

dies. The nuclei are initially situated in the ventricular zone, then in the subventricular zone, and less in the intermediate zone. The processes, sometimes with a subpial arborization, run from the ventricular zone to the pial surface, while some terminate on the blood vessel walls [435].

This and other observations [1495, 2756] seem to prove that in man the maturation of astrocytes with features of radial glia takes place in the first 3 months of fetal life. The production of glia, therefore, either preceeds or occurs at the same time as that of neurons. It continues after the production of neurons has ceased [2531] and persists into late fetal development, by division both of cells of the subventricular layer and of cells which have already migrated to other regions.

A discrepancy exists between the positivity for GFAP of radial glia in primates and negativity in mice, rats and chickens [201, 2546, 2809]. When identifying GFAP in the radial glia, the role played by species differences, mode of fixation, and procedures aiming at preserving the immunoreactivity of GFAP in the embryonal tissue has to be taken into account [432]. The radial glia in the rat is, instead, strongly positive for vimentin [203] (Fig.1.7a). The positivity appears at the same time as that for neurofilaments (NF) in other structures and, therefore, may be indicative of differentiation. In the rat, the precursors of glia and neurons may not express vimentin, as occurs in the chicken [2809]. A few short GFAP-positive fiber tracts with radial orientation have been observed in the rat embryonal brain at the 18th day of gestation [2209]. Cells and fibers marked by GFAP increase in number until the 1st postnatal week, in parallel with the disappearance of the radial glia.

Notwithstanding the fact that GFAP may be identified at an early stage, its appearance in great quantity occurs at the end of neuronal migration and the formation of long fiber tracts [2893]. At the same time that the GFAP increases in the fetal rat brain, a drastic reduction of vimentin and glial radial processes [2209] occurs. The time of maximum expression of GFAP and minimal expression of vimentin is at the 2nd–3rd postnatal week, i.e., while the rapid myelination phase is in progress [550]. In adult rat glia, vimentin is very scanty unless the glia becomes reactive, hypertrophic, or hyperplastic [552, 2514]. The radial glia is GFAP-positive in the mouse spinal cord and is vimentin-positive in the whole brain [689]. The telencephalic radial glia of mice has been shown on cryostat sections to express GFAP by the 17th day of gestation [1044]. GFAP-positive radial fibers appear with a rostrocaudal and dorsoventral gradient during embryonal development, and disappear with the same gradient after birth, without correlations with the development of the cortex.

The role in guiding migrating neurons has been attributed to the radial glia both for the monkey [2261, 2263] and man [2639]. The rationale for this is its presence at the time of maximum neuronal migration and the close structural relationships between radial fibers and migrating neurons. The distribution of radial fibers is different in each area. Their orientation is modified during development according to morphogenesis in various areas and structures. A close correlation seems to exist between the position of a neuroblast in the ventricular zone and its final position. The concept of "proliferative unit," meaning that all neurons are generated in the same position are guided by a single radial process, has been proposed [2264].

The radial glia seems, therefore, to have an important role in the embryonal development of mammals. It is also present in lower vertebrates, and while in these it persists after the end of development, it is found in adult life [1188, 2734]. In mammals, it transforms into other cellular types or degenerates [361, 2263, 435, 2531, 2595, 2209]. The transformation into protoplasmic and fibrous astrocytes has been observed in monkeys by means of silver impregnation techniques, showing intermediate forms between radial glia and astrocytes [2531]. The radial glia transforms first in the areas where cellular migration terminates first, i.e., at the same time its guiding role is completed [1631]. In the human fetal brain, between the 21st and the 30th weeks, the cytological basis of the transformation of the radial glia into astrocytes has been identified: increase in lysosomal activity and in the number of autophagic vesicles, which are necessary events for the reabsorption of the long processes [1332]. In the mouse, the predominant orientation of the mitotic spindle seems to indicate that the radial glia disappears through repeated divisions, with progressive de-

tachment of the daughter cells from the cell attached to the pial surface [1044]. It has been hypothesized that oligodendroglia may also derive from radial glia, both directly and through intermediate astrocytic forms [436].

In the postnatal period of the mouse, the radially oriented fibers arising from the ventrolateral angle of the lateral ventricle persist [1044]. This is the zone in which cells retaining proliferative capacity in adult life are found [2671].

In the diencephalon, the radial glia undergoes minor modifications as compared with the other areas of the prosencephalon. In fact, the only zone of the mammalian adult encephalon in which radially oriented fibers may be observed is the hypothalamus, which belongs to the phylogenetically older part of the encephalon [2595, 1631]. This finding may be interpreted as representing a phylogenetic residuum of the diffuse system of radial glia which is present in lower vertebrates [1188].

The cells of the ependymal covering of the third ventricle, which are provided with a long process reaching the sub-pial layer, are called "tanycytes" (Fig.1.7b). These cells also form the dorsoventrally oriented raphe fibers in the adult brain stem and spinal cord. The term "tanycyte" was initially used to indicate cells of the ependymal layer of the entire adult ventricular system of selachians, which is provided with a radially oriented process [1188]. Tanycytes are different from the cuboidal or columnar cells of the ependymal coverings in microscopic, ultrastructural, and histochemical properties [1897, 1898]. In the rat,they originate mostly in the postnatal period [43] or towards the end of fetal life [2423]. Their appearance is closely tied to the embryonal and fetal development of the ependymal covering.

The neuroepithelial cells which become ependymal cells begin to proliferate in the rat shortly after the formation of the neural plaque, i.e., before the tenth embryonal day [1491]. This begins on the 12th day in the mouse [2265]. In the rat, the production of ependyma proceeds with a caudorostral gradient, beginning on the 14th day in the fourth ventricle, on the 15th day in the third ventricle and on the 17th day in the lateral ventricles. It continues until the end of gestation, peaking at the 18th–19th day in the third ventricle and the 20th–21st day in the lateral ventricles [563]. The tanycytes, in contrast, are generated mostly in the postnatal period [43], even though they begin to appear during the last days of fetal life [2423]. In the rat, the tanycytes of the third ventricle do not mature completely until the 3rd week after birth [2461, 2423, 311].

In the monkey, mouse, and rat the tanycytes of the third ventricle acquire GFAP in the embryonal period and keep it in adult life (Fig.1.7b) [1631, 1044]. Human tanycytes, on the other hand, are only transiently positive for GFAP, between the 15th gestational week and birth [2343]. On the basis of these immunohistochemical data, tanycytes have been considered as a modified form of embryonal radial glia [1332], as a differentiated form of ependyma which develops in parallel with the normal ependyma [2343], or as astrocytic cells [595].

Most authors have not detected proliferative activity in the ependyma of the adult rat [313, 2265]. In the ependyma of the prosencephalon, there is a significant decline in proliferative activity in the first 2 postnatal weeks. The remaining cellular turnover is very low in adult life [418].

Even though tanycytes are considered to be specialized ependymal cells, their precise function is unknown. It has been proposed that they may form a connection between the cerebrospinal fluid (CSF) and the hypophyseal portal system [1685], transporting "hormones" secreted into the CSF to the anterior hypophysis [1458], in parallel with axonal transport, or conversely, to the CSF from the hypothalamic neurons [2840].

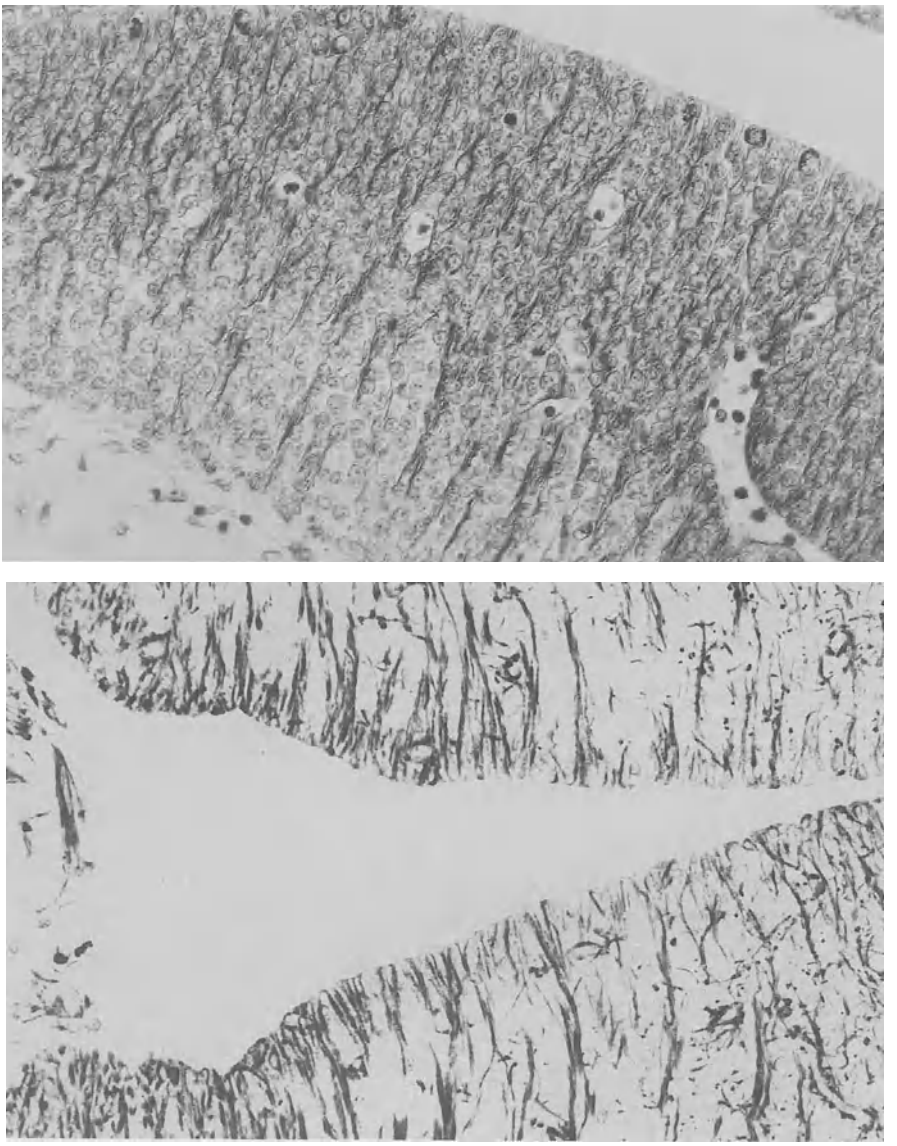


Fig.1.7. a Rat embryo on the 14th day of i.u. life: vimentin- positive radial glia, PAP-DAB, ×200
b Adult rat: GFAP-positive tanycytes of the third ventricle, PAP-DAB ×200

Other functions have been attributed to tanycytes: regulation of ionic concentration in the extracellular periventricular spaces [1616], guides for migrating neuroblasts of the mediobasal hypothalamus as radial glia [2898], and a limiting barrier to the movement of neurohormones inside the compartments of the mediobasal hypothalamus [2898, 2302].

2 Factors of the Transformation Process

2.1 Molecular Aspects

The technological advances in molecular genetics of the past 10–15 years have permitted a new approach to the study of carcinogenesis and are also providing a remarkable and promising volume of data on CNS tumors [2534, 1790, 1845, 546, 2587, 477]. The reader is referred to specialized publications on the theoretical basis of biology and molecular genetics. In this chapter, an overview of the most recent discoveries in this field relating to CNS tumors is presented.

A tumor which may be considered paradigmatic is the retinoblastoma [894], which may be sporadic but in 40% of cases is familial and transmitted as an autosomal dominant trait. Epidemiological considerations have suggested the hypothesis that retinoblastoma may represent the result of two separate mutations [1463]. The first, i.e., the "predisposing" mutation, may be inherited with germ cells (heritable cases) or acquired somatically in single cells of the retina (in sporadic cases). In either case, this first mutation is insufficient to cause the tumor, which is produced only after a second genetic alteration affecting the remaining normal allele in the same retinoblastoma locus. The probability of occurrence of the second mutation is very high. In fact, in 90% of those individuals who have inherited a defective gene, retinoblastoma will develop [834]. It is, therefore, understandable how the "predisposing" mutation, even if transmitted as a dominant trait, is in reality recessive at the cellular level. Cytogenetic investigations and studies carried out with RFLP (restriction fragment length polymorphism) analysis have led to the localization of the retinoblastoma locus (RB1) on the q14 band of chromosome 13 [399, 400, 666]. The RB gene behaves, therefore, as a suppressor or repressor of tumor development, or as an "antioncogene" [1464], and its loss or inactivation leads to the development of the tumor. Different chromosomal mechanisms may be responsible for homozygosity of the mutant RB1 gene in tumors, such as nondisjunction, nondisjunction with duplication, mitotic recombination, small deletions, and point mutations [894].

Recently, the target of mutations leading to retinoblastoma has been isolated [834, 1597]. The gene extends for 150 kilobases (kb) and produces a transcript of 4.7 kb, coding a 105-kDa nuclear phosphoprotein with DNA binding capability [835, 1598]. The availability of the gene has led to a more precise description of the mutational events affecting retinoblastoma genes. In both forms of the disease (hereditary and sporadic), a variety of different mutations have been described, ranging from subtle base changes to large deletions and mimicking spontaneous mutagenesis mechanisms [894]. The biochemical mechanism through which the product of the RB gene exerts its antioncogenic effect is unknown, but its ability to bind DNA leads one to believe that it participates in the control of the transcription or of the replication of DNA. In fact, the levels of phosphorylation of the RB1 gene product are variable during the cell cycle, increasing in the S and G_2 phases

[490, 421]. Moreover, it has been shown that some viral transforming oncoproteins, such as the "large-T antigen" of SV40, the E1A of adenovirus and the E7 protein of human papillomavirus, form stable complexes with the RB1 protein [3033, 1703, 691]. This finding suggests that the tumor suppressor activity of the RB1 gene product may be abolished by different mechanisms comprising the binding with retroviral oncoproteins. The primary role in retinoblastoma tumorigenesis of inactivation of the RB1 tumor suppressor activity is demonstrated also by the observation that reintroduction of the missing RB1 gene into retinoblastoma tumor cells leads to a normal phenotype [1218].

A common mechanism, involving a "tumor suppressor gene" [1782], has been proposed for different tumors of the nervous tissue which appear in the central form of neurofibromatosis or NF2 [1790, 2587]. In this hereditary autosomic dominant condition, multiple tumors originating from different types of cells of the CNS may arise, such as bilateral acoustic neurinomas, multiple spinal, peripheral or cranial nerve neurinomas, astrocytomas, and meningiomas. The hypothesis focuses on the loss of a putative suppressor gene located in the long arm of chromosome 22, to which the NF2 gene has been mapped [2377]. In fact, monosomy, deletions, or loss of heterozygosity for chromosome 22 are frequently found in human sporadic meningiomas [3114, 387, 2589, 686] and neurinomas [2588, 503, 797]. Using RFLP analysis, the tentative tumor suppressor gene of meningiomas has been localized to the region 22q12.3-qter. This region is located in the long arm of chromosome 22, distally to the myoglobin locus [478]. The analysis of a large family indicated that the locus of NF2 lies close to the anonymous chromosome 22 locus D22S1 [2377, 3017]. Moreover, recent studies of the same NF2 family suggested that the NF2 locus maps in a 13 centimorgan (cM) region, between loci D22S1 and D22S28 [2378]. Considering that the D22S28 locus is probably proximal to the myoglobin locus, it appears that the NF2 and meningioma loci are distinct [478]. Thus, the increased risk of developing meningiomas in NF2 patients probably is not due to the involvement of an unique gene in these two diseases, in agreement with everyday experience showing that the majority of meningiomas, as well as neurinomas and astrocytomas, arise sporadically without any connection with NF2 or other inherited conditions.

Linkage studies in pedigrees affected by the peripheral form of neurofibromatosis (NF1) have led to the localization of the genetic defect in this disease to band 17q11.2 [127, 960]. A candidate NF1 gene, located in this region, has been recently cloned [403, 2944, 2971]. This gene extends for more than 100 kb and shows mutant alleles in individuals affected with NF1 [403, 2971]. The NF1 gene encodes a large transcript (11-13 kb) and a protein of at least 2485 amino acids, ubiquitously expressed. This protein shows significant homology with the *ras* GTPase-activating protein [314, 3084, 3085], suggesting a role in the regulation of $p21^{ras}$ activity.

The germline mutation in the NF1 gene leads to the development of skin lesions (café-au-lait spots) and of benign tumors such as neurofibromas, but probably is not sufficient for the development of malignant neurofibrosarcomas. It is possible that inactivation of the second allele is necessary for the genesis of neurofibrosarcomas [1782]. In fact, losses of genetic material on the short arm of chromosome 17, in addition to changes at the NF1 locus, have been demonstrated in neurofibrosarcomas but not in benign neurofibromas [2661, 1872]. Probably, these deletions result in inactivation of one allele of the "tumor suppressor" gene p53 (located on chromosome 17p) which, moreover, may show mutations in neurofibrosarcomas [1873].

Several cytogenetic analyses have demonstrated important chromosome abnormalities in human gliomas. Chromosomes 7, 9, 10, 17, and 22 are frequently involved by these alterations [3089, 2305, 2306, 211, 1309, 857]. The majority of malignant gliomas have near diploid stem lines, but usually numerical and structural chromosomal abnormalities are present. Generally, with increases in the degree of malignancy, chromosomal anomalies become more marked and involve greater numbers of different chromosomes [2602, 208]. In the more malignant gliomas, therefore, it is difficult to evaluate which chromosomal anomalies are specific and significant in the genesis of the neoplasia and which instead are nonspecific epiphenomena which accompany the process of anaplasia. Rearrangements involving the short arm of chromosome 9 are the most common, particularly the loss of most of 9p [211]. In the short arm of chromosome 9, precisely at 9p21-22, α- and β-interferon genes are located. Thus, the 9p deletion may have important consequences for the control mechanisms of tumor progression. Loss of chromosome 22 has been shown frequently in malignant gliomas and is particularly common in polyploid tumors [3089, 2305, 1309]. Other very common changes are gains of one or more copies of chromosome 7 occurring in ≈80% of malignant gliomas [208].

Partial or complete allelic loss for sequences of chromosome 10 has recently been demonstrated using karyotypic and RFLP analysis [857A, 857B, 700A, 211, 1278, 845, 2988]. A 188-cM region of loss of heterozygosity common to three glioblastomas has been found [845]. This region mapped between 10q23.3 and the middle of 10p. Loss of heterozygosity on chromosome 10 is reported only in anaplastic astrocytomas and in glioblastomas, while nonrandom allelic losses involving chromosome 17 have also been shown in well-differentiated astrocytomas [857, 857A, 857B, 700A, 1278, 1279]. A region of the short arm of chromosome 17, telomeric to 17p11.2, is probably involved in these rearrangements [1279]. These studies on chromosome 10 and 17 abnormalities suggest a possible developmental sequence of genetic changes during tumoral progression of gliomas. The gene defects in the short arm of chromosome 17 (as well as abnormalities involving chromosome 9p and 22) may be important in the early phases of glioma development. Allelic loss involving chromosome 10 may occur later in tumoral progression and could be linked to a malignant phenotype [207, 477].

In some cases, chromosomal abnormalities similar to those found in gliomas of adults (partial trisomy of 7, deletions in 10, and loss of chromosome 22) were found in ependymomas [2306, 1005, 2749]. Recently, abnormalities of chromosome 17 have been reported in three out of four ependymomas [2749]. These changes, represented by translocations onto 17p or chromosome 17 loss, were different from abnormalities usually detected in astrocytomas and medulloblastomas (isochromosome 17q).

Chromosomal abnormalities found in medulloblastomas are different from those described in malignant gliomas. Structural changes, such as isochromosome 17q (resulting in loss of one copy of 17p), translocations (8;11), unbalanced translocations of 20q13, and deletions of 6q, 11, and 16q are more common than gain or losses of whole chromosomes [212, 1005, 365].

Loss of heterozygosity on chromosome 17p is one of the most common genetic abnormalities in human brain tumors and is particulary interesting because the p53 gene resides on this chromosome. This gene encodes a nuclear phosphoprotein which might act as a tumor suppressor [1782]. Several mutations of the p53 gene have been described which abolish the ability to suppress transformation: moreover, the mutation of a sin-

gle allele may have a dominant negative effect, inhibiting the function of normal p53 and plasmatic transformation [1782]

A limited amount of data on p53 mutations in brain tumors is available at this moment [2029A, 2066A, 857A]. Mutations have been found frequently in glioblastomas and anaplastic astrocytomas, but also in some nonastrocytic brain tumors (oligodendrogliomas, ependymomas, and medulloblastomas); never in well differentiated astrocytomas. In particular, p53 mutations have been found in about 60% of patients with loss of heterozygosity on chromosome 17p. Moreover, the association of loss of heterozigosity on chromosome 10 with p53 mutations was found only in patients with glioblastoma [857A], indicating that during astrocytomas progression different genetic changes may accumulate.

Overexpression of p53 has been immunohistochemically demonstrated both in benign and malignant gliomas as well as in about 40% of malignant tumors of other sites [2224A].

Double minute chromosomes occur in approximately 30% of malignant gliomas [211]. Since double minutes are thought to be an expression of gene amplification, many efforts have been addressed to the detection of amplified oncogenes in gliomas. The gene most frequently amplified in malignant gliomas is *erbB1*, coding the epidermal growth factor receptor (EGFR) [1644, 3071]. The EGFR belongs to a group of products of oncogenes having phosphotyrosine kinase activity. There is evidence that this activity is crucial in the mechanisms of neoplastic transformation involving numerous oncogenes [1226, 1227, 216]. In response to the binding with EGF, the receptor is capable of autophosphorylation on tyrosine residues and of analogous phosphorylation of numerous other proteins, activating a cascade of biochemical events which transmit a mitogenic signal and induce cell proliferation [1226, 524, 374]. Approximately one half of malignant gliomas show EGFR amplification, and over 80% of tumors with amplification contain double minutes [209]. Moreover, a strong correlation between amplification of the gene and increased expression of the EGFR has been shown, whereby *erbB1* is amplified in all tumors showing overexpression of the receptor [3071].

In some malignant gliomas EGFR is not only amplified, but also shows rearrangements of the 5'-end, in the region coding the EGF-binding domain of the receptor [1224, 3095, 1742, 207]. These mutant glioma EGFR proteins can be selectively recognized by specific antibodies produced using a synthetic peptide [207]. These observations suggest the possibility of overproduction by gliomas of a truncated receptor, capable of autophosphorylation in the absence of EGF. However, despite much evidence which indicates a key role for EGFR gene amplification in malignant gliomas, this amplification does not clearly correlate with the degree of histological and/or clinical malignancy of these tumors [210]. However, if one discriminates between EGFR gene amplification and EGFR gene dose alterations due to aneuploidy involving chromosome 7, the amplification appears associated with shortened survival [1227A].

In a glioblastoma cell line, a new gene located on chromosome 12 called *gli* has been identified [1429]. It has been shown to be amplified over 10 times in 2 of 45 glioblastomas [210].

In a small number of malignant gliomas or glioma cell lines, amplifications for N-*myc* [884, 3071, 846, 1227a] and c-*myc* [2863, 1227a] have been observed. Of some interest is the observation that there are no reports of c-*myc* amplification in adult glio-

mas. A single report of c-*myc* amplification was obtained in a childhood glioblastoma cell line [2863]. Amplification for N-*myc* and c-*myc* was found in a few medulloblastomas and cerebellar primitive neuroectodermal tumors (PNET) [2032, 2376, 101], whereas amplification of *myc* genes seems to be a relatively common feature of medulloblastoma cell lines [213, 2987]. N-*myc* belongs to the family of *myc* protooncogenes which is thought to be capable of modulating genetic expression and cellular proliferation by binding to DNA, even in normal cells [724]. Also in the nervous system, relationships between *myc* and proliferative and differentiation processes have been described many times. In the immature brain, N-*myc* is expressed at high levels [2663, 988], but during maturation, simultaneous with differentiative processes, the levels of transcription of N-*myc* decrease to those characteristic of the adult [2534]. The expression of the *myc* genes is furthermore induced by the mitogenic effect of different growth factors [724, 1227], while it is repressed as a consequence of the cellular differentiation and of the loss of the proliferative potential [2534].

Amplification of N-*myc* is particularly important in childhood neuroblastomas, where it is a more reliable indicator of a poor prognosis than classical morphological criteria [294, 2568]. This gene, which has a limited homology with the c-*myc* oncogene, is present in single copies in normal adult cells, while in neuroblastoma cells it is possible to identify up to hundreds of thousands of copies. In 24 of 63 (38%) neuroblastomas studied, N-*myc* was amplified from 3 to 300 times [296]. Moreover, a significant correlation between the aggressiveness and prognosis of neuroblastoma and the level of amplification of N-*myc* was demonstrated, in the sense that amplification is frequently associated with more undifferentiated tumors and a worse prognosis. There is a significant correlation both with the stage of the disease and with the histological features of malignancy [2582, 2873]. It has furthermore been observed that in patients with neuroblastoma, the levels of amplification of N-*myc* are constant in time and in samples taken at different locations of the tumor [297]. Several cytogenetic, molecular, and flow cytometric avenues of evidence indicate that neuroblastomas can be divided into three genetically distinct groups, with corresponding distinct clinical behavior [295]. N-*myc* amplification associated with deletion of chromosome 1p, double minutes, and homogeneously staining regions (both cytogenetic expressions of DNA amplification) probably characterizes a neuroblastoma type with a poor outcome [294].

Expression of different oncogenes has been detected in some glioma biopsies (N-*myc*, c-*myc*, v-*fos*, n-*ras*) [846, 714, 901] and in several glioma cell lines (c-*myc*, c-*mil/raf1*, *neu*, n-*ras*) [714, 1547, 901]. The significance of these findings is unknown and further studies are needed to correlate the oncogenic expression with histological and clinicopathological features of glial tumors.

Important findings arose from studies concerning the expression of PDGF and PDGF receptor genes in gliomas. The first important finding is that the PDGF.B chain is encoded by the c-*sis* protooncogene, the cellular homologue of the oncogene v-*sis* of the simian sarcoma virus (SSV) [655, 2989]. SSV, when injected intracranially in a newborn marmoset, may induce gliomas, and its oncogenic action is mediated by a growth factor that binds to the PDGF receptor [2336]. Moreover, it has been reported that many human malignant glioma cell lines express PDGF genes and, in some cases, PDGF receptors as well [2038]. These findings suggest that in glioma cell lines, an autocrine loop of growth stimulation involving PDGF may be present. Recent studies have demonstrated coexpression of PDGF genes and of PDGF type B receptor in vivo, in bi-

opsies of human astrocytic gliomas [1113, 1827, 1825]. These results suggest the presence in these tumors of an autocrine growth loop that may contribute to neoplastic progression, even in the absence of major structural changes of the c-*sis* gene [2232, 1825].

Evidence for PDGF type B receptor expression by vessel cells of human gliomas has been reported [1113, 1827, 1825]. This finding may be extremely important in understanding the pathogenetic mechanisms of endothelial hyperplasia in malignant gliomas. A paracrine growth stimulation mechanism, involving PDGF produced by glioma cells and the receptor expressed by endothelial cells, may be active. However, it has been reported that hyperplastic endothelial cells of glioblastomas may also express PDGF.B mRNA [1113, 1827]. This suggests the possibility of an autocrine loop as well [1113]. An autocrine mechanism may account for the pseudotumoral growth of endothelium and for sarcomatous proliferations that originate from hyperplastic vessels of glioblastomas, giving rise to mixed tumors like gliosarcomas.

PDGF is furthermore implicated in mechanisms of glial differentiation, and it has been demonstrated to play a key role in the proliferation and differentiation of glial cell lines of the optic nerve [2316, 2042, 2252, 2242]. The proliferation of the bipotent O-2A progenitor, which gives rise to oligodendrocytes and to type 2 astrocytes of the optic nerve, is induced by PDGF which is produced by type 1 astrocytes. In the absence of PDGF, the O-2A progenitors differentiate precociously, and, therefore, PDGF is crucial for the control of myelination in the CNS [2249].

2.2 Familial Incidence of Tumors and Genetic Factors

The familial occurrence of medulloblastoma is known. Up to 1986, 21 cases had been reported [2845]. Eight involved monozygotic twins, nine occurred in brothers, and eight occurred in brothers of cases with other tumors. Of all these cases, two were congenital. There are many reports in the literature of familial astrocytomas and glioblastomas [2552, 2478, 2439, 1124, 1592, 2934, 1692]. In some cases there was concordance for site [2478] and for multicentricity [1124]. Very peculiar is the case in which two brothers, 2 and 5 years old, simultaneously manifested a glioblastoma [683]. True hereditary factors, however, have not been identified, even though families of patients with astrocytomas have a higher risk of developing brain tumors than the general population [1692]. There have been discussions on whether the probability of occurrence of cerebral tumors was equal [1071, 955, 2234, 1160] or greater [2905, 437] in the relatives of patients with tumors, but the role of heredity has not been [1472] and is not recognized [750].

Retinoblastoma and phacomatoses, such as tuberous sclerosis, neurofibromatoses 1 and 2, and von Hippel–Lindau disease, are certainly hereditary and are discussed in the relevant chapter.

2.3 Congenital Tumors

Tumors appearing within 60 days from birth used to be considered congenital [77], but opinions then diverged on this point. Other authors have, in fact, considered as "certain-

ly congenital" tumors producing symptoms at birth, as "probably congenital" tumors producing symptoms in the first week of life, and as "possibly congenital" tumors producing symptoms in the first month [2693]. This subdivision was later reviewed, and the term of "possibly congenital" tumor was extended to those producing symptoms within the first 2 months of life [2963]. The limits of the three categories were later fixed at 6 weeks, 6 months, and 12 months, respectively [705].

Within the first 2 months of life, cerebral tumors are very rare and represent a proportion which is not greater than 1.5% of all cerebral tumors of infancy. Up to the end of 1984, 115 cases had been described, 12 of which were "probable" and 66 "possible" congenital tumors [1324]. An additional six were found incidentally at autopsy [2963]. In the distribution of oncotypes, teratomas figured in first place (36.5%), followed by medulloblastomas, astrocytomas, and plexus papillomas. Supratentorial localizations prevail, and, importantly, the majority of teratomas are not of the pineal region but of the third and lateral ventricles. Still, note worthy is the numeric importance of mesenchymal tumors, excluding meningiomas. In a series of 17 cases [1323], a prevalence of supratentorial tumors was found, but only two teratomas were observed. Following teratomas, medulloblastomas were the most frequent, 13 of 55, in a series of fetal and neonatal tumors [1285]. Up to 1986, 26 examples had been reported [778]; two cases, besides being congenital, were also hereditary [1004].

Twenty-six congenital tumors, representing 11.3% of tumors in the first year of life, were found in a Japanese series [2068]. Teratomas were the most frequent type, whereas astrocytomas were the most frequent form in the first year of life in five Far Eastern countries [2069]. In a series of 100 cases, representing 7.7% of all intracranial tumors of childhood, medulloblastomas were the most frequent. However, in a recent review of 886 cases of tumors of the first years of life, collected from five geographical areas, astrocytomas turned out to be the most frequent tumors, followed by medulloblastomas, ependymomas, etc. [630]. In a series of 93 cases during the first 18 months of life in the UK, the most frequent tumors were medulloblastoma, ependymoma and astrocytoma. Only one teratoma was found [1530].

2.4 Risk Factors: Epidemiological Data

The source of data relating to risk factors for cerebral tumors in man is twofold: descriptive clinicopathological studies and epidemiological studies. The former have described the association of cerebral tumors with various factors (individual characteristics, professional and nonprofessional exposures, diseases, etc.), while the latter (more often case-control studies) have tried to confirm the significance of the associations previously suggested and to identify others which are still unknown. All the case-control studies have shown a certain number of methodological problems, which may explain the contrasting data which often emerge [2550, 1628].

In general, when many risk factors are analyzed simultaneously, a certain number of the observed associations may be purely casual. The choice of controls to compare with cases of cerebral tumor is always a crucial problem. If only healthy controls are used, a potential limit is the so-called selective recall, i.e., a greater anamnestic effort from relatives of the index case with brain tumor, who are more emotionally motivated than the relatives of the healthy controls, with conse-

quent disparity of information on the risk factors. As a consequence, there would be a need to utilize, apart from healthy controls, which by themselves guarantee a greater generalization of the data obtained, sick controls and, in particular, patients with a noncerebral tumor. Sometimes, however, the utilization of different types of controls may lead to uncertain results: The consumption of barbiturates was found to be increased in mothers of patients with brain tumors, when compared with control mothers of patients with other types of neoplasia, but the difference became much less evident when the comparison was made with mothers of healthy controls [954]. Another fundamental problem, especially in the study of professional exposure, is how a given exposure is measured: A different measurement of the intensity and of the duration of the exposure to the same risk factor may lead even to opposite and anyway not comparable results. An extremely serious risk is not to measure an exposure which really occurred ("misclassification of exposure"), especially if this occurs in a different manner for tumor cases and controls.

The majority of analytic epidemiological studies on cerebral tumors put different histological types in the same category, even with specific incidence and survival, so that available data for single categories, for example, gliomas, medulloblastomas, etc., are very scanty.

2.4.1 Family Characteristics

The majority of the familial characteristics investigated in case-control studies of infantile and adult cerebral tumors have not been found to be associated with a significant increase in the risk for cerebral tumor. These characteristics are: congenital diseases [955], maternal or paternal age at birth of the index case [437, 955, 2005], the mother's average age of menarche [955], maternal diseases preceding the birth of the index case [437], type of religion and schooling [2005], and ethnic group [330] of the parents. Equivocal results have emerged for other maternal characteristics, such as a positive history of abortion and complications of delivery [1854, 437] or for epilepsy and "stroke" [955], while, in the only available study [955], the association between infantile cerebral tumors and epilepsy in consanguinous brothers and sisters has been found to be statistically significant.

The association between maternal habits and increased risk of infantile cerebral tumors has been found to be negative for the use of contraceptives by the mother before the birth of the index case, tobacco consumption before pregnancy, and use of hormones during pregnancy [955]. The suspicion that barbiturates employed as medication for epilepsy may cause brain tumors has been a matter of debate. The possibility was raised in a case-control study [954]. In an investigation on barbiturate exposure during childhood and in utero [961], an association was found only for barbiturate use during childhood, but it was reduced to insignificance when the history of epilepsy was considered. The use of phenytoin alone or in association with barbiturates during pregnancy has been correlated with infantile CNS tumors [1666]. Also, for drugs with CNS actions, i.e., sedatives and antidepressants, employed during pregnancy, the association was uncertain, in particular for neuroblastoma [1503]. A positive association was found for maternal antinausea medication [1460] and for the consumption of food with potential sources of N-nitroso compounds, such as variously treated meats, e.g., smoked, pickled [2235].

The importance of parental occupations have been taken into account as risk factors. Paternal exposure to hydrocarbons does not seem to be significant [3112, 2444, 956, 2005]. Studies [2081, 2005] have not confirmed the original suggestion of a risk

connected with the work of the father in the aerospace [2191], cellulose, or wood-pulp industries [1545]. Paternal exposure in the chemical industry [956, 2005], in the petroleum industry, and in industries involving the use of electromagnetic fields [2005] is not significant. In the last case, however, some doubts remain for peripheral nervous system (PNS) tumors [2710]. The association is negative for maternal exposure to ionizing radiation, while it is equivocal for paternal exposure [2005].

Parental occupations have also been taken into account for risk factors, with wide discrepancies. A case-control study [3042] relying mainly on the Hoar job-exposure matrix, revealed a pattern of greatest excess risk for paternal jobs held prior to conception in agriculture, transportation, construction, involving exposure to metals, paints, hydrocarbons, or nitrocompounds, whereas few associations emerged for maternal employment characteristics. In another study [933], potential risk factors for brain tumors were analyzed in 200 patients under 15 years old with verified brain tumor and compared with controls. No factor was definitively identified.

2.4.2 Individual Factors

The order of birth does not represent a risk factor for cerebral tumors in adults [437, 330]. Being the first born and being heavy at birth is positively associated with infantile cerebral tumors, but without statistical significance [955]. The blood group A has been found to be positively associated with intracranial tumors in males [315] and with gliomas in general [2592], and blood group O with hypophyseal tumors [1830]. By contrast, some authors deny the importance of blood groups [879, 437]. Religious affiliation and tonsillectomy are not important [955, 330]. Patients who are immunosuppressed because of renal transplants have a 350-fold greater risk than controls of developing lymphoma, many of which are cerebral [1176].

Various diseases have been reported to be associated with CNS tumors, but for none of these has a thread of significance emerged. This applies to diabetes mellitus [2143, 79] and toxoplasmosis [2567]. The association between breast cancer and meningioma [2552], likely on a hormonal basis, and that between osteosarcoma and hereditary retinoblastoma [6, 661] are, however, significant. In ataxia telangectasia, extracranial tumors occur more frequently than expected [559], but it is not known whether this disease represents a significant risk for CNS tumors too [1628].

2.4.3 Multiple Sclerosis

The association between gliomas and multiple sclerosis is not frequent. Up to 1991, no more than 25 cases had been described. The majority of the tumors were astrocytomas/glioblastomas; only two cases were oligodendrogliomas [131, 924].

In the majority of cases, the tumor has not been clinically diagnosed; in some cases, demyelinating plaques have accidentally been found at autopsy in patients with gliomas. This association has been considered as casual by some [288, 270, 87, 55, 924, 1], while others considered the tumor as originating from the transformation of reactive glia [2476, 2284]. The finding that tumor and demyelinated areas are contiguous would militate in support of the latter hypothesis [2476,

288, 2284, 537, 2419, 55, 1555], but in many cases this is not observed [1970, 131, 270, 87, 1798, 537]. It is also possible that the growing tumor obliterates the demyelinated areas.

Oligodendrogliomas could originate from the proliferation of oligodendrocytes in the plaques [1235, 1712], but the rarity with which oligodendrogliomas are associated with multiple sclerosis would be inconsistent with the importance of oligodendroglial proliferation in the process of demyelination.

Some of the associated tumors were multiple [2476, 2284, 537]. The hypothesis of a common viral origin has not been confirmed [1339]. The postulated causal association is in contrast with the finding that the number of described associations is lower than that expected on the basis of the prevalence of multiple sclerosis and the tumor mortality [2817]. However, the association in reported cases may not reflect the real frequency of association [924].

2.4.4 Virus

There are reports of positivity for viral antigens, for example, SV40, or of DNA or RNA sequences in different tumors, but decisive proof for a viral origin of cerebral tumors is lacking. Sometimes, the sequences were left after infections in infancy by human viruses with widespread diffusion [1439].

2.4.5 Head Injuries

The appearance of cerebral tumors after head injury has repeatedly been reported to occur. This would directly imply the neoplastic transformation of reactive astrocytes. Despite reports that posttraumatic neuroepithelial tumors are not rare [2541], cases which satisfy the criteria of acceptability are few [2951, 2189, 1499]. These are [3134]: adequately serious trauma, origin of the tumor at the site of trauma, absence of CNS diseases before injury, reasonable latency period between trauma and onset of the tumor, histological demonstration, and direct continuity with the traumatic scar [1759]. In a recent case [2870], as in others previously reported [777, 3065], trauma was due to a splinter from a bomb. On the whole, it can be said that there does not seem to be a positive association between trauma and primitive cerebral tumors [437, 61], even considering only gliomas [330, 2238], unless the head injury has been severe [1159, 1213].

By contrast, the association between head injury and the development of meningiomas suggested by single reports [2307, 2974, 2800] has subsequently been confirmed in case-control studies both in females [2234] and in males [2237, 2238]. A limiting factor in these studies was, however, represented by the impossibility of evaluating the etiogenetic role of the head injury separately from that of exposure to X-rays, as radiography was employed in the same patients to evaluate the consequences of the trauma. A complete review of the subject is available[1922].

Experimental data concerning the putative relationship between trauma and the development of brain tumors until now have given contrasting results. In transplacentally by ethylnitrosurea (ENU) treated rats injured by an intracranial needle-trauma at 12 days of age, no effect on the number and location of tumors was observed [1871]. In another study in similar rats, a greater percentage of gliomas was found on the traumatized side [1923]. In our experience with the same rats, trauma seems to act as a factor anticipating the appearance of gliomas [2520].

2.4.6 Irradiation

Data on the risk of development of cerebral tumors after prenatal exposure to X-rays for diagnostic use are contrasting: The 60% increased risk reported by McMahon (1962) [1854] has not subsequently been confirmed [437].

Postnatal exposure (skull and dental X-radiography) has been found to be positively associated with the development of meningiomas [2237] in both females [2234] and males [2237]. Repeated dental X-radiography, especially before 1950 when this procedure entailed exposure to very high radiation doses, have been thought to increase the incidence only of tentorial or infratentorial tumors.

There are many reports indicating exposure to X-rays as a treatment for tinea capitis as a risk factor in children. Worldwide, 250,000 children underwent the Adamson–Kienböck irradiation technique for tinea capitis during the years 1910–1959, i.e., a radiation dose of from 70 to 200 rad [3016]. Evidence indicates a relationship between small doses and tumors such as meningiomas [1911, 2385] and gliomas [2629, 2351]. A glioblastoma associated with multiple meningiomas, a malignant cerebellar astrocytoma, and a diffuse astrocytoma have been described in patients many years after exposure to low-dose irradiation [2684]. The induction of meningiomas by irradiation is now well established, and radiation-induced meningioma seems to be a recognizable entity. A supplementary case has been reported [2135].

There are many reports of second CNS tumors arising after radiotherapy for intracranial tumors. They are usually meningiomas [1753, 2682, 2385, 1528, 1950, 2683] and sarcomas [2044, 95, 179, 2844, 1528, 2802]. Gliomas are much less frequent: 24 cases had been reported up to 1985 [1674], but others have been published subsequently [1327, 1725, 2889, 1217, 799, 2532, 636, 2124, 1434, 2605, 402, 2441].

In the reported cases, the dose varied between 150 and 6000 rad. Usually, the irradiation was given for infantile tumors, so that the majority of published cases were in the first 3 decades of life. Irradiated primary tumors were mostly medulloblastomas, craniopharyngiomas, and acute lymphoblastic leukemias.

Criteria are available to determine whether a correlation between radiotherapy for a first neoplasm and the development of a second tumor exists: (1) Both tumors have to be histologically verified; (2) the second tumor has to develop in the irradiated area; (3) there must not be similarities of site and histological appearance between the two tumors; (4) the latency period has to be sufficiently long to exclude the presence of the second tumor at the time of irradiation. The role played by radiotherapy in the induction of the second neoplasm is very controversial, even though the cases reported in the literature and experiments in monkeys are in favor of a causal role of radiotherapy [1382, 2864, 1088, 1511]. Our knowledge of radiobiology is not in contrast with this hypothesis. Theoretically, the risk of a second intracerebral neoplasm after therapeutic irradiation is more than 100 times greater than in controls [402].

2.4.7 Nonprofessional Exogenous Exposures

Smoking has never been found to be a potential risk factor [437, 2234, 1978, 1160]; however, in the wide Canadian case-control study published in 1987 [330], the use of cigarettes without filter was found to be significant.

The positive association with the use of hair dyes or hair sprays recently reported [330] must be reevaluated, because many of these products, being oxidants, are well known as potent mutagens [2926] and have been found [2630] to be positively associated with extraneural tumors such as, for example, mammary carcinoma.

The exposure to N-nitroso compounds and their precursors or modulators in food has been actively investigated, in the light of experimental data on the very well known carcinogenetic potential of such substances on nervous tissue, but the results have often been contrasting or even incongruent. High risks for gliomas have been found for the consumption of salted, smoked, and pickled fish [330]. The latter represents an important source of nitrosoamines and perhaps of nitrites. The consumption of other meat products, also important sources of nitrites, was found to be positively associated with the risk of infantile and juvenile tumors [2235]. In the Los Angeles area, it was found to be a significant risk factor for meningiomas in females [2234], but not in males [2237]. The consumption of alcohol is not significant in some series [437, 1978, 1160], while in others [330] wine consumption represents a risk factor for gliomas. Analogous discrepancies have been found for beer consumption [330, 1213], which contains higher concentrations of nitrosoamines than wine. From a case-control study [330], a protective role of fruit consumption has emerged. This could be in relationship to the elevated content of vitamins C and E, which are known as inhibitors of the formation of N-nitroso compounds from nitrites and other precursors [1905, 2990].

The use of oral contraceptives has not been found to be associated with a risk for pituitary adenomas in American women [60].

Two cases of children with high urinary levels of lead who subsequently developed an astrocytoma were reported [2562]. Even if anecdotal, this datum is not to be undervalued in the light of the demonstrated experimental inducibility of gliomas in rat with diets rich in lead citrate [2100].

Different nonprofessional exposures have been examined [955] in a case-control study in children. Positive associations have been found with living on a farm and a history of contact with farm animals. Some associations, even if not achieving statistical significance, have been emphasized because of their potential biological significance, for example, that with insecticides and sick pets. This association was subsequently denied [1213].

2.4.8 Professional Exogenous Exposures

The increased risk for cerebral tumors in rubber industry workers is controversial. Equal numbers of reports confirm [1749, 1917, 330] and deny [1855, 1849] it. The same uncertainties remain for workers in the petrochemical [2838, 2992, 1601, 93, 2836], pharmaceutical [2835, 1849], and textile [1978, 1849] industries, for chemical workers [2076, 330], for glassmakers [716, 3056, 1849], and for subjects exposed to vinyl chloride [2993, 330]. Some studies, however, indicate an excess mortality for cerebral tumors in workers in the petrochemical industries [2027, 28].

An excess mortality from cerebral tumors in various categories of subjects exposed to electromagnetic (nonionizing) radiation, such as electrical and electronic engineers, electricians, telephone and telegraph line operators [2236, 1748, 1889, 1653], has been reported. Different studies have reported a shorter latency between the initiation of the

exposure and the onset of tumors than that known for other forms of professional carcinogenesis, for example, that due to asbestos [2584, 3018]. It has been hypothesized [1653] that the oncogenic action of electromagnetic radiation might occur through a mechanism of facilitation more than initiation of the neoplastic growth. This hypothesis may be in agreement with the finding in extracerebral experimental tumors of a "promoting" effect of such radiation [2748, 976], even if, for now, the only actions demonstrated on the nervous tissue concern the possibility of inducing gliosis [1411] or modifying the bond with calcium ions [14]. Recent studies, especially case-control ones, however, denied [2077, 1849] or attenuated [2837] the carcinogenic risk for the CNS of electromagnetic radiation. In particular, the increased risk of gliomas in the electronic industry involves categories both exposed and nonexposed to electromagnetic radiations [2837]. The hypothesis, therefore, is that the increased risk of cerebral tumors was due, at least in part, to the exposure to various chemical products used in the electronic industry, especially solvents (trichloroethane, tri- and tetrachloroethylene, etc.), which may induce gliotic phenomena in cerebral tissue [2366].

The increased risk of gliomas in agricultural workers, originally suggested in a descriptive epidemiological study [301], is controversial [1978, 330, 1849, 1979, 1899]. A significant increase has been found in agricultural workers who used fungicides and insecticides, but not herbicides and fertilizers [1979]. Some of the fungicides commonly added to copper sulfate compounds used in vineyards contain alkyl ureas, which are the precursors of the N-nitroso-alkyl ureas.

An increased incidence of gliomas has been hypothesized in various health workers. The risk would seem significant for pathologists [1063] and anatomists [2755], perhaps following exposure to formaldehyde or other chemical agents, and for dentists and their assistants [20] who handle mercury and various metal amalgams.

Both descriptive and analytical studies agree in attributing an increased risk of gliomas to welders [716, 375, 1849], while there are single reports for categories with exposures similar to those of welders (plumbers, millers, etc.) [1849]. A recent case-control study on occupational risks in Sweden [1849] has suggested, for the first time, an increased risk of gliomas in ceramic, porcelain, and brick workers.

A risk of cerebral tumors has been found to be elevated even in attorneys and lawyers [668, 1849]. It is possible that these categories are prone to a greater diagnostic accuracy.

2.4.9 Multiple Tumors

One of the arguments supporting the theory of the multicentric growth of cerebral tumors, particularly of gliomas, is the occurrence of diffuse and multiple gliomas. From diffuse gliomas, mostly astrocytomas and oligodendrogliomas, gliomas with multicentric growth and diffuse glioblastosis, also called diffuse spongioblastosis [3134], must be kept separate. Diffuse glioblastosis is a rare form which especially affects the young, in the brainstem or in the hemispheric white matter, and has a recognized dysontogenetic origin. Multicentric gliomas are tumors in which growth centers may be very distant from each other. According to Courville (1936) [502] 10% of glioblastomas and 6% of astrocytomas are multiple.

The majority of multiple gliomas are found only in one hemisphere, but they can also be symmetrically distributed and often have similar dimensions. Glioblastoma prevails, but other histological types are also represented. Although rare, contemporaneous cerebral and cerebellar locations have been described [3134, 2420]. Periodically, cases of multiple gliomas are reported in the literature [2803, 407, 130, 1906] with an incidence varying from 2.5% to 8.75%.

The main problem concerning multiple gliomas is whether they actually represent true multicentric foci [502, 247] or are expressions of metastases within the nervous system. Solitare (1962) [2692], critically reviewing the problem in relation to a cerebral-cerebellar glioma, warned against the possibility that multiple foci are not distinct foci but appear so because of insufficient examination of the intervening nervous tissue, as others have [3134, 146].

Still, it has recently been reiterated that the pathogenesis of multiple gliomas may be an expression of a true formation of multiple primary growths, of contemporaneous disturbance of development leading to coordinated tumors [2093], or of metastatic disseminations along CSF pathways [324]. Obviously, the entire brain must be examined in order to accept a tumor as multicentric. It has, in fact, been demonstrated that some apparently multicentric glioblastomatous foci are connected by a diffuse astrocytomatous proliferation. This case might represent a multicentric malignant transformation of a diffuse astrocytoma [2483]. Some multicentric growths on CT scan may be found to belong to this category after histological examination. True multicentric gliomas occur in 8% of our autopsy series.

Multiple tumors of diverse nature are considered separately, because the pathogenetic problem is different. They may belong to hamartoblastomatosis, such as von Recklinghausen's disease, in which multiple neurinomas, meningiomas or astrocytomas are associated. Also, combinations of mesodermal tumors, such as multiple meningiomas, or of mesodermal and neuroectodermal tumors may occur. Not infrequent is the association between meningiomas and gliomas, usually astrocytomas and glioblastomas, but also oligodendrogliomas. In all, 18 cases from the literature plus a personal one of meningiomas associated with gliomas of various type were reported [702] . The number amounted to 25 some years later [783]. Single cases are periodically reported in the literature [2754, 75]. The association of glioma and meningioma has been found to be the most frequent one [58, 609].

Other associations found were between glioma and hemangioblastoma, craniopharyngioma and meningioma, meningioma and neurinoma [609], and craniopharyngioma and astrocytoma [384], and craniopharyngioma and pinealoma [1090]. The association astrocytoma–neurinoma is rare [504, 1109, 348]. Sarcomas not infrequently appear in association with other tumors [1829], and this involves the more general problem of mixed sarcomatous tumors. Also rare is the association between pituitary adenomas, gliomas, and meningiomas. The association between primary lymphoma of the brain and meningioma has been reported only once [2666]. From the pathogenetic point of view, it is important to note that in the majority of cases, the tumors belong to anatomically adjacent areas and, therefore, stand in probable causal relationship [348].

3 Experimental Tumors

3.1 Chemical Carcinogenesis

3.1.1 Topically Acting Carcinogens

The experimental induction of cerebral tumors was initially accomplished at the site of application of the carcinogens. Polycyclic aromatic hydrocarbons such as 20-methylcholantrene [3124], 1,2,5,6-dibenzanthracene [76], and 3,4-benzopyrene [3125] were the ones most used, by means of pellets implanted in the brain. The histological type of tumor obtained depended on the site of implantation [3123]: ependymomas in the ventricles, glioblastomas and oligodendrogliomas in the white matter, medulloblastomas in the cerebellum, etc. It was clear that the subependymal zone could play an important part in the development of these tumors [1180].

3.1.2 Resorptive Carcinogens

A tumor was not induced at the site of application of the carcinogen, but in different organs towards which it shows a specific tropism. The first studies were based on the observation of occasional tumors in rats, produced by 2-acetylaminofluorene [2918, 1158, 2780], 8-orthohydroxycholine [1157], and 2,7-fluorenbisacetamide [2676]. Subsequently, a systemic induction was obtained, after the demonstration of the hepatic carcinogenic activity of nitrosamine [1730], with compounds belonging to the nitrosourea group. Numerous nitrosourea derivatives have been studied [664]. Nitrosamides appeared to have a strong neurotropism.

Two compounds in particular have been found to be ideal for developing an experimental model: methylnitrosourea (MNU) and ethylnitrosourea (ENU). Tumors could be produced in the adult animal, in the neonate, and transplacentally, with in every case a relationship between administration route, dose of carcinogen, and latency period being demonstrated (see Table 3.1). The tumors seen are mostly gliomas, arising mainly from periventricular areas and from the hemispheric white matter [2999, 1474, 664], and neurinomas of the fifth nerve or of the spinal roots [1010, 2778], which are morphologically similar to spontaneous tumors in humans and animals. More tumors may develop in the same animal, and tumors in different phases of development may be found at the same time in the same animal.

MNU is active in the adult animal, while ENU is active in the neonate and transplacentally. MNU repeatedly administered by the intravenous route produces gliomas in

Table 3.1 Induction of tumors in the rat

Carcinogen	Animal	Administration		Site	Dose (mg/kg)	Latency period (days)
		Route	Day of pregnancy			
Prenatal induction (transplacental)						
Ethylnitrosourea	Rat	Intravenous	15–17	SNC SNP	80 5	150 250
Ethylnitroso-biuret	Rat	Oral	15	SNC SNP	100	190–330
1,2-Diethylhydrazine	Rat	Intravenous	15	SNC SNP	50–150 5– 10	126–560 560
Azoethane	Rat	Inhalational	15	SNC SNP	300 600	220 126–480
Azoxyethane	Rat	Intravenous	15	SNC SNP	50	142–300
Ethyltriazenes	Rat	Intravenous	15	SNC SNP	110 55	350 450
1,2-Dimethylhydrazine Azoxymethane	Ineffective					
Methyltriazene	Ineffective					
Neonatal induction						
Ethylnitrosourea	Rat	Intravenous Subcutaneous Intracerebral		SNC SNP	5– 80 1st–30th day	180–600
Butylnitrosourea	Rat	Subcutaneous		SNC SNP	120, 1st day	130–180
Ethyltriazenes	Rat	Subcutaneous		SNC SNP	50, 1st day	190–250
Methylnitrosourea Ethyltriazenes	Ineffective					
Induction in the adult animal						
Methylnitrosourea	Rat Rabbit	Intravenous Oral		SNC SNP	5 mg/g per week	280–500
	Dog	Intraperitoneal				
Dimethylnitrosourea	Rat	Intravenous Oral		SNC SNP	3 mg/g per week 40 mg/Kg per week	450 210
Trimethylnitrosourea	Rat	Oral		SNP	3 mg/g per day	450
Ethyltriazenes	Rat	Intravenous Subcutaneous		SNC SNP	25 mg/g per week 50 mg/g per week	410 250
Ethylnitrosourea	Ineffective					

The frequency of tumors and multiple tumors is dose-dependent.

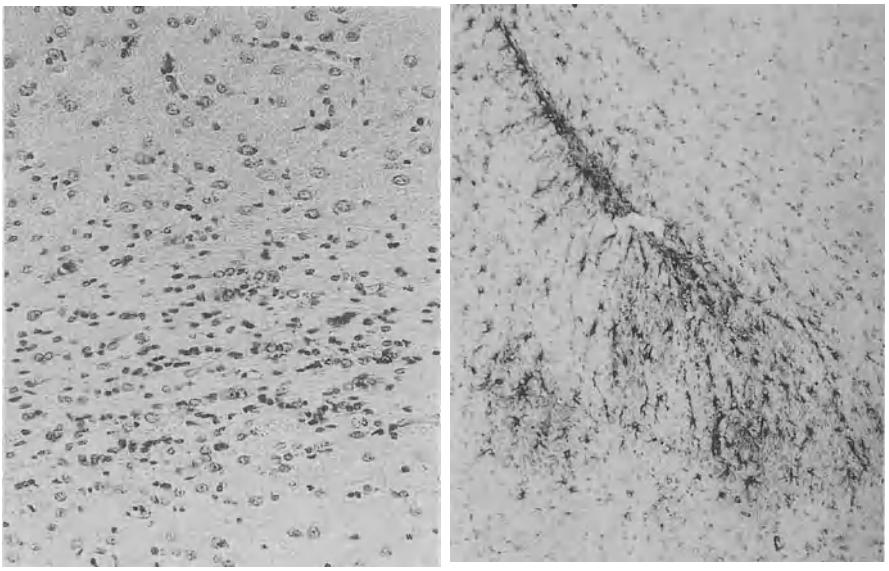


Fig.3.1a,b. Rat transplacentally treated with ENU. **a** Early neoplastic proliferation (ENP) in the white matter, H&E, ×200. **b** ENP: intense GFAP staining of reactive astrocytes, PAP-DAB ×200 [1822]

the brain and in the spinal cord and neurinomas of the gasserian ganglion within 280–500 days.

Very important and widely used is the transplacental model with ENU. A single i.v. dose of 20 mg/kg in the rat on the 17th day of gestation causes cerebral tumors in 90% of the offspring. Increasing the dose of ENU increases the number of tumors per rat and decreases the latency period [664]. The period of clinical latency, i.e., between birth and the the first appearance of symptoms, is 5–6 months [2278, 266]. At this age, however, neoplastic lesions at different stages of development are found; if animals are systematically studied starting from birth, the first tumors are found at the 2nd month of extrauterine (e.u.) life in the periventricular white matter [2501, 1572], known as early neoplastic proliferations (ENPs) (Fig.3.1a). Histologically, they are not very well defined [1441, 2777, 1569]: Astrocytes and oligodendrocytes are present, apart from cells of uncertain nature [2501]. The abundance of reactive astrocytes in these lesions is striking [2503, 1822] (Fig.3.1b). Between the second and the third month of e.u. life, microtumors of a diameter between 300 and 500 μm, with higher cell density, frequent mitoses, and proliferation centers of densely packed cells, develop from these lesions [1474]. Microtumors continue to appear between the fourth and the fifth month (Fig.3.2a), while oligodendroglial foci begin to be evident in the cortex and in the white matter between the third and sixth month (Fig.3.2b). Isomorphous tumors develop from microtumors and become polymorphous. Adult isomorphous oligodendrogliomas (Fig.3.3) develop from oligodendroglial foci and may become polymorphous. Malignant growth is reached at the stage of microtumors [2999]. The entire temporal sequence is reported in Fig.3.4.

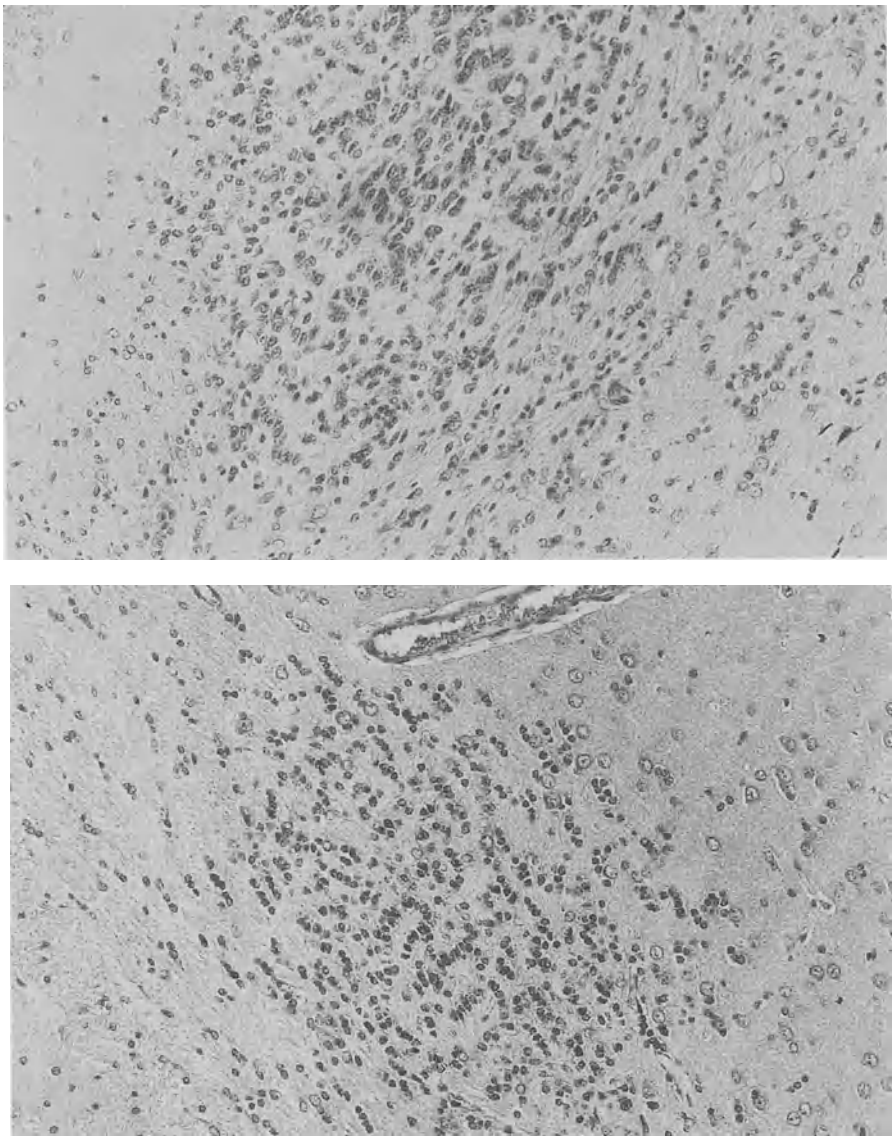


Fig.3.2a,b. Rat transplacentally treated with ENU. **a** Microtumor, H&E, ×200. **b** Oligodendroglial focus between white matter and cortex, H&E, ×200

Proliferative centers with high cell density can be recognized in many microtumors and tumors (Fig.3.5).

Neurinomas represent 41% of all experimental tumors and occur more frequently (53%) in postnatal induction experiments [3139]. They arise from Gasser's ganglion (Fig.3.6) and from posterior spinal roots, and resemble the human ones but are more ma-

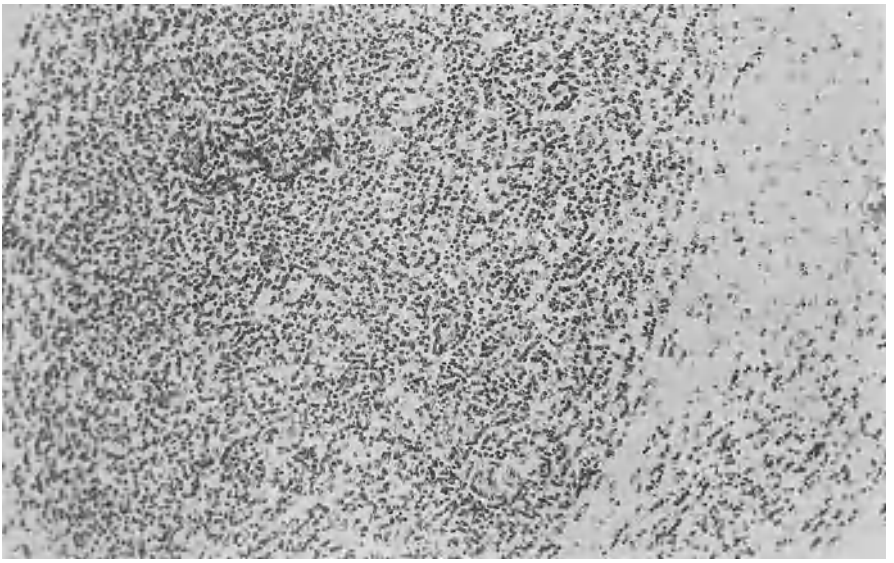


Fig.3.3. Rat transplacentally treated with ENU; isomorphic oligodendroglioma, H&E, ×150 [2525]

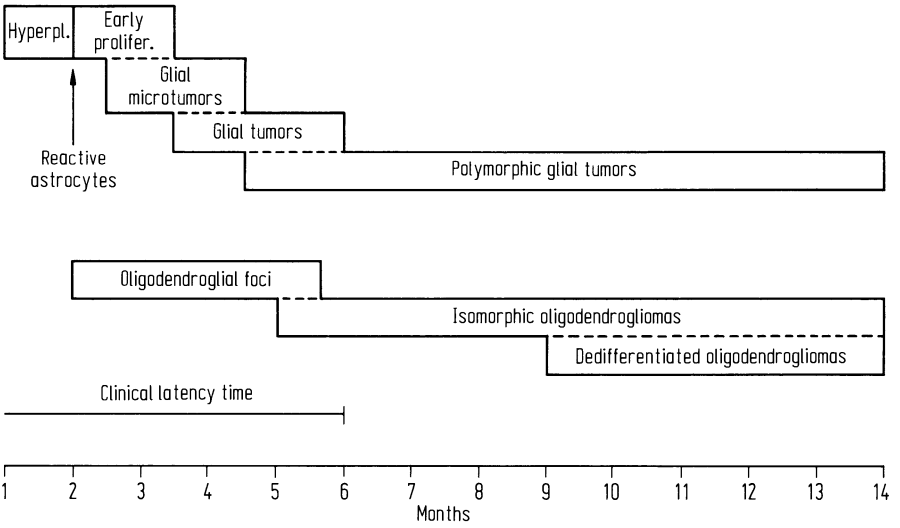


Fig.3.4. General scheme of tumor development after transplacental administration of ENU [2503]

lignant and tend to diffuse in the subarachnoid spaces (Fig.3.7). In culture, they grow rapidly, and their cells are similar to Schwann cells [513, 801, 1870]. If transplanted into subcutaneous tissue or the brain, they do not differ from those of the original tumor [514].

With the intraperitoneal administration of ENU 100 mg/kg in Syrian golden hamsters on the 16th day of gestation, multiple peripheral tumors, mostly subcutaneous

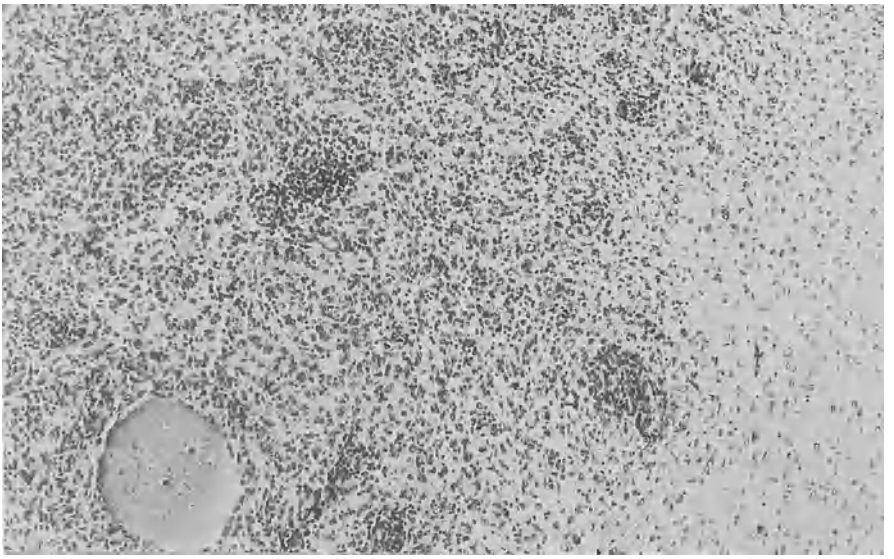


Fig.3.5. Rat transplacentally treated with ENU; tumor with proliferative centers, H&E, ×150

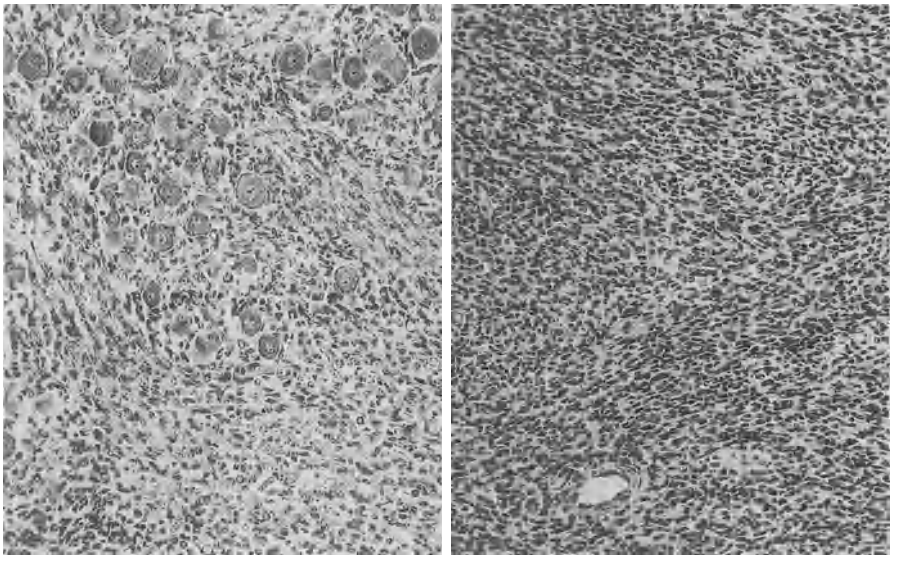


Fig.3.6. Rat transplacentally treated with ENU; neurinoma of the Gasser ganglion

neurofibromas, appear. They have a plexiform structure similar to neurofibromas in von Recklinghausen's disease. Simultaneously, but with lesser frequency, melanomas, pheochromocytomas, and nephroblastomas have been observed. This led to the suspicion that the target of ENU in this animal is the ganglial crests [1998]. It must be stressed that foci of melanotic cells were present in the neurofibromas. Similar tumors had

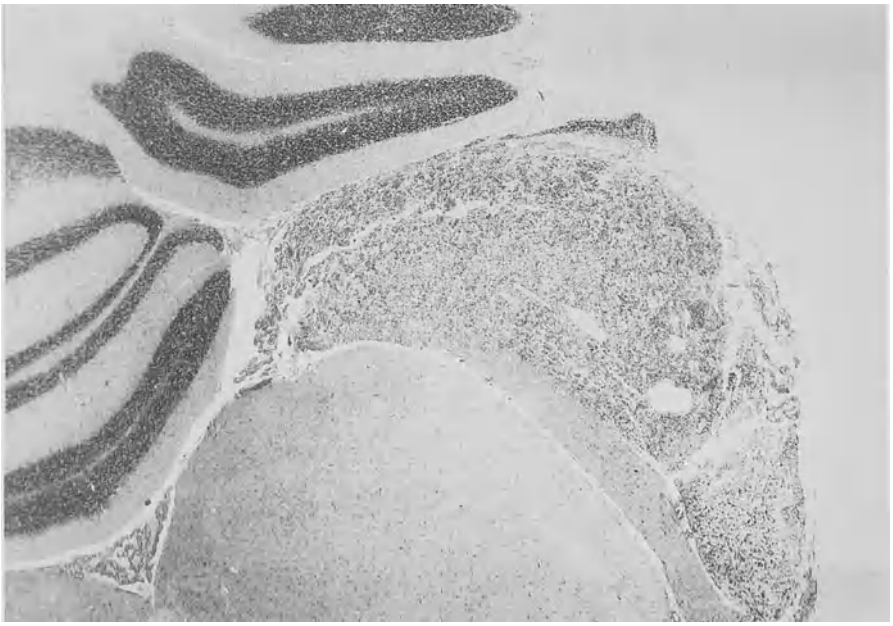


Fig.3.7. Rat transplacentally treated with ENU; neurinoma of the fifth cranial nerve diffusing in the subarachnoidal space, H&E, ×50

already been obtained in the same animal with the combined administration of ENU through the placenta and on the skin [2165].

3.1.2.1 Pathogenesis of Nitrosourea-Induced Tumors

The crucial moment in this model is represented by the histological latency period. However, the identification in vivo of the phenotypic changes of the presumed tumor cells is very difficult [1549]. This is due both to the polymorphous cellular composition of the CNS and to the fact that only a minimal fraction of the constituent cells undergoes changes leading to malignant phenotypes because of the effect of the carcinogen. It has furthermore to be taken into account that between the 17th day of i.u. life, when ENU is administered, and the 60th day of e.u. life, when the first tumors appear, the CNS undergoes substantial modifications due to the proliferation, migration, and differentiation of neuroepithelial cells which, starting from the matrix, will form the cortex and the white matter. The target of ENU is represented by the germinal zone which derives directly from the germinal layer of the neural tube [1283, 1571]. For this reason, three points have to be considered: proliferation and cellular differentiation, structural modifications of the DNA, and phenotypic alterations which occur in the target cell population.

The first point has already been considered in Chap. 1. As for the structural changes in the DNA, it is known that the most important effect of ENU is the oxygen alkylation with coupling errors during transcription, due to the substitution at the O6 of gua-

nine, O2 of the cytosine, and O2 and O4 of the thymidine. The alkylation at the N7 position of guanine and the N3 of adenine may instead be responsible for the cytotoxic effects of the carcinogen [1440]. The defective ability to repair DNA seems to be responsible for the susceptibility of the CNS to the neuro-oncogenic effect of alkylating agents. Within a week from the administration of ENU to 10-day-old rats, the quantity of O6 alkyl guanine in cerebral DNA is 20 times higher than in hepatic DNA [978]. The effect of ENU diminishes as e.u. life progresses, due to the decrease in the mass of the target cells [2259]. The inefficacy of ENU administered before the 15th day of i.u. life is due to the fact that at this moment neuroblasts are no longer dividing, and gliogenesis has not yet started [1440].

The phenotypic changes must be discussed while taking into account that the target cells of ENU are cells of the germinal matrix, cells of the subependymal layer, the migrating glial cells, and immature subpial glial cells in the spinal cord [1993]. Short- and long-term effects can be observed in these cells. The former include cell death, nuclear pycnosis, and momentary arrest of cell division in the ventricular zone [266]. An increase of cell proliferation has to occur [1551] for a genetic fixation of the promutagenic structural changes. In fact, the cytocidal effect of ENU is followed by cellular proliferation in the subependymal zone, in the peripheral neural plexuses and in the proximal part of the cranial nerves, especially the fifth [2779]. The roots of the fifth cranial nerve are composed of a peripheral part, with myelin of peripheral type and Schwann cells, and a central part with myelin of central type and oligodendrocytes with the line of demarcation being the zone of Obersteiner-Redig. The first proliferations of Schwann cells are observed 1 month from the administration of ENU [2997]. When tumors develop, they may simultaneously be neurinomas in the peripheral part and oligodendrogliomas in the central part of the roots, and they may often be interpenetrating [2482].

Different observations have demonstrated a cell-lineage specific mutation of the *neu/erbB-2* gene in the neoplastic trasformation of Schwann cells induced by transplacental ENU administration [2175A, 2763A, 2029B]. ENU-induced trigeminal neurinomas carry a TAAT transversion mutation at nucleotide 2012 of the transmembrane region of the *neu* gene. This mutation produce the substitution of glutamic acid for Val-664 of gp185^{neu} (125), a phosphoglycoprotein with thyrosine kinase activity and structural homology to EGFR. The mutation can be identified in trigeminal Schwann cells as early as 7 days after carcinogen administration [2029B], but is always absent in the ENU-induced CNS tumors other than neurinomas [2175A, 2763A, 2029B]. The presence of a mutated *neu* allele represents a selective advantage for Schwann cells whose proliferation rate largely exceeds that of wild-type trigeminal cells [2029B]. Moreover, loss of heterozygosity for the mutant *neu/erbB-2* gene, i.e., loss of the normal *neu* allele in cells previously heterozygous for the *neu* mutation, seems to represent a critical second step in the progression of ENU-induced schwannomas towards a malignant phenotype [2029B].

Between the 17th day of i.u. life and the 60th day of e.u. life, no morphological change can be observed in the areas which have in the meantime developed from the ventricular zone. However, if cerebral fetal cells are put in culture after exposure to ENU in vivo, they demonstrate phenotypic modifications up to the development of tumors if they are transplanted into 5–10-day-old rats [1549]. If brain cells obtained when the neoplastic transformation in vivo has reached the stage of microtumors are cultured,

it is still possible to find transformation in vitro [2357]. The transformation of the brain fetal cells in culture occurs in four stages, which require 100 days [1551]. Obviously, this interval is influenced by the dose of ENU administered. The cell phenotype changes before the cells become biologically malignant, i.e., before they become tumorigenic if transplanted into rats. It has to be noted that GFAP is negative or weakly positive in these cells [1550]. If, however, "glial maturation factor" is added to the culture, fetal glioblasts rapidly become mature astrocytes [1651, 1083].

Fetal rat brain cells exposed in vivo to ENU and transplanted into syngenic hosts after 200 days of culture form tumors which are morphologically similar to those induced with transplacental ENU [1550, 453]. Aggregates of malignant cells put into contact with the hearts of 9-day old chick embryos invade the explant. This demonstrates that invasiveness is a property associated with tumorigenicity in vivo [592, 1551].

In the period of histological latency, no morphological change is found; however, if the cells of the white matter between the ventricular germinal zone and cortex are counted on the 30th day of e.u. life, their number will be higher than in controls. Cell hyperplasias are thus recognized and represent the most precocious neoplastic manifestations [2503]. The number of mitoses is not different from controls in these areas, and the DNA histogram, obtained cytofluorometrically, demonstrates that the majority of cells are diploid. This means that cells in cycle are few, as in controls, and justifies the 30-day latency period. The labeling index (LI) with [3H]thymidine does not vary between treated and untreated animals in the subependymal cells and also remains low in the early tumor manifestations [1238, 1239].

More cell generations must take place between the moment of ENU administration and that of tumor appearance. As a matter of fact, a glial reaction elicited by trauma at the end of the latency period can enhance glioma formation [1923] and anticipate the tumor's appearance [2525], adding some more generations of genotypically transformed cells. In the long run, however, the number and cell composition of tumors are not modified by trauma [1871, 2525].

If suspensions of fetal forebrains of rats born from i.v. ENU-treated mothers are injected into adult rat brains treated with supplementary ENU, only oligodendrogliomas develop. This may indicate that neoplastic transformation does not require pluripotential stem cells, but that it can occur on oligodendrocytes or on precursor cells committed to oligodendrocytic differentiation [342].

In experiments with MNU administered in adult rats, where tumors develop from the transformation of already differentiating and migrating glia, there is no sensitivity to the drug of the reacting glia after a stab wound; the trauma then has no influence on tumor appearance [3091].

3.1.2.2 Cellular Composition

ENU-induced tumors are essentially glial microtumors, ependymomas, astrocytomas, and oligodendrogliomas, both isomorphous and polymorphous.

A large number of GFAP-positive reactive astrocytes characterizes the early neoplastic manifestations [1822, 2624] (Fig.3.1b). In microtumors and in developed tumors, practically the only GFAP-positive cells are the reactive astrocytes which, as the tumors grow, become progressively confined to the periphery and to the surrounding healthy tissue [1822, 2291] (Fig.3.8). The scarcity of GFAP-positive tumor cells could be due both to the immaturity of the cells, which are still

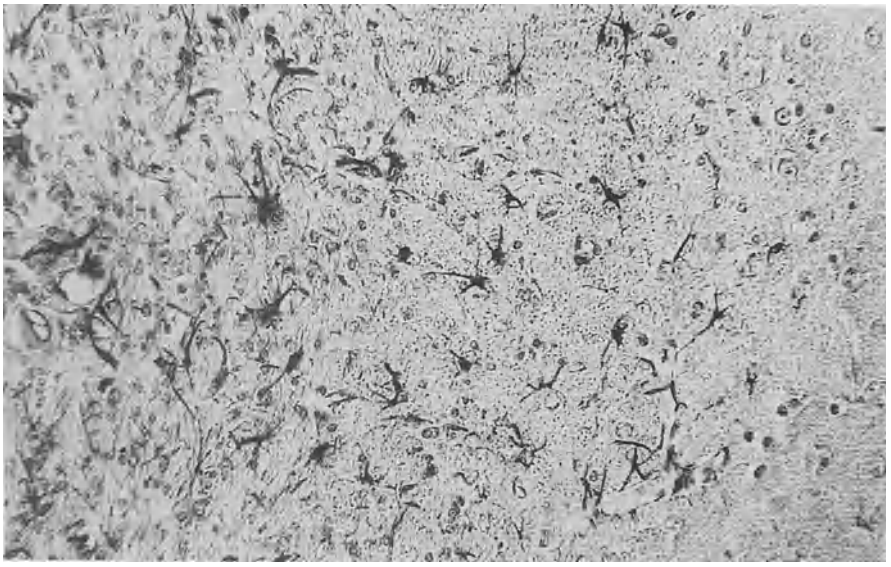


Fig.3.8. Rat transplacentally treated with ENU; GFAP reactive astrocyte confined to the periphery of an oligodendroglioma, PAP-DAB, ×300

not capable of expressing GFAP, and to the anaplasia, meaning that the cells have lost the capacity to express GFAP [581]. The abundance of reactive astrocytes in early lesions has been variously interpreted. It could be due to the existence of hidden myelin damage [1572] or to the normal rich complement of stellate astrocytes around the ventricles. Necrotic lesions experimentally produced by trauma are equally rich in GFAP-positive reactive astrocytes [2514]. Oligodendrogliomas are the most frequent fully developed tumors and are very similar to the human ones.

Vimentin is coexpressed with GFAP in adult and reactive astrocytes [550]. However, since it appears before GFAP during cytogenesis, it has been considered as a marker of immaturity if it is the only intermediate filament antigen expressed [2546, 203, 753]. The cells of proliferative centers of microtumors and developed tumors are vimentin-positive (Fig.3.9) and GFAP-negative [928, 2291]. They have been interpreted as undifferentiated elements. It is also possible that they correspond to radial glia which is vimentin-positive and GFAP-negative in the rat and a possible target of ENU, as they are already present when the drug is transplacentally administered [929].

A precise recognition of the various cytotypes on an immunohistochemical basis is not easy. For example, carbonic anhydrase C, a typical marker for oligodendroglia [1531], (also in man [1532]), is positive in normal rat oligodendrocytes but not in tumor oligodendrocytes [928] (Fig.3.10). It may be that these cells are too immature to express the marker, which first appears during ontogenesis after 3 weeks of e.u. life.

With progressing growth, the tumors spread to the entire hemisphere, to the contralateral one, to the brainstem, and to the subarachnoid spaces, achieving the picture of "total cancerization" of the brain. This may also be accomplished by the confluence of multiple tumors, which are often found after higher doses of carcinogen and in different stages of development. In more advanced stages, sarcomatous components develop [1281]. The tumors are therefore highly invasive. In fact, by cocultivating cells from ENU-induced tumors with fragments of normal rat brain, they progressively invade it and replace it [2733], perhaps by secreting toxic substances [2732].

Experiments with implants of cell lines of tumors, induced by in ENU given transplacentally, in the brains of rats have demonstrated that there is a degradation of collagen I and III at the border zone between tumor and healthy tissue and that there is collagen of unknown origin in the extracellular matrix [2407].

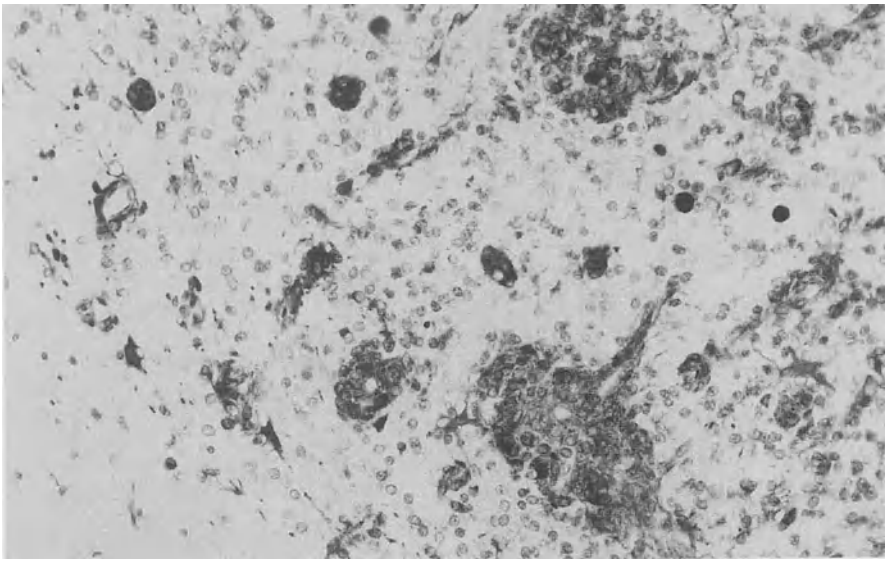


Fig.3.9. Rat transplacentally treated with ENU; proliferative centers of a microtumor containing vimentin-positive cells, PAP-DAB, ×300

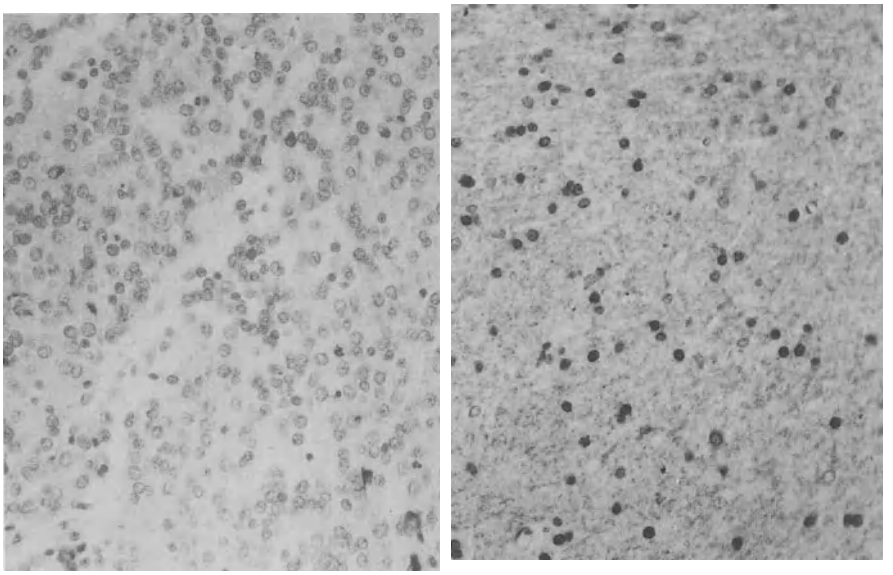


Fig.3.10a,b. Carbonic anhydrase C: **a** the cells are negative in oligodendroglioma; **b** in the normal white matter the cells stain positively, PAP-DAB, ×400

In early tumor proliferations, in oligodendroglial foci, and in isomorphous oligodendrogliomas, but not in polymorphous ones, an accumulation of glycosaminoglycans (GAG) has been found with alcian blue staining techniques [2487]. The hypothesis was that oligodendroglial cells underwent neoplastic transformation after having acquired during cytogenesis the capacity to interfere with the metabolism of the GAG, before and after myelinogenesis. In the rat, in fact, the myelination period and that of sensitivity to ENU overlap both in the brain [2503] and in the spinal cord [1993]. The involvement of oligodendroglia in neoplastic transformation had also been confirmed in the in vivo, in vitro system [282]. In the process of dedifferentiation this capacity may be lost.

This interpretation, however, is inconsistent with the observation that in man alcianophilia is found in all gliomas, hence also in astrocytomas [233]. It has been explained by the presence of normal nervous tissue included in the tumor and to degenerated areas of the tumor itself [925]. The same interpretations can be given to alcianophilia of ENU-induced tumors [1823], and the observations have been confirmed by histoautoradiographic studies with Na_2SO_4 and [3H]glycosamine [1811]. In MNU induced tumors, an accumulation of GAG in the tissue has been described as preceding their histological identification [715], while in ENU-induced tumors, this does not occur. It may also be that part of chondroitin sulfate, at least, is involved in cell proliferation [185]. Also, in experimental tumors, GAG may be involved in the relationship between cell motility and invasiveness and the intercellular matrix. They might be important in differentiating oncotypes.

3.1.2.3 Vascularization of ENU-induced Tumors

ENU-induced tumors transplanted into rats may grow up to 3–4 mm using host blood vessels; thereafter, they must form their own vessels. In the transplant, three zones are formed: an internal avascular one, an intermediate vascular one, and a peripheral one [596, 2034]. Buds and immature capillaries are formed in the peripheral zone by "sprouting" and are not dissimilar from those found during embryonal angiogenesis [1085, 40]. All these processes may be stimulated by angiogenic factors. During normal embryonal angiogenesis, the factor believed to be active only in the earlier phases in tumor angiogenesis, may also be active subsequently, hampering the differentiation of blood vessels. It has also been observed [597] that small blood vessels increase in the peripheral zone of the transplant, while endothelial hyperplasia is typical of the intermediate zone. In transplants of ENU-induced tumors in the rat, it has recently been demonstrated that there is no real increase in the number of blood vessels in the peritumoral tissue; on the contrary, there appears to be an increase in the diameter of the blood vessels towards the center of the tumor [1720]. These data are in agreement with observations on human tumors, which show that in the tissue immediately surrounding the tumor (BAT) and in the infiltrated cortex, the neoformation of small blood vessels does not precede—but follows—the infiltration itself [1626, 2521].

In tumors from rat glioma clones transplanted into the rat, a blood vessel density below that of normal tissue was found with an increase in the diameter of blood vessels [2586]. It must, however, be noted that in these experiments, because of their short duration, the three zones mentioned above have not been found. Similar experiments have demonstrated that the blood flow is low in both the central and peripheral zones and high in the intermediate one [3090].

3.1.2.4 Utilization of MNU-ENU Models

Models of autochthonous MNU tumors have been created [2535, 664]. The C6 clone obtained from a MNU induced glioblastoma [163] has been transplanted into the brain of rats in different therapeutic experiments [1370, 1254, 3103, 748], and the optimal conditions have been codified [2443].

ENU-induced tumors show a notable resemblance to human ones, but there are also many differences on the morphological level, in the prevalence of oncotypes, loca-

tion, multiplicity or uniformity [1570]. Fundamental is the consideration that ENU-induced tumors are produced by administering the carcinogen at a precise moment of cytogenesis, while human ones may derive through a constant exposure of target cells to possible carcinogens. Nevertheless, the pathogenetic mechanisms recognizable in the experimental model may be hypothesized for human tumors of the adult, but much less so for the infantile ones. The concept of genotypically transformed "stem cells" may explain the insurgence of tumors at any time.

The ENU model has been useful in neurooncology more for studies on the genesis of tumors than for therapeutic applications for which more simple and reliable models, such as the MNU or avian sarcoma virus (ASV) astrocytoma, are preferable [2556]. The occurrence of multiple tumors and the impossibility of knowing all tumor parameters in vivo are the most important failings. However, radiotherapy experiments utilizing explants of ENU-induced tumors have been carried out [895, 2703]. Irradiation after neonatal administration of ENU has caused a decrease in the incidence of the tumors [1461]. Carmustine (BCNU), lanustine (CCNU), and other chemotherapeutic derivatives of nitrosourea administered to rats born of ENU-treated mothers cause a decrease and a delay in the development of the tumors [2500]. If nerve growth factor (NGF) is administered before or after ENU, a lower number of neurinomas at the 90th day of e.u. life is obtained [2938].

3.2 Viral Carcinogenesis

Up to now, no virus has been etiologically associated with cerebral tumors in the traditional sense. Instead, it is possible to produce tumors experimentally with a certain variety of virus. Among DNA viruses, adenoviruses and papovaviruses are those most efficaciously used. Human adenovirus 12 causes tumors in various animals after intracerebral or intraorbital inoculation and after different latency periods. The tumors produced are malignant and undifferentiated, of sarcomatous type or neuroblastomas and retinoblastomas [1958, 1959].

With the same virus, PNS embryonal neuroepithelial tumors have been obtained in rodents after intraperitoneal inoculation [2064]. The tumors demonstrated multiple morphological differentiations. Simian adenovirus (SA7), which produces tumors difficult to classify [2664], simian virus 20 (SV20), chicken-embryo-lethal orphan (CELO) viruses, etc., have also been inoculated intracerebrally.

Papovaviruses isolated from human cases of progressive multifocal leukoencephalopathy produce tumors, among which are mainly cerebellar medulloblastomas [2112]. JC-, EK-, BK-, and MNV strains of papovavirus which produce ependymomas, have also been employed [495, 326]. Nonhuman papovaviruses such as the bovine papillomavirus (BPV) have also been demonstrated to be useful. Polyomavirus and simian vacuolating virus (SV40) have been tried as well (Fig.3.11). In particular, in hamsters, medulloblastomas were induced by JCV which is a human DNA virus of polyoma type.

Among the RNA viruses (oncoviruses, retroviruses) the avian sarcomavirus (ASV), the murine sarcomavirus, and the simian sarcomavirus have to be considered. The most

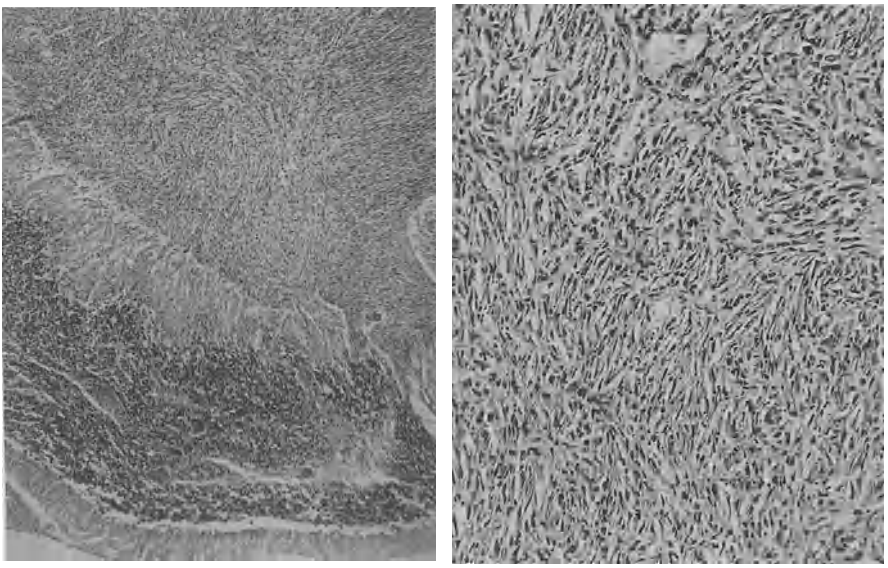


Fig.3.11a,b. Tumor induction by SV40 in hamster; **a** location in the posterior fossa, H&E, ×50; **b** meningiomatous aspect, H&E, ×200 [2486]

frequently utilized has been the ASV [492]. Since the first gliomas obtained by Rabotti and Raine [1964], the production of experimental tumors, especially with C and D subgroups, has been codified in different animals. Sarcomas have been obtained in the chicken, astrocytomas and sarcomas in mammals; in the dog and rat, most of the tumors have been anaplastic astrocytomas if the inoculation was into the cortex or the subependymal zone. The ASV model represents one of the best in that it fulfils a whole series of criteria: it is glial, spontaneous, and intraparenchymal, and it may be cultivated in vitro and transplanted subcutaneously or into the brain. It has allowed a whole series of immunological and chemotherapeutic experiments [205, 326].

Because of the biological similarities between monkey and man and the better possibility of manipulation in the former, an experimental model has always been advocated in this animal. Positive results have been obtained with the Rous sarcomavirus [1282, 1522, 2321]. The model seems to have been perfected in *Macaca fuscata* [2786].

3.3 Transplantable Animal Models

Various modalities have been followed. First of all, there are syngeneic tumors, i.e., tumors which are independently produced with chemical or viral carcinogens and then transplanted into syngenic animals. Another modality is that of heterotransplants carried out in immunologically incompetent animals or at such privileged sites as the brain,

anterior chamber of the eye, or facial pouch in normal animals. A typical example of an immunologically incompetent animal is the athymic mouse. The great advantage of these models is given by the uniformity of experimental conditions which can be obtained.

Among the syngeneic transplantable tumors there are, first of all, those induced in the rat with polycyclic hydrocarbons, such as murine ependymoblastoma and types 26 and 261 murine glioma, and those induced in the rat with nitrosourea, C6, 9L, and RG-2. Ependymoblastoma has been the object of numerous chemotherapeutic studies [2610, 91, 896], even though it is hardly comparable with human tumors.

Among nitrosourea-induced tumors, the most frequently used have been the C6 glioma, the MNU-induced 9L gliosarcoma, and the ENU-induced RG-2 glioma. The C6 has been found to be unstable in its cellular type [515]; however, it has been used in different experiments for various purposes [1369, 1368, 748, 3103, 1254]. The model characteristics have been improved in order to use it for therapeutic studies [2443]. The 9L has found more consensus for kinetic cellular studies, radiotherapy, and chemotherapy [2362]. The RG-2 has a stable cellular population [3000].

Other syngenic models include the spontaneous murine VM astrocytoma which occurs in inbred VM-dk mice [815] and the anaplastic astrocytoma induced by the Schmidt-Ruppin ASV. The spontaneous VM mouse astrocytoma corresponds to the criteria of the ideal model of Wilson [3052], because it is glial and spontaneous. It was seldom used as it was limited to in vivo experimentation. Cell lines have, however, been established [2594] and characterized [2203, 2204]. The cells which most resemble normal astrocytes are the less tumorigenic ones if injected intracerebrally in syngeneic animals, while the opposite holds true for the less differentiated ones. This line, VMDKP 497, is heterogeneous and has produced six clones different from each other [562], with characteristics varying from astrocytic to anaplastic. Five of these have been found to be tumorigenic when injected into syngenic animals [1483].

The heterotransplants have received a great impulse because of the advent of the "nude mouse" model, into which both tumors and permanent cultured cell lines may be directly transplanted: The morphology, karyotype, and antigenic model are maintained. Glioblastomas, astrocytomas, gliosarcomas, meningiomas, etc., have thus been grown. In general, the constancy of the morphological similarity with original human tumors has been emphasized [2270, 2982], even if different opinions are not lacking [2289]. Chemotherapy [2556] and radiotherapy [2612] evaluation studies have been carried out with these models. Cell lines derived from gliomas grow without changing their morphology.

3.4 Gene Transfer Models of Neural Tumors

Experimental models obtained by genetic manipulation appear to be higly promising for identifying in vivo effects of isolated genes and for studying molecular pathogenetic mechanisms. Transgenic mice are obtained by microinjection of genetically manipulated embryonal stem cells into fertilized murine ova [1274A]. As a consequence of the

stable integration of DNA in the zygote, all somatic and germ cells of these animals contain single or multiple copies of the transgene. A different method of gene transfer, which gives rise to chimeric animals, employs introduction of DNA constructs into embryonal stem cells and transfer of these cells into blastocyst stage embryos [2962A]. Recently, a third experimental model has been developed which utilizes a retrovirus-mediated gene transfer into neural transplants [1443A, 19]. Using a replication-defective retroviral vector, foreign transforming genes are introduced into fetal rat brain cells wich are grafted intracerebrally into syngenic host animals. These transplants develop with formation of pseudocortical highly differentiated architectures and provide a good model to study the expression of retrovirally transmitted genes in different CNS cell types. Several oncogenes have been introduced by this route into fetal brain transplants (polyoma *medium T* gene, v-*src*, human K-*fgf/hst*, SV40 *large T* gene, v-Ha-*ras*, v-*myc*), demonstrating a cell-type specific transformation potential [3036A]. Hemangiomas and anaplastic gliomas have been obtained with polioma *medium T* gene, different glial tumors and sarcomas with v-*src*, and capillary angiomas with K-*fgf/hst*, a protooncogene encoding a member of the fibroblast growth factor family. Transfer of SV40 *large T* gene into CNS grafts produced primitive neuroectodermal tumors similar to human medulloblastomas [19]. In agreement with this finding, different recent experiments using transgenic mice indicate that the expression of SV40 *large T* antigen can induce brain tumors such as primitive neuroectodermal tumors of the pineal gland, retinoblastomas, and choroid plexus papillomas [2830A, 1485A, 288A, 1877A].

The simultaneous introduction of v-Ha-*ras* and v-*myc* into fetal brain transplants have demonstrated a significant complementary transforming effect of these two oncogenes [19]. In fact, the simultaneous expression of both oncogenes in fetal brain transplants induced, after a short latency period, multiple highly anaplastic undifferentiated tumors, composed of cells with a limited potential for astrocytic differentiation. On the contrary, transfer of retroviral vectors harboring only v-*gag/myc* sequences produced rare tumors with features of primitive neuroectodermal tumors, whereas v-Ha-*ras* alone induced anaplastic astrocytomas after a long latency period [3036A]. A complementary transforming effect of *ras* and *myc* has been observed also in later stages of CNS development [3036A]. Microinjection of the retroviral vector harboring both oncogenes into the brain of newborn rats, induced different tumors, including primitive neuroectodermal tumors, hemangioendotheliomas and gliomas. The occurrence of primitive neuroectodermal tumors in this experiment is of particular interest because it suggests that neural progenitor cells, which are the target of the neoplastic transformation, persist in the newborn rat brain [3036A].

4 Antigens of Phenotypic Expression and Differentiation Markers

The diagnosis of brain tumors is based on the recognition of phenotypes which are typical of a cytogenetic line in a given differentiation stage. This recognition is not easy, because the nervous system is composed of a variety of cell types which may derive from common precursor cells. Neoplastic transformation modifies cell phenotypes, usually towards less mature stages. It would be very useful to have markers which characterize every cytotype in the different maturation stages or even only specific markers of some oncotypes.
The study of structural and surface antigens has produced a tremendous amount of data in this field. The technology of monoclonal antibodies (Mabs) has provided a large quantity of antibodies towards specific antigenic determinants. Of particular value has been the identification of various antigens of nervous cytotypes during cytogenesis [2250, 699, 1554, 814, 1086, 1381, 2463, 2547, 1141], even though they have been studied mostly in normal cells in culture and only rarely in tumors.

4.1 Brain Tumor-Associated Antigens

In the late 1960s glioma-specific rabbit sera began to be produced [1733, 1732, 463], but the results were poor, because they contained a heterogeneous mixture of antibodies without a tumor specific binding. The technique of Mabs represented a great improvement in this regard and today the number of Mabs against tumor-associated antigens is countless. It goes beyond the goal of this book to list them. It must be said that their specificity is evaluable only in relation to the patterns of staining described in the different tissues and under particular physiological and pathological conditions. It may also happen that Mabs produced in different laboratories, and differently labeled, recognize the same antigens. Complete reviews of these problems are available [594, 327, 464, 3040, 593].

Most antibodies against tumor-associated antigens recognize the following categories of antigen: (a) biochemically defined antigens, including structural proteins, such as intermediate filaments, or enzymes, like neuron specific enolase; (b) antigens common to different tumors and tissues of neuroectodermal origin, both central and peripheral [1641, 359, 3101, 594]; (c) glial antigens, expressed mainly by glioma cells, but also by reactive astrocytes and other nonneuroectodermal tissues [593]; (d) oncofetal antigens, typical of fetal tissues and expressed in the adult only in tumor cells [3039]; (e) lymphoid differentiation antigens, expressed by circulating lymphocytes and by cells of malignant gliomas [998, 1379, 593], such as HNK-1 antigen.

The possibility of utilizing them in vivo for diagnostic purposes is limited. Tumors and especially gliomas are heterogeneous and antigenically complex [2603, 204, 3038, 3040], so that the probability for an antigen to be expressed in the same way by all gliomas of a given type is not high; moreover, the quantity of cells expressing a single antigen in a glioma cannot be determined.

Mabs are often produced from cultured tumor cells which represent only partially the antigenicity of the tumors in vivo. The growth in vitro, moreover, can modify the cell surface, either introducing new antigens or eliminating antigens, so that the antigenic heterogeneity may be increased [3040]. Most antigens are expressed also by normal cells in various tissues, and all the possible specificities of Mabs against tumor-associated antigens can be demonstrated only by in vivo studies, while not considering the fact that surface antigens usually do not tolerate routine fixation and embedding procedures.

The pattern of expression in human astrocytomas of two typical cell-surface antigens (A4 and A010) has been recently described [881]. It has been shown that they are expressed in a large proportion of astrocytomas as well as in some normal cells of different origin.

4.2 Antigens Employed in the Histological Diagnosis of Brain Tumors

Currently, the number of markers used is slightly less than 20. Complete reviews are available on this subject [251, 580, 2512, 2181, 1821]. Immunohistochemistry is today routinely applied and must be regarded as an indispensable diagnostic tool; however, some precautions must be taken. Polyclonal antisera contain a large amount of immunoglobulin (Ig) against different regions of the same antigenic molecule and also against molecules different from the antigen employed in the immunization. Mabs contain one type of Ig against a single epitope, so that they are more specific, even though their specificity is not absolute.

Applying immunohistochemistry to brain tumors, it is necessary above all to demonstrate the specificity of Mabs, since rat Ig may nonspecifically bind astrocytes and myelin sheaths [2101, 2179]. This can be obtained by immunoblotting; controls, moreover, must be performed by preabsorbing primary antibodies with the corresponding antigen or substituting the antibody with class-specific Ig. It must be taken into account that Mabs are more specific than antisera, but generally they are also less sensitive [1125], so that in material processed for histology, since the epitope may be destroyed or lacking, an antigenic protein has a greater probability of being revealed by antisera. The best "immunohistochemical reagent" would be a mixture of Mabs against different antigenic determinants of the same molecule [251].

In histological material, many antibodies are useless because of false negative reactions due to fixation. All fixatives affect the molecular structure of antigens to greater or lesser degree, destroying the antigenic sites or simply masking the antigen or making it inaccessible to antibodies [307, 1875, 1824, 2245]. Sometimes it is useful to perform

a predigestion of the tissue in order to avoid the antigen masking [307, 1875, 1840, 1824]. This can be done, for example, for factor VIII/RAg, fibronectin, and laminin with collagenase [1824]. However, many antigens do not tolerate fixation, so they must be demonstrated on frozen sections. This is true especially for surface antigens. It is interesting to note that 35 different Mabs against intermediate filaments systematically studied on cryostat sections of brain tumors gave unexpected reactivities. Four major sources of the artifactual staining were found, suggesting care is indeed needed in interpreting immunohistochemical results in brain and tumors [813A].

4.2.1 Glial Markers

4.2.1.1 S-100 Protein

S-100 is an acid protein of low molecular weight (20–25 kDa). The name is due to its solubility in 100% ammonium sulfate [1997]. Considered at first as specific for the nervous system, it has now been found in many normal, nonnervous cells: chondrocytes, adipocytes, myoepithelial cells of the mammary gland, Langerhans cells, melanocytes, etc. There is no general agreement regarding its occurrence in neurons [2787, 1233]. It is considered more a glial than a neuronal marker, being positive in astrocytes (Fig.4.1) [1817, 1708, 1233], oligodendrocytes [1708], and ependymal cells [1997]. In the PNS, Schwann cells and satellite cells are positive [1996, 2723].

From the many studies on cerebral tumors [1041, 2000, 3011, 2793] it can be deduced that: (a) in astrocytic tumors the protein content decreases with increasing anaplasia, so that in glioblastoma there are few positive cells; in ependymomas and oligodendrogliomas only occasionally are positive cells found [710]; (b) neurinoma cells are strongly positive [2723], but the usefulness of the marker in the differential diagnosis of the malignant form is limited [2723, 3011].

The documented occurrence of the protein in many extranervous tumors, carcinomas included [1996, 1997, 3011], obliges one to use great caution in the diagnosis of brain tumors [251, 725].

4.2.1.2 Glial Fibrillary Acidic Protein (GFAP)

Glial fibrillary acidic protein (GFAP) is the most studied and utilized glial marker. Its partially hydrosoluble protein was initially purified from plaques of multiple sclerosis [713] and subsequently also from normal white matter [551]. The molecular weight is about 50 kDa, and the protein represents the chemical subunit which characterizes gliofilaments. The latter are a subclass of intermediate filaments (IF) which includes a group of filamentous proteins with a diameter of ≈10 nm. The other IF are vimentin, neurofilaments (NF), desmin, and keratin, each of which shows a peculiar cell distribution [861, 1590, 987]: GFAP is present only in glial cells, NF only on neurons, desmin in the muscle tissue and keratin in epithelial cells. Vimentin, mainly found in mesodermal cells, has been identified in cells of every embryologic derivation and, characteristically, in vitro cultured cells [813].

Proteins of the different IF belong to a multigenic family and share some amino acid sequences [2244, 892], so that immunohistochemically some antisera and Mabs may

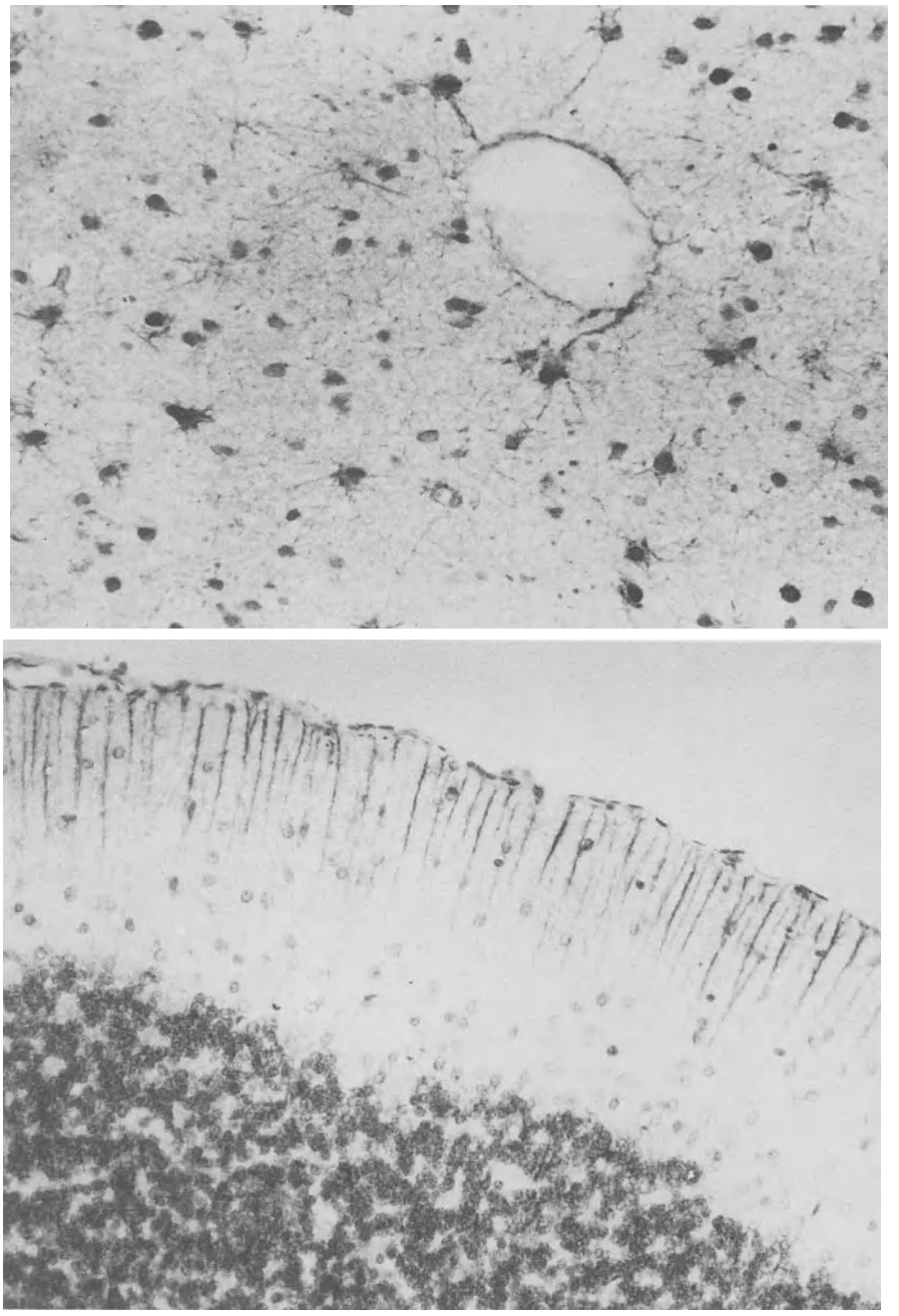


Fig.4.1. a S-100 protein: positive reactive astrocytes, PAP-DAB, ×30. **b** GFAP-positive Bergmann's glia, PAP-DAB, ×300

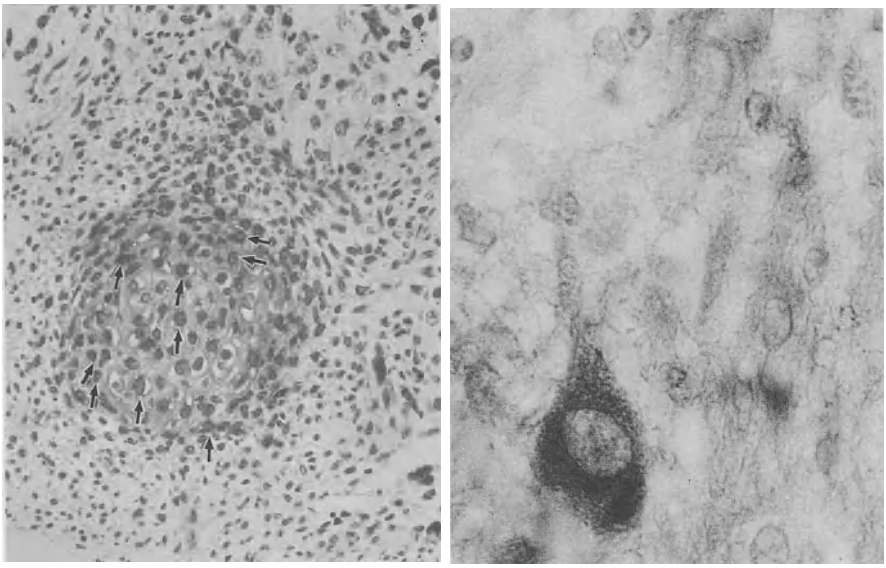


Fig.4.2. a GFAP-positive cartilage in a teratoma, PAP-DAB, ×200. **b** NSE-positive reaction in neurons of a gangliocytoma, PAP-DAB, ×1000

react with more than one IF. There may be a cross-reaction for GFAP and vimentin for every antibody produced against both antigens [2244, 2266].

In the CNS, antisera and Mabs against GFAP stain specifically normal astrocytes of the gray and white matter and Bergmann's glia in man, mammals, and other vertebrates [551] (Fig.4.2). Occasionally, unexpected staining has been observed outside the CNS: Schwann cells, enteric cells, cells of salivary gland tumors [322], chondrocytes of normal epiglottis and of cartilage tissue found in glial tumors [1399] and in teratomas [1821, 2053] (Fig.4.2a).

The interpretation of these findings is not easy, once proven that they are not artifactual. However, the usefulness of GFAP as a marker of glial tumors remains beyond doubt.

GFAP in brain tumors has been widely studied [680, 1819, 603, 2903, 581, 2923, 1027, 2509]. It is positive in all astrocytic tumors (Fig.4.3a), pleomorphic xanthoastrocytoma [1395], subependymal giant cell astrocytoma [1999, 255], astroblastomas [603, 1027, 2509] and subependymomas [2509] included, as well as in the glial component of gliosarcomas, sarcogliomas and gangliogliomas [1556, 2511]. Also, ependymomas and oligodendrogliomas contain GFAP-positive cells [603, 712, 1115, 681, 581] for reasons which will be discussed in the relevant chapters.

Nonglial tumors may also contain GFAP-positive cells, such as cerebellar hemangioblastomas [603, 602, 37], medulloblastomas [1756, 2126, 2526, 926, 2344], and plexus-papillomas [2398, 2811]. In the first tumor, reactive astrocytes or stromal cells which phagocytosed GFAP from the microenvironment [602, 2512] may be responsible; in plexus-papilloma GFAP is sometimes coexpressed with cytokeratin [642] and is inter-

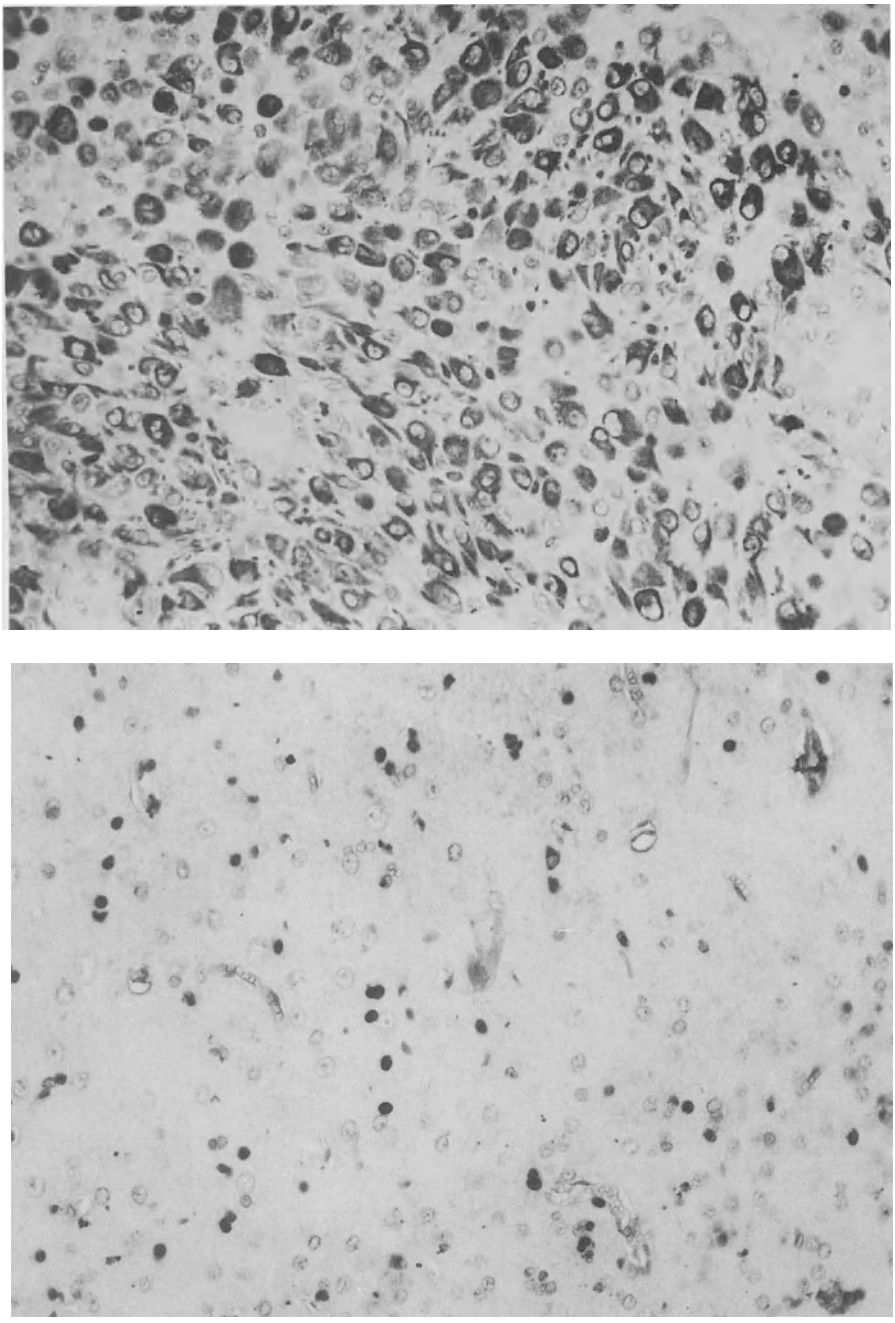


Fig.4.3. a GFAP-positive reaction in tumor astrocytes and their processes in human astrocytoma, PAP-DAB, ×400. **b** Carbonic anhydrase C-positive reaction in normal oligodendrocytes of rat brain, PAP-DAB, ×400

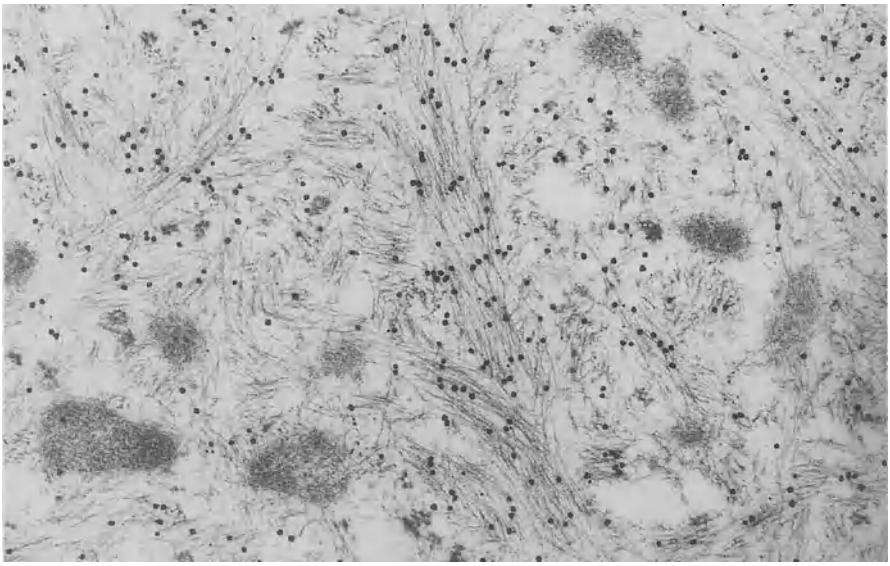


Fig.4.4. Human astrocytoma; immunogold staining for GFAP on IF, ×60 000

preted as a sign of focal ependymal differentiation. Neurinomas also may contain GFAP-positive cells [2814, 1865, 981, 2290] in line with the positivity of some normal Schwann cells [554, 1312, 8].

With immunoelectron microscopy, GFAP can be demonstrated by the immunogold technique on IF [1885] (Fig.4.4).

4.2.1.3 Glutamine Synthetase

Glutamine synthetase (GS) is an enzyme which has been localized in glial [2048] and retinal cells and has been considered as a specific marker for rat CNS astrocytes [2047]. It is diffusely positive in astrocytomas, inversely proportional to anaplasia, scarcely positive in ependymomas, and negative in oligodendrogliomas and meningiomas. Groups of cells may be positive in medulloblastoma. The usefulness of GS in the diagnosis of brain tumors is limited by the observation that the enzyme is also positive in such cells of other human tissues as hepatocytes [2202].

4.2.1.4 Carbonic Anhydrase

Carbonic anhydrase (CA.C) is an enzyme which is widely diffused in nature. It occurs in animal cells as two isoenzymes. In the CNS the isoenzyme C is present, localized in the human [1532] and murine [1531] oligodendroglia (Fig.4.3b) and in Müller's cells of the retina. Human and experimental oligodendrogliomas, however, do not stain [928].

4.2.1.5 Myelin Basic Protein

Myelin basic protein (MBP) is present in the rat myelin by the 10th day of e.u. life. It has been immunohistochemically demonstrated in the cell body and processes of oligodendrocytes of the newborn rat [2736, 2737]. It is seen also in human immature oligodendrocytes, but never in the human adult oligodendroglia [1262]. There is some evidence of MBP positivity in human oligodendrogliomas [1869]. We and others have found these tumors to be MBP-negative [251, 580].

4.2.1.6 Myelin-Associated Glycoprotein

Myelin-associated glycoprotein (MAG) is present in central and peripheral myelin, in Schwann cells, and in immature oligodendroglia. It is correlated with antigen HNK-1 and recognized by antibody Leu-7, which in turn also recognizes an epitope of MAG [2041]. Human oligodendrogliomas are generally MAG-negative [2420].

4.2.2 Neuronal Markers

4.2.2.1 Neuronal-Specific Enolase

Enolase isoenzymes are a group of 5 dimeric proteins, a combination of 3 subunits from 40 to 50 kDa, belonging to the glycolytic pathway where they catalyze the interconversion of 2-phospho-d-glycerate and phosphoenolpyruvate [1762]. Neuronal-specific enolase (NSE) is a homodimer composed of 2 χ-subunits, once called protein 14.3.2. Under normal conditions NSE is restricted to CNS and PNS neurons, but when applied to tumors it gave good results [251]. Cells of the APUD system also showed positivity for the markers [1762]. This has been regarded as a specific marker of neurons, axons, and neuroendocrine cells [2530, 1678]. Widely used in the diagnosis of neuroendocrine tumors, its usefulness in diagnosing brain tumors is controversial, because although it may be positive in tumors with neuronal differentiation (Fig.4.2b) such as medulloblastomas or central neuroblastomas, it may also be positive in normal nonneuronal cells [1042], in reactive astrocytes of malignant glial tumors and in nonneuroepithelial tumors [251, 2597]. Its specificity may be strongly decreased in pathologic conditions and tumors, even though different staining patterns and specificities have been shown between Mabs and polyclonal antisera [2597].

4.2.2.2 Neurofilaments

Neurofilaments are the IF of neurons, composed of a triplet of proteins of different molecular weight, 68, 150 and 200 kDa. These proteins are not regularly distributed, either among the different populations of neurons or inside single neurons. The 200 kDa subunit is the main component of axons and not observed in dendrites or cell bodies of cortical or hippocampal neurons, whereas the 68 kDa subunit is typical of cell bodies and dendrites of Purkinje cells (Fig.4.5). Very important for their localization is the phosphorylation of NF: Phosphorylated and nonphosphorylated forms distribute differently

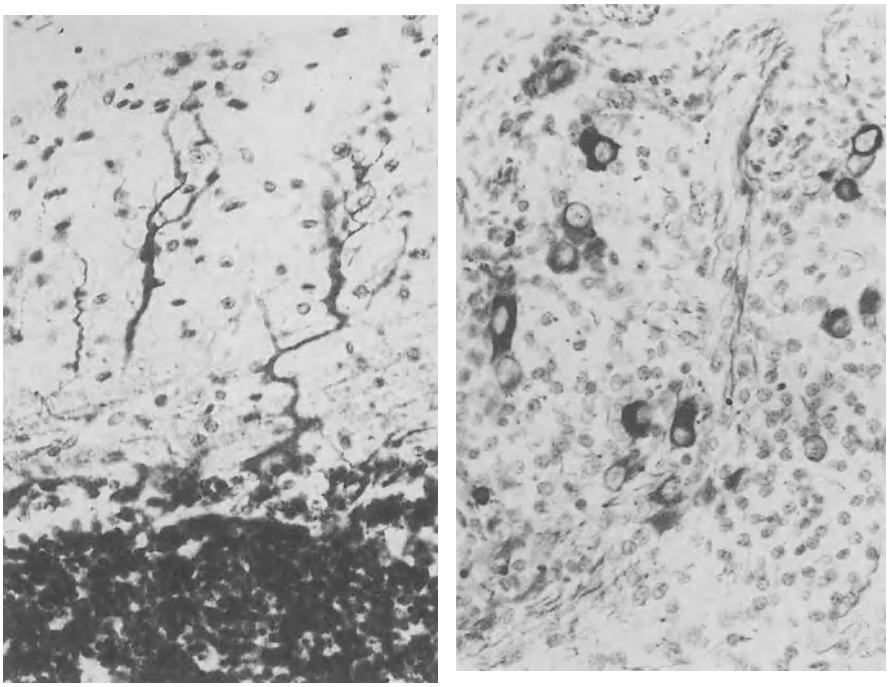


Fig.4.5a,b. Positive reaction for NF in **a** apical dendrites of Purkinje cells and **b** neurons of a teratoma, SM31 antibody, ABC-DAB, ×400

in axons and cell bodies [2735]. In human tumors, NF are positive when ganglion cells or a neuronal differentiation are present, such as ganglioneuroblastomas, gangliocytomas, gangliogliomas, pheochromocytomas [2344, 1957, 1821, 2867, 2868], teratomas (Fig.4.5b), and in tumors of neuroendocrine origin, such as carcinoid tumors, paragangliomas, and oat-cell pulmonary carcinomas.

Paraffin embedding and fixation are limiting factors in the demonstration of NF. In frozen sections they are, in fact, demonstrable in many tumors and reveal a neuronal differentiation where it was not suspected [983], for example, in primitive neuroepithelial tumors.

4.2.2.3 Synaptophysin and Chromogranin

Synaptophysin is a 38-kDa glycoprotein found in synaptic vesicle membranes [3034, 1276, 1892] and playing a major role in synaptic vesicle exocytosis [2865], which appears to be a reliable and specific marker for neuronal and neuroendocrine tumors, useful in fixed and paraffin-embedded tissues [1892]. It has been demonstrated in gangliogliomas, gangliocytomas, PNET, including medulloblastomas [2574, 983], and neurocytomas [2949]. Its expression is prominent in ganglion cells of these tumors, due to their increase during maturation. The reliability, however, is reduced when ganglion cells are absent.

Chromogranin is the major protein isolated from vesicles in adrenal chromaffin cells [2694]. It has been demonstrated in a variety of neuroendocrine cells and tumors, and also in neurons of the CNS and PNS, but never in tumors of the CNS.

4.2.3 Markers Nonspecific for the Nervous System

HNK-1 (Mab Leu-7) was at first considered a marker specific for human natural killer cells. Since it also reacts with myelin, oligodendrocytes, and Schwann cells, HNK-1 has been proposed as a marker for oligodendrogliomas [1952]. Leu-7 has actually been shown to stain human oligodendrogliomas intensely, as well as other neuroectodermal tumors [2180, 2290] and carcinomas of various origin. In spite of the diffuse cross-reactivity, it is considered useful to solve specific problems, for example, the distinction between a Leu-7-negative meningioma and a positive oligodendroglioma invading the meninges [2394].

Anti-Leu-M1 (MMA) is another hematopoietic-specific antibody which cross-reacts with anti-Leu-7 and anti-Leu-11a (NKP-15), is partially positive in astrocytomas and oligodendrogliomas, and is intensely positive in ependymomas [2785]. It recognizes cell surface epitopes of monocytes, granulocytes, and activated T lymphocytes [1056].

4.2.4 Vessel Markers

Neovascularization and endothelial proliferation are characteristic of many brain tumors, and thus the recognition of endothelial cells may be of great importance. The antigen correlated with factor VIII of coagulation (FVIII/RAg) is the most often used endothelial marker. It is one of the components of factor VIII (anti-hemophiliac factor) and is produced only by endothelial cells and megacaryocytes. It is specific and widely employed in the demonstration of endothelial differentiation in many extranervous tumors [1955].

In gliomas, the marker identifies endothelial cells of normal vessels as well as of the proliferating ones (Figs.4.6–4.8) [3015, 1841, 1824, 2511]. It is found in Weibel–Palade bodies and in large intracytoplasmic vacuoles which discharge into the lumen (Fig.4.7). In the glomeruli of glioblastoma, it reacts positively only in the cells lining the lumen and not in those far from it [3015]; however, by immunoelectron microscopic procedures employing colloidal gold, it has also been found in Weibel–Palade bodies of cells which do not line the lumen (Fig.9.33) [1886].

Laminin and fibronectin are of great help in the study of the vasculature of tumors. Laminin is a glycoprotein occurring only in basal lamina. In the CNS, it can be demonstrated only around vessels (Fig.4.8a) or between neuropil and pial membrane [927]. In gliomas, antibodies to laminin demonstrate thickened and pluristratified basal membranes in and around endothelial proliferations. An inner, thickened membrane appears to be separated by the vessel wall from an outer, often interrupted membrane, in turn separating the vessels from the neuropil [927] (Fig.4.8b).

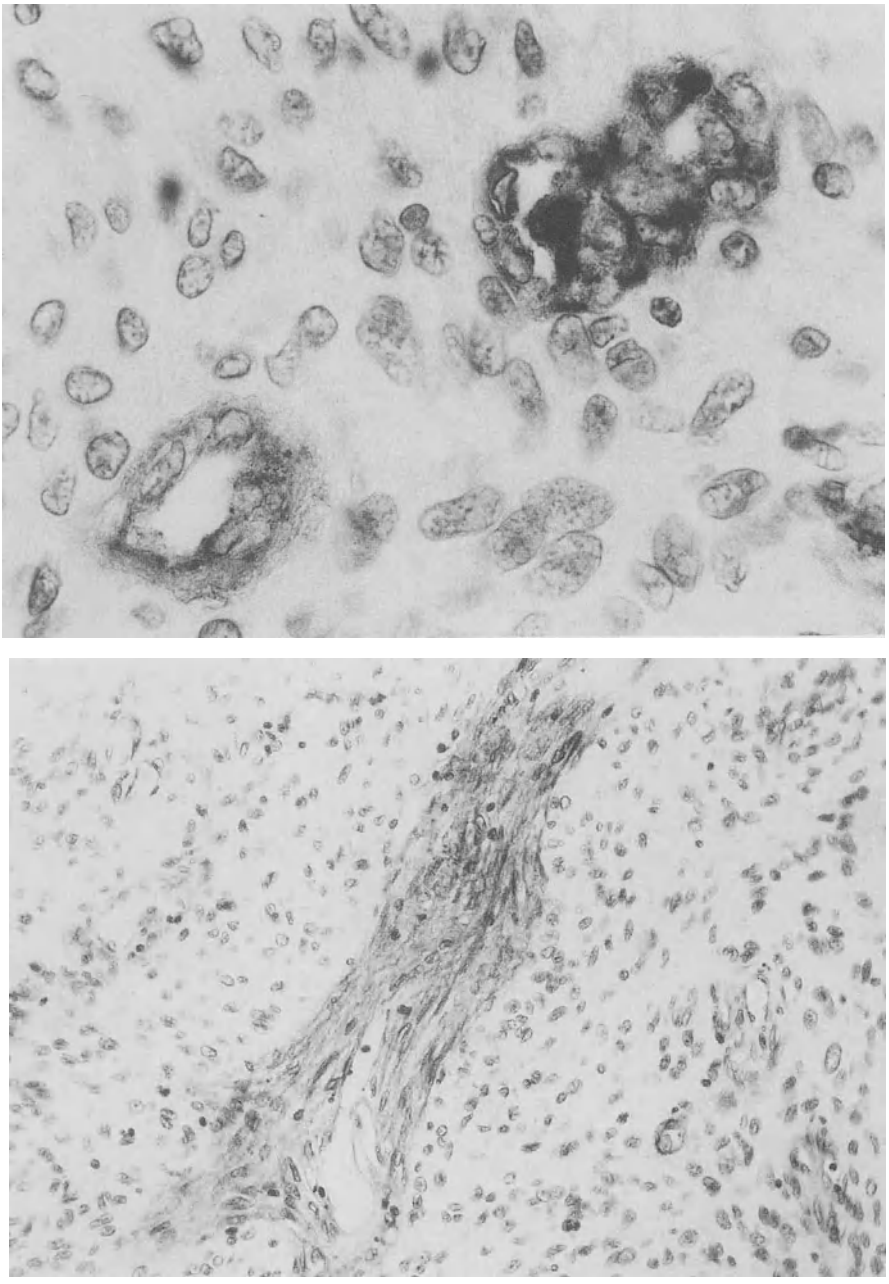


Fig.4.6. **a** Positive reaction for factor VIII/RAg in hyperplastic endothelial cells in a malignant glioma, PAP-DAB, ×1000. **b** Fibronectin-positive reaction in the mesodermal component of gliosarcoma, PAP-DAB, ×200

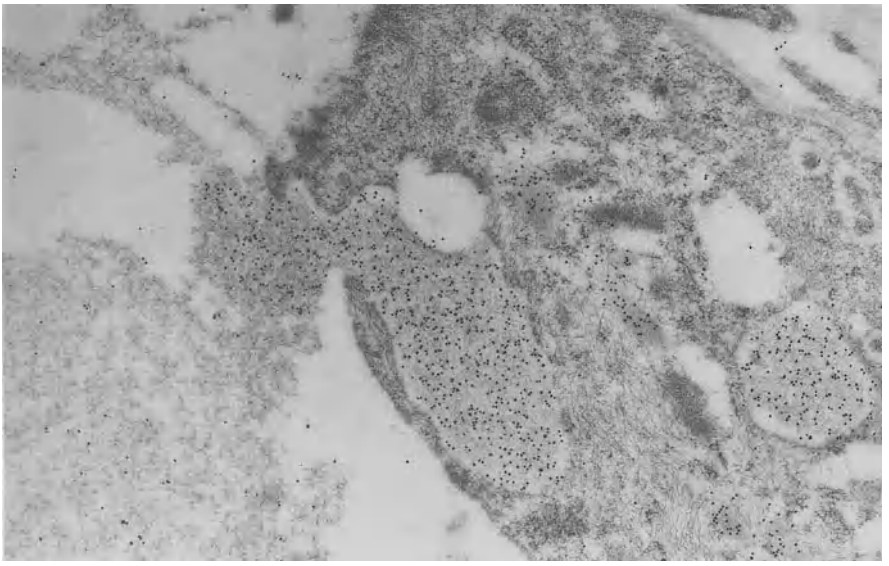


Fig.4.7. Immunogold staining for factor VIII/RAg in a large cytoplasmic vacuole of an endothelial cell discharging into the lumen, ×24 000

Fibronectin is a protein widely distributed in connective tissue, demonstrable not only in basal membranes but also in the CNS vessel walls. Even though its positivity in astrocytic cells in culture has been shown repeatedly, it is not positive in astrocytes in histological sections. In gliosarcomas, the mesodermal component is diffusely positive for fibronectin (Fig.4.6b), thus being differentiated from the glial one, which is GFAP-positive [2511].

4.2.5 Other Intermediate Filaments

Vimentin is a protein of 57 kDa; it is the first IF to appear in the course of development, regardless of the cytotype. In adult cells, it is usually replaced by the IF characteristic of each cell type; however, it remains the only IF of endothelial cells, fibroblasts, macrophages, chondrocytes and lymphoid cells. In some cell types, vimentin coexists with another IF: In the CNS, this coexpression occurs in astrocytes and tanycytes which contain concurrently vimentin and GFAP or cytokeratin [2546, 2266]. During development, the appearance of vimentin precedes that of GFAP in astrocytes [553, 2546, 753]. In normal glia, it is weakly positive, but in reactive astrocytes it is intensely positive (Fig.4.9b) [2513, 2514]. Vimentin is demonstrable in gliomas in both endothelial (Fig.4.9a) and tumor cells, where it distributes like GFAP [1117, 2513]. Its occurrence, therefore, cannot be considered as a sign of immaturity in gliomas: the cells should be immature for the occurrence of vimentin and differentiated for that of GFAP at the same time. Meningioma and neurinoma cells are also intensely positive for vimentin [2266,

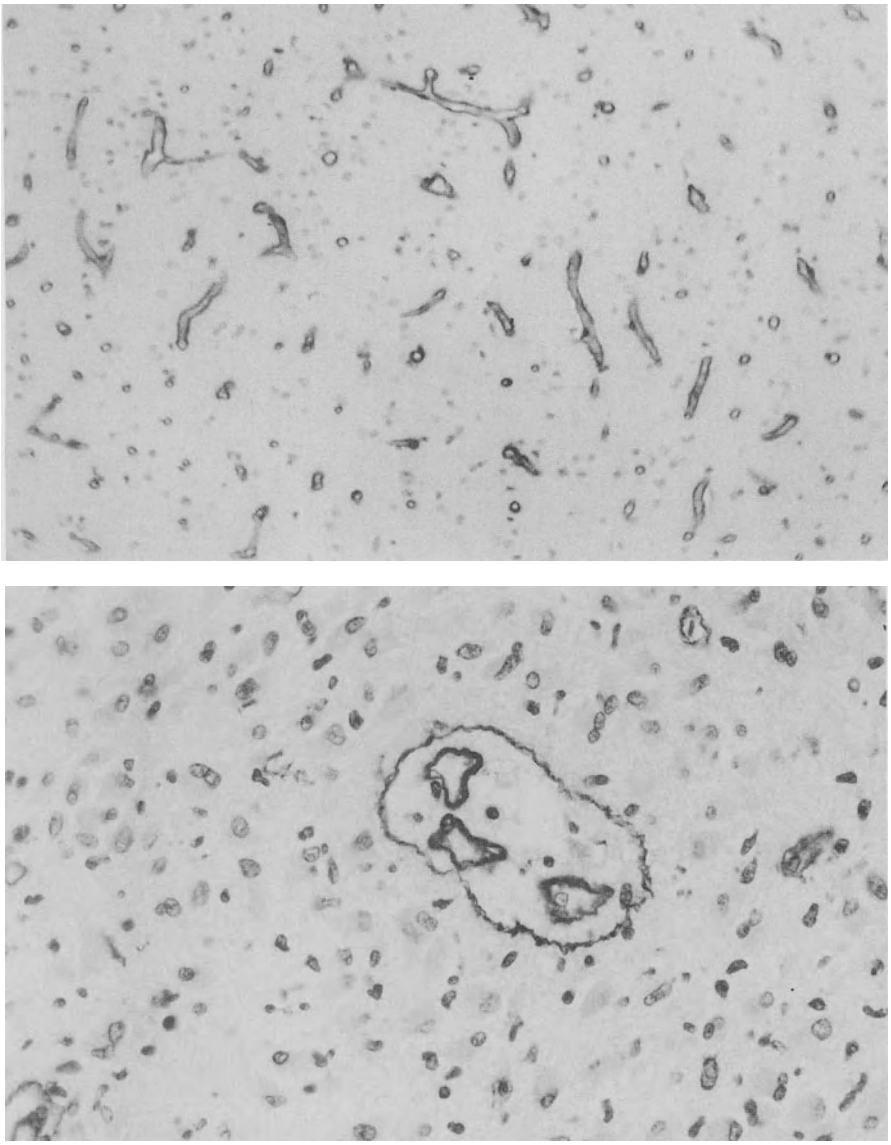


Fig.4.8a,b. Laminin-positive reaction **a** in the basement membrane of capillaries in the normal cortex, PAP-DAB, ×300, and **b** in the inner and outer basement membranes of the vessel wall in gliomas, PAP-DAB, ×400 [927]

1687, 2513]. The same is true for stromal cells of hemangioblastomas [2513] and chordoma cells [1884].

Since most carcinomas contain cytokeratin, independent of the degree of differentiation [251], antibodies to it can be used to recognize carcinoma metastases (even undifferentiated) in the CNS. Also cells of epithelial origin, such as those of craniopha-

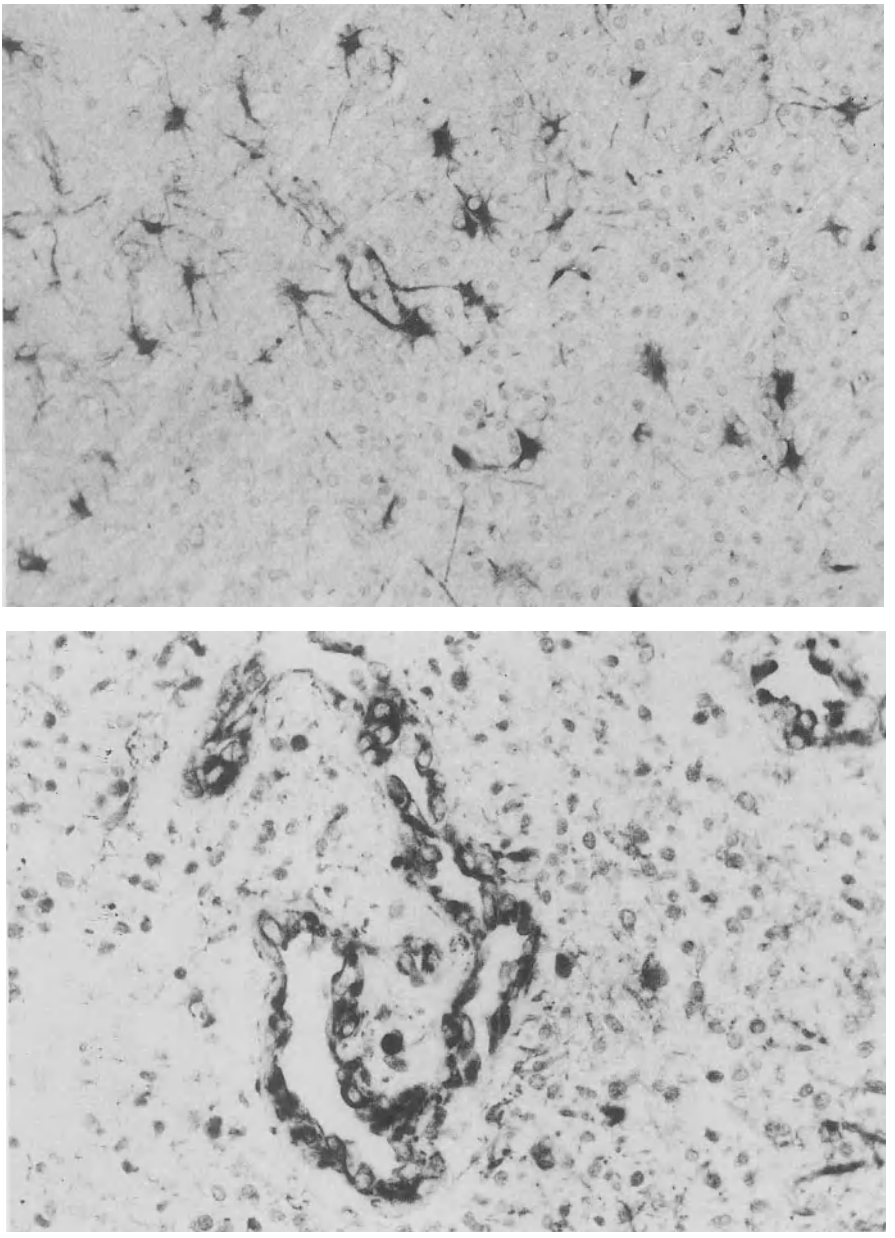


Fig.4.9a,b. Positive reaction for vimentin in **a** hyperplastic endothelial cells in a glioma, PAP-DAB, ×400; **b** peritumoral reactive astrocytes, PAP-DAB, ×400

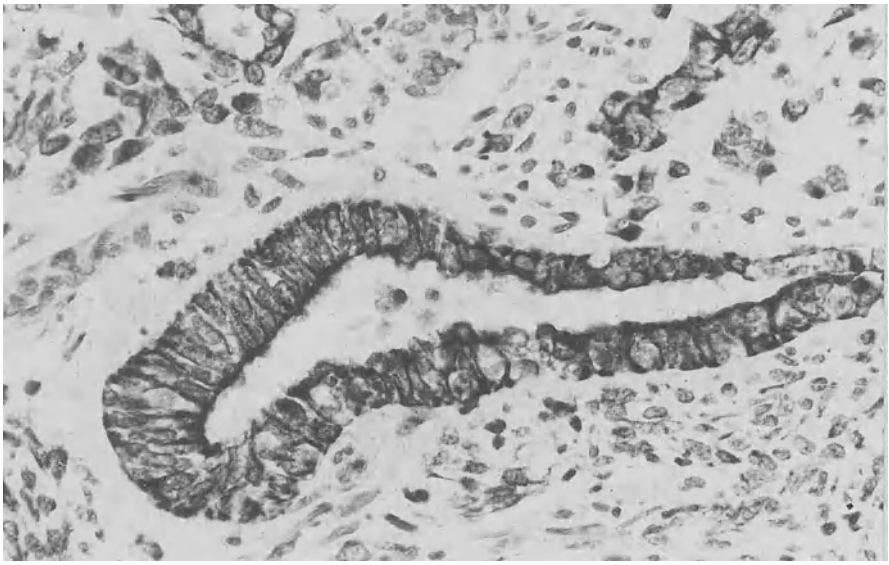


Fig.4.10. Positive reaction for cytokeratin in epithelial cells of a teratoma, PAP-DAB, ×300

ryngioma, dermoid and epidermoid cysts, and teratomas may similarly be recognized (Fig.4.10). Positive staining for cytokeratin may also be observed in meningiomas [1859, 2829, 1173] and in epithelial-like foci of glioblastomas and gliosarcomas [1946].

The usefulness of desmin, the IF typical of muscle cells, is limited in the tumor pathology of the CNS because it occurs only in the very rare rhabdomyosarcomas [1884].

4.2.6 Epithelial Membrane Antigens

Epithelial membrane antigen (EMA) is a membrane glycoprotein occurring in most normal and tumor epithelial cells. Positive staining for it is characteristic of a carcinomatous metastasis, but it may also be observed in meningiomas [1859, 2543, 2829] and in epithelial-like structures of glioblastomas [1946].

Two other markers need to be mentioned, α-fetoprotein (AFP) and human chorionic gonadotropin (HCG), which are specific for germ cell tumors. AFP is usually not found in pure germinomas [1540], but it is positive in embryonal carcinomas and endodermal sinus tumors [3105, 2049, 1540]. HCG has been demonstrated in choriocarcinomas and in trophoblasts occurring in tumors mixed with germ cells [2049].

5 Pathology of the Host–Tumor Interaction

5.1 Peritumoral Changes

5.1.1 Glial Reaction

Peritumoral tissue changes are related to various factors: edema, anoxia due either to edema or compressive action of the tumor, the release of substances from the destruction of tumor cells, etc. The most important change is glial reaction. This is a progressive or progressive-regressive process, the intensity of which varies in relation to a large number of events. The main aspect is the appearance of reactive astrocytes, either with much cytoplasm and short processes (Fig.5.1a) or with thick and long processes (Fig.5.1b). They are found in the peripheral parts of the tumor, in the immediate peritumoral area, or even at a distance. The first is typical of invasive tumors, whereas the latter two are typical of sharply delimited tumors.

Hypertrophic reactive astrocytes are easily recognizable with silver impregnation techniques (Fig.5.2) and by their intense GFAP reactivity. They are also positive for vimentin. The less recent literature described them as strongly positive for oxidative enzymatic activities [828, 2489, 2404] with all the importance that such high metabolic

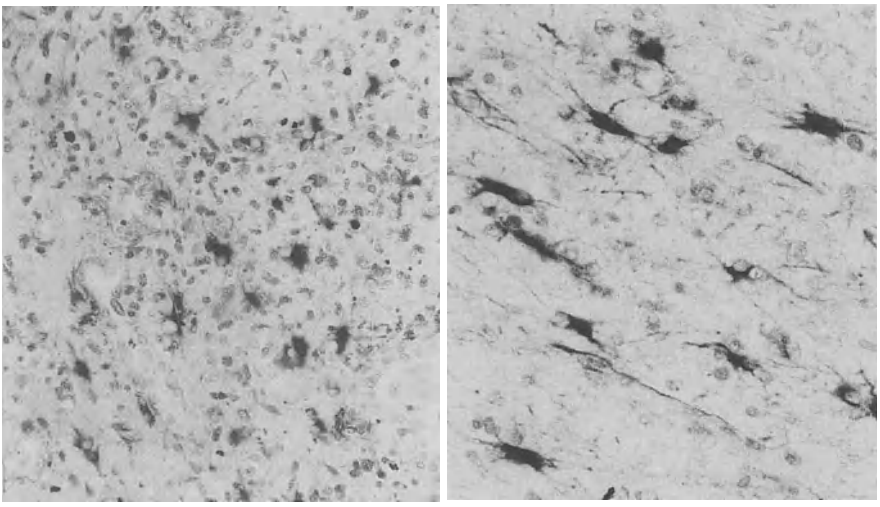


Fig.5.1a,b. GFAP-positive staining in **a** reactive astrocyte in the periphery of a glioma, PAP-DAB, ×300; **b** hypertrophic reactive astrocytes in peritumoral white matter, PAP-DAB, ×300 [2484]

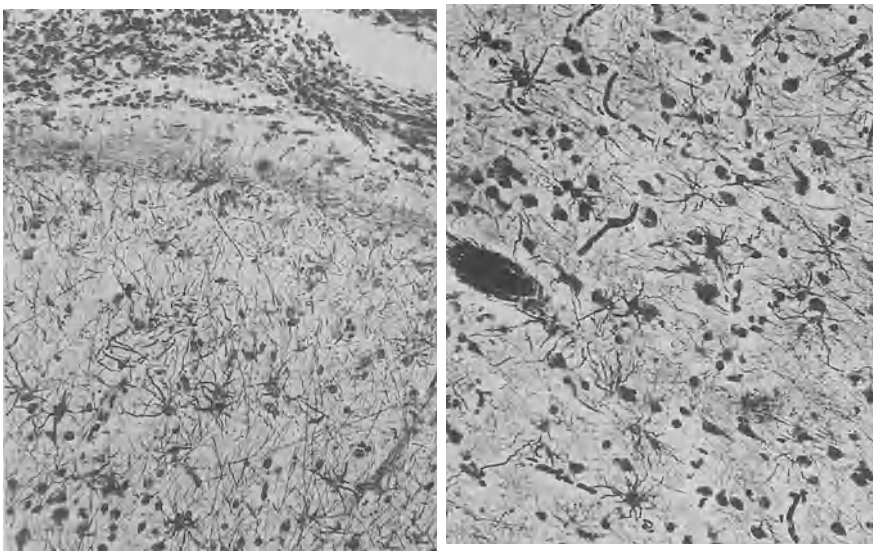


Fig.5.2a,b. Hypertrophic reactive astrocytes in **a** the molecular layer and **b** in the middle layers of the cortex, Hortega silver carbonate, ×400 [2486]

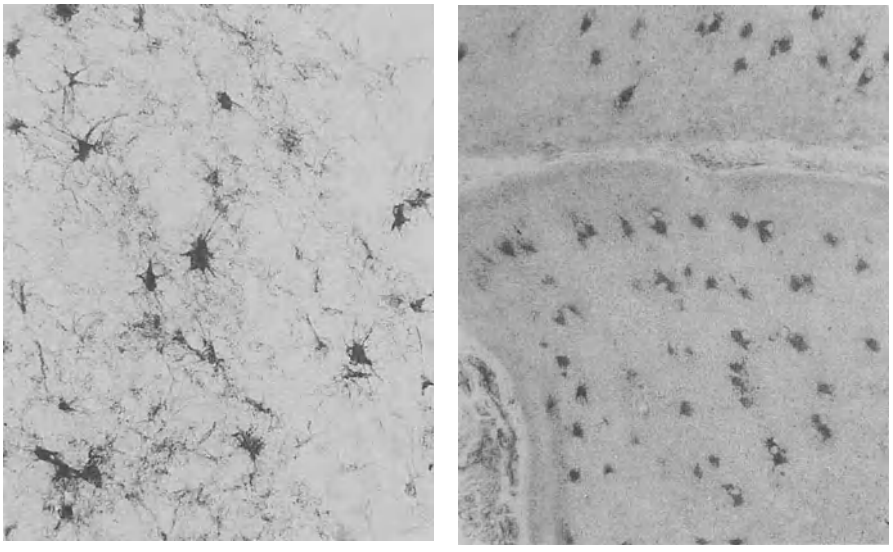


Fig.5.3a,b. Hypertrophic reactive astrocytes in **a** the white matter and **b** the molecular layer of the cortex, NADH tetrazolium reductase, ×400 [2486]

activity could have (Fig.5.3). Also, hydrolytic enzyme activities, acid phosphatase, and nonspecific esterases are evident, with different biological implications [2497].

The appearance and distribution of reactive astrocytes varies depending on whether the glial reaction occurs in the white matter, in the cortex, or in the first cortical layer and on whether recent necrosis with macrophage infiltrates is present.

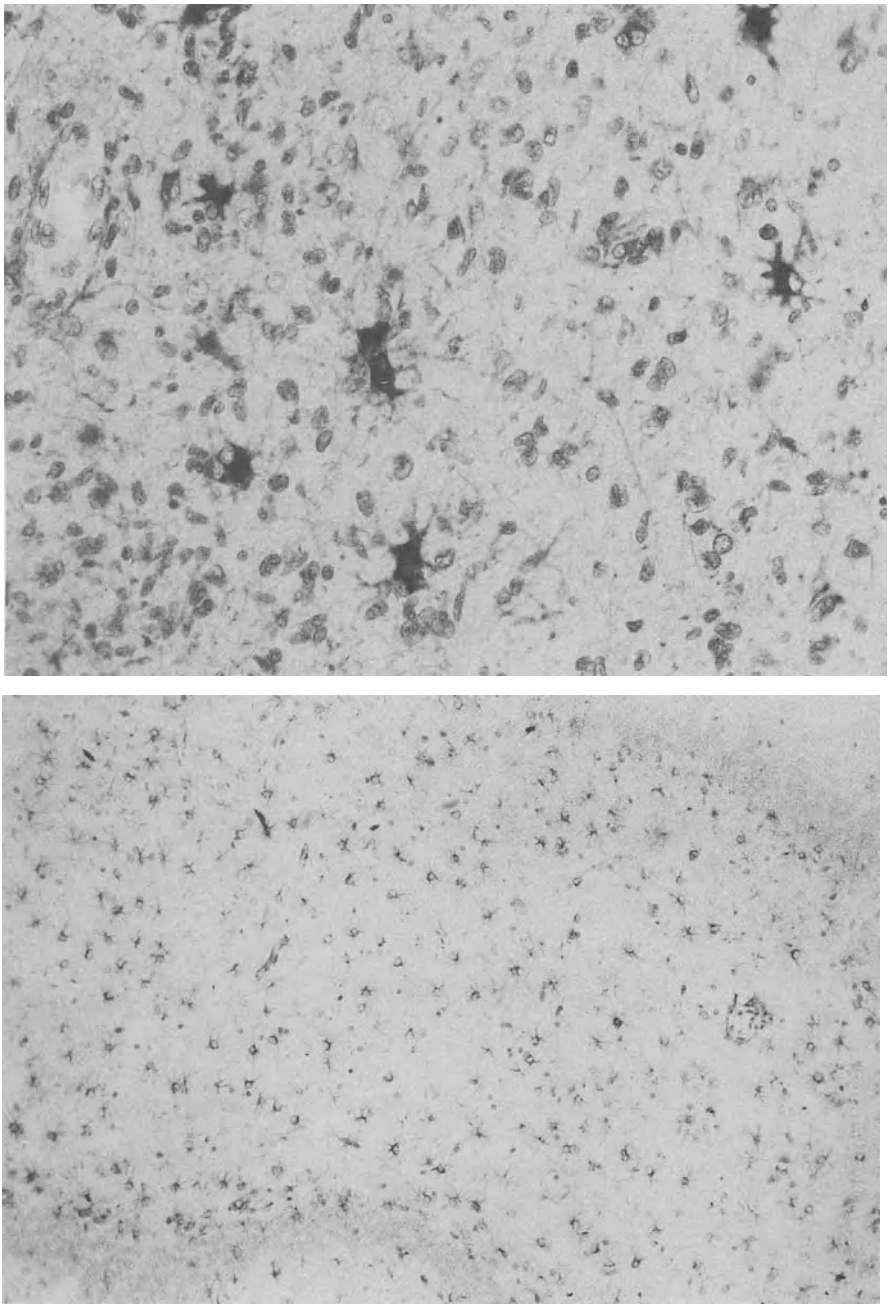


Fig.5.4. a Peripheral area of a glioblastoma: large GFAP-positive astrocytes of reactive or neoplastic nature, PAP-DAB, ×400 [2518]; **b** extensive GFAP-positive gliosis in the rat hippocampus following a lesion in the cortex, PAP-DAB, ×200 [2514]

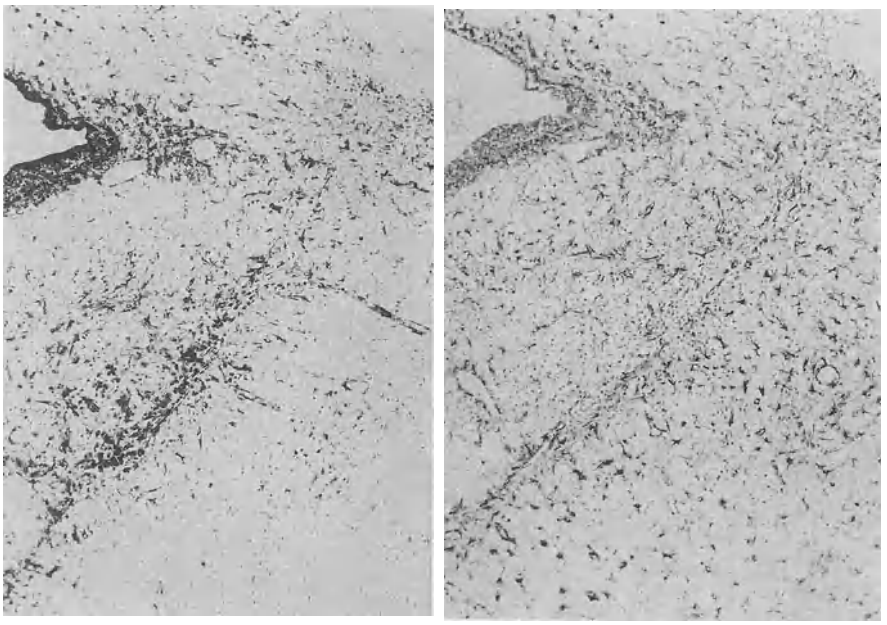


Fig.5.5a,b. Experimental reactive gliosis in the rat; reactive astrocytes are vimentin-positive around a necrotic lesion (**a**) and GFAP-positive also at a distance (**b**), PAP-DAB, ×200

Reactive glia which has remained included in the tumor, or became reactive thereafter, is of special interest because in oncotypes such as medulloblastomas, oligodendrogliomas, and ependymomas it has led to endless discussions regarding its real nature: Neoplastic differentiation or reactive glia. In other oncotypes, such as those of the astrocytic series, the problem is more complicated, because of the real difficulty in distinguishing tumoral from reactive glia. This is especially true in peripheral parts of the tumor (Fig.5.4a) even when mitoses are present, for they may be seen in GFAP-positive reactive glia [2518]. The development of peritumor reactive gliosis poses a series of biological problems which have yet to be fully resolved although they have been studied by many experimental investigators.

The glial reaction is accomplished through processes of hyperplasia, hypertrophy, and lengthening of cellular prolongations. Hyperplasia occurs through mitotic division [396]. The responsible factors have been identified in the degeneration of neurons [138], increase of extracellular spaces [485], disaggregation of myelin [2092], ionic imbalance [306], influence of serum proteins [1437], and possibly release of gliogenetic factors [678]. Many experimental data demonstrate that the glial reaction is directed towards the pathogenic noxa and that it is stereotyped and unidirectional [711].

In light of what has been discussed in Chap. 1, it may be said that in the adult, new astrocytes must derive from cells which have maintained the ability to proliferate [2921], independent of their localization in the subependymal zone or in situ. It is known that the capacity to proliferate is maintained along with that to express GFAP [1585].

In experimental models, the occurrence of necrosis has an important influence on the distribution of the glial reaction. In general, if there is necrosis with death of neurons, the astrocytic response is hyperplastic, not only hypertrophic. In experimental models, if there is necrosis the glial response may be extensive [200, 1706, 1799]. This may be due either to the spread of the edema [759] or the peculiar distribution of astrocytes in animals. The hippocampus and the corpus callosum are, for example, the structures most affected in the rat (Fig.5.4b) [2514]. An important finding is that, close to the lesion, astrocytes are not only GFAP-positive but also strongly vimentin-positive (Fig.5.5) [2209]. Considering the significance of vimentin in cytogenesis, this could demonstrate that they are hyperplastic, and not only hypertrophic [2514], mobile [1687], or derived from astroblasts [754]. An alternative to the origin of reactive astrocytes from preexisting astrocytes [2007] is the hypothesis that they may derive from precursor cells [754, 1896].

Both in the reactive astrocytes in situ and in those induced in vitro with cAMP, a 48-kDa protein with a distribution similar to GFAP is associated with IF. This protein, which is present in normal astrocytes, could be responsible for the aggregation of the filaments within the processes by cross-linking and, therefore, for the formation of the processes [83].

On the basis of autoradiographic and electron microscopy findings, the hypothesis has been put forward that in traumatic lesions, and not only around them, there is a proliferative response of the oligodendrocytes [1706].

5.1.2 Included Neurons

Tumor growth often spares or encompasses neural structures, leaving them recognizable for a long time. The cortex may be totally invaded but its gross structure maintained, and neurons may be recognizable even within the depth of the tumor (Fig.5.6). They may be well preserved and remain recognizable by the presence of Nissl's granules, lipofuscin, and enzyme activities or by immunohistochemical markers. They may also show signs of atrophy, progressing to disappearance. This, in the main, is the destiny of included neurons.

In some tumors, namely in those susceptible to showing neuronal differentiation, included neurons may be the source of mistakes or contribute to fuelling the discussion regarding the problem of cellular differentiation. This is especially important in tumors such as medulloblastoma, or those of ascertained or supposed neuronal origin, in which the finding may be "expected" on the basis of a preconceived nosographic concept.

5.1.3 Ventricular Walls

During growth, the tumor may reach the ventricular walls. Two different possibilities can be entertained: The tumor may cross the subependymal layers and abut upon the ventricle, or these layers may arrest the tumor. In this latter case, the tumor gradually merges with a zone featuring intense glial reaction, not infrequently containing mon-

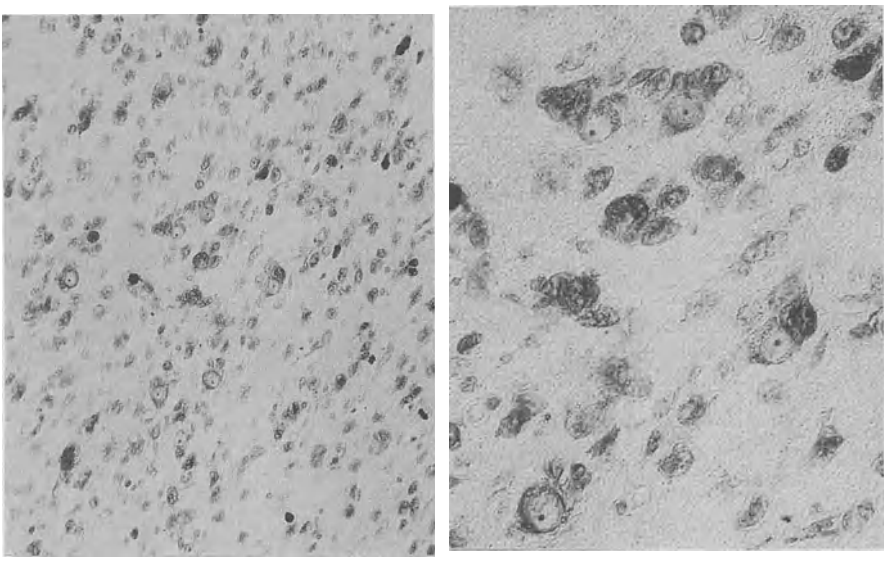


Fig.5.6a,b. Neurons are recognizable in the cortex completely invaded by a glioma, H&E, **a** ×200, **b** ×400 [2486]

strous cells, which do not necessarily belong to the tumor. They may well be reactive cells, such as those forming subependymal gliosis with broad fiber bundles. The ependymal lining may remain intact or be destroyed or engulfed by the tumor. When the subependymal glial reaction takes a chronic course, Rosenthal's fibers may form even if the tumor is non astrocytic as, for example, in oligodendroglioma, craniopharyngioma, and hemangioblastoma, because these fibers originated from reactive subependymal spongioblasts. A frequent event is the precipitation of pseudocalcium/calcium in peritumoral tissue.

5.2 Regressive Events in the Tumor

Regressive processes may alter the morphology of a tumor so profoundly as to modify its primary architecture and render it unrecognizable. However, both the type and degree of regressive events may be of diagnostic value. This is useful when the pathologist is given minute tissue fragments for diagnosis.

Necrosis is, without a doubt, the regressive event of major importance. Three types may be distinguished: (1)large, usually with a coagulative appearance and situated at the center of the tumor (Fig.5.7); (2) circumscribed, with pseudo-palisading (Fig.5.8a); (3) small, with or without pseudo-palisading (Fig.5.8 b).

The first type (large) may be the consequence of thromboses, with occlusion of blood vessels or insufficient blood supply to the central part of the tumor due to the excessive growth.

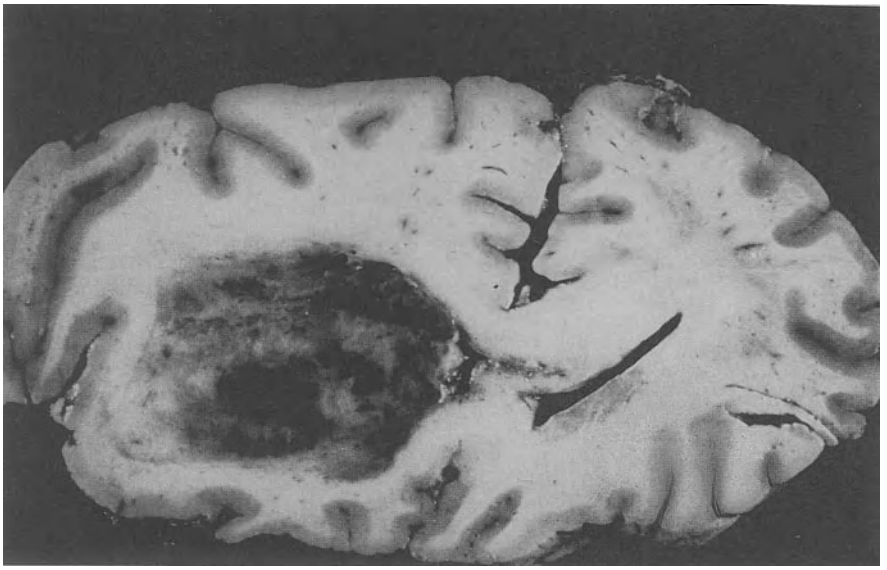


Fig.5.7. Large central necrosis in a glioblastoma

The second type (circumscribed) is found at the periphery of large areas of necrosis, and mainly towards meninges and vascular walls. The pseudo-palisading can be regarded as a result of crowding of tumor cells, because these cannot get beyond an obstacle in their infiltrative displacement.

Small necroses with pseudo-palisading usually occur in areas with very high cell density and many mitoses. A mitotic imbalance between endothelial and tumor cells may be the source [1007, 1202], as previously demonstrated outside the CNS [2807]. Necroses of this type are mostly and abundantly found in proliferative areas and indicate rapid growth (Fig.5.8a,c). They may even disappear after radiotherapy, as a consequence of the temporary halting of tumor proliferation, and reappear later with tumor regrowth [2508]. The highly proliferating areas are GFAP-negative, quite often formed in the newly invaded tissue where large, GFAP-positive reactive astrocytes occur. They remain randomly distributed and do not crowd around necrotic areas [2518]. Small areas of necrosis may be observed in almost all oncotypes such as oligodendroglioma and ependymoma, but in many cases they are very small (Fig.5.8b) and sometimes limited to a few or single cells (apoptosis).

Another important regressive event is the appearance of cysts. These may be of variable dimension, from those visible macroscopically to microcysts. They may originate through necroses, various degenerative processes, or tissue liquefaction. Cysts may be rare in some tumors, such as glioblastoma, and numerous and very large in others, such as cerebellar hemangioblastoma, in which the entire tumor may be reduced to a small mural nodule and a large cyst. Microscopic cysts may, however, be present in almost all cerebral tumors.

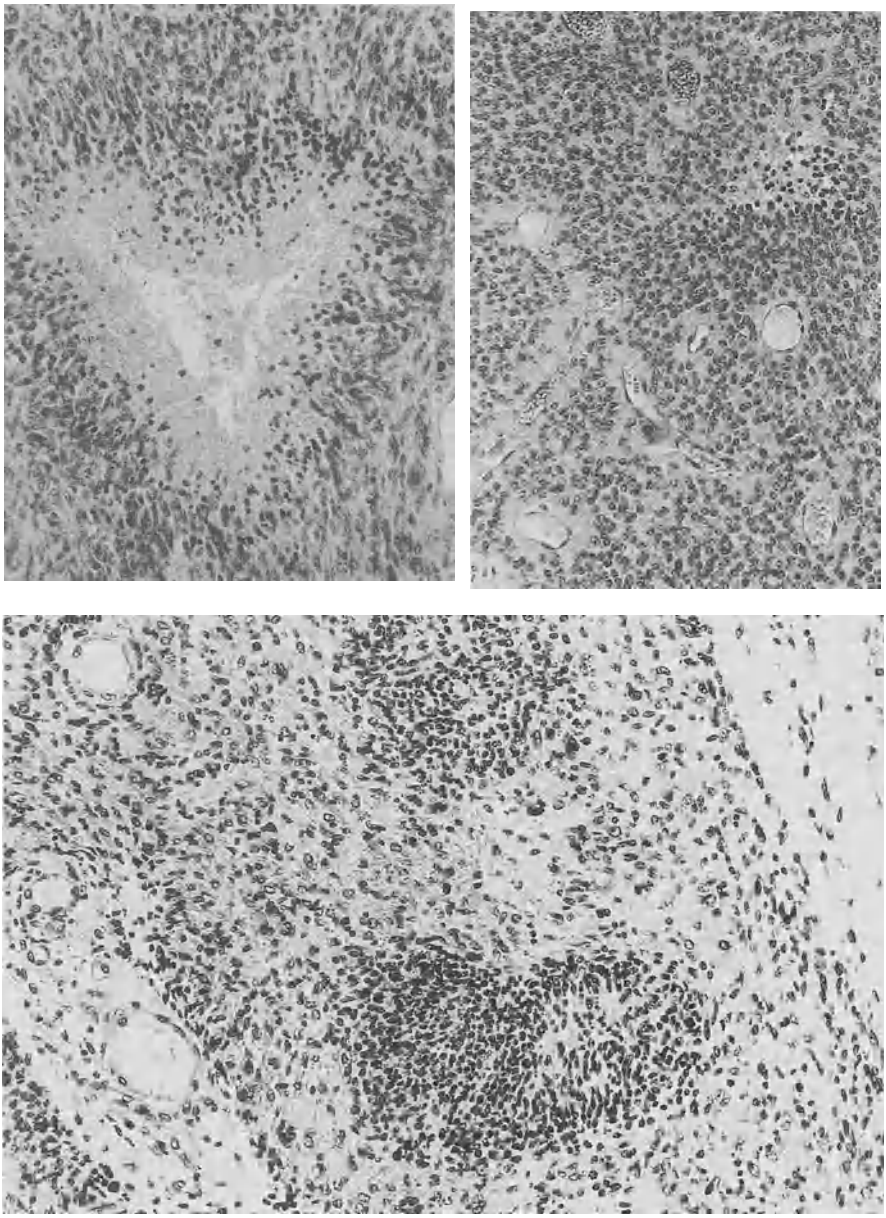


Fig.5.8. a Circumscribed necrosis with pseudo-palisading in glioblastoma, H&E, ×200; **b** very small necrotic focus in an ependymoma, H&E, ×200; **c** glioblastoma : transformation of areas with high cell density into circumscribed necroses, H&E, ×200

Hemorrhages are other frequent regressive events in cerebral tumors. They may occur in all CNS tumors to a varying degree and extent and even be so massive as to assume clinical significance (e.g., apoplexy in a glioma). These massive ones occur mostly in glioblastoma, oligodendroglioma, and pituitary adenoma.

Still other regressive events are hyalinization and fat degeneration. The former occurs in connective tissue and is particularly frequent in meningiomas, but it is also found in the blood vessels of neuroepithelial tumors, especially glioblastoma. Fat degeneration is the result of a slowly evolving necrobiotic change.

5.3 Cerebral Edema

5.3.1 Definition and Pathogenesis

Cerebral edema is an important pathological event which occurs in association with cerebral tumors and is capable of influencing cerebral blood flow, metabolism, and intracranial hypertension. It may seriously aggravate the hypertension, if already present. Generally, three types of cerebral edema are acknowledged: vasogenic, cytotoxic, and ischemic [1438, 785, 469].

Cytotoxic edema is related to the direct effect of noxious agents on cells of the cerebral parenchyma so that neurons, glia, and endothelial cells become swollen. There is an increase in the water and sodium content in the cells because of a disturbance of the ATP-dependent sodium pump. At the same time, the volume of the extracellular spaces reduces, while capillary permeability remains normal. Ischemic edema is initially cytotoxic and progresses with the development of necrosis. The blood–brain barrier (BBB) is subsequently damaged, so the edema becomes vasogenic. The latter accompanies tumors, inflammatory processes, and necrosis. It is due to a change in the permeability of the BBB.

The concept of BBB arises from the observation that small molecules pass freely from the blood to many tissues but poorly or not at all into nervous tissue, as though a barrier existed. For example, in the old experiments of Ehrlich and Goldmann, trypan blue penetrated various other body tissues from the blood but not the brain, unless it was administered via the CSF. The abundant subsequent research led to four basic observations: (1) Some substances, such as trypan blue and proteins, penetrate tissues from the blood vessels but not the brain; (2) some normal metabolites may increase in concentration in the blood but not in the brain; (3) the majority of substances penetrate the brain more readily via the CSF than via the blood; (4) the majority of substances penetrate the liver and kidney more rapidly than the brain.

Today, we know that trypan blue does not cross from the blood vessels into the brain because it binds to serum proteins which do not cross the BBB, and that it enters the brain via the CSF, because of the low protein concentration of the latter, which leaves it mostly unbound. The best demonstration of the existence of the BBB was given in the peroxidase experiment of Reese and Karnovsky [2276], which demonstrated that the anatomical site of the BBB is at the level of the endothelium of cerebral capillaries, which differs from that of other organs in accordance with various characteristics. First of all, the cerebral capillaries are mostly of the "continuous" type, e.g., the endothelium and the basement membrane are uninterrupted, and a true extracapillary space does not exist, as the perivascular zone is occupied by astrocytic processes. Second, the endothelial cells of cerebral capillaries have tight junctions which are "tighter" than those found in other organs. Lastly, cerebral endothelium contains fewer pinocytic vesicles [2288], as compared with the endothelium of other tissues. There are, however, some areas in which the BBB does not function: the ar-

ea postrema, the insertion line of the choroid plexus, the median eminence of the hypothalamus, and the pineal gland (in which the capillaries are of fenestrated type, e.g., have small openings in the wall which allow macromolecules to cross into the extravascular space).

The endothelium is, therefore, the site of the BBB, so that the brain is protected from noxious substances and biochemical homoeostasis is maintained. The passage of various substances into the cerebral parenchyma is regulated by different mechanisms. First of all, the endothelium is polarized. It harbors Na^+ and K^+ pumps on the abluminal surface and specific receptor proteins on the luminal plasmalemma [193]. Lipid soluble and apolar substances easily cross it, whilst larger molecules and proteins do not. The BBB is, however, actively and selectively involved with respect to small molecules; for example, saccharose and inulin seem to enter the brain less easily than other tissues. It is possible that the CSF may carry out an important "washout" function in reducing the intracerebral concentration of these substances, apart from the obstacle represented by the tight junctions. Because the CSF is in equilibrium with the fluid in the extracellular spaces and is continuously being renewed, molecules penetrating from the blood into the extracellular cerebral spaces may rapidly pass into the CSF, thereby being quickly washed away.

A specific active transport system (a sort of "pump") is, instead, the basis of the entry into the brain of many metabolites. For example, d-glucose, mannose, and maltose, but not l-glucose, galactose or fructose, rapidly cross the BBB. The plentiful mitochondria in brain endothelial cells, in contrary to endothelial cells elsewhere in the body [2074], indicate an active transport, as this process requires a great amount of energy [785].

Other substances, such as glutamic acid, do not seem to cross the BBB, because they may increase in concentration in the blood without increasing in the brain. However, it has to be said that this could also be due to a rapid washout from the CSF. For substances such as ethanol, lipid-soluble molecules, and certain gases such as CO_2, O_2 ,N_2O and Xe, there would be no barrier impediment.

Blood-borne proteins may enter the central cerebral endothelia by fluid phase, adsorptive, and receptor-mediated endocytosis in which secondary lysosomes are involved, degradating the proteins [290]. For example, in adsorptive transcytosis of lectins, the Golgi saccules are reached and the molecules are packaged for intracellular transport and exocytosis at the abluminal surface [291]. The receptor-mediated transcytosis is highly specific and very quick.

Vasogenic edema is due to the breakdown of the BBB, resulting from damage to the endothelium. This results in an increase in vascular permeability with extravasation of serum components, including proteins, which under hydrostatic pressure diffuse into the extracellular space, first into the tumor and then around it. The modalities of this process may be multiple and changes have first to be looked for in the structure of the blood vessels.

Tumor blood vessels are frequently fenestrated, and the junctions between endothelial cells are wide. The endothelial surface is irregular, with the formation of deep folds which facilitate the passage of material through the endothelium [2961]. The endothelium of tumor blood vessels shows an increase in pinocytic vesicles as compared with normal cerebral endothelium. In analogy to what has been observed in other models of edema, the vesicles may form at the luminal surface of the endothelium and be transported to the opposite side, where their content may be discharged outside the endothelial cell. In other instances, because of the confluence of numerous vesicles, true channels traversing the endothelium may form [2230].

In tumor blood vessels, a true pericapillary sheath as formed by glial processes under normal conditions is lacking. One may say that in tumors there is an absence rather than a breakdown of the BBB [1689, 2217]. Under different conditions and particularly in the acute phase of inflammatory processes, leukocytes traverse the endothelial cytoplasm or wedge themselves between two adjacent endothelial cells to reach the perivascular space by a process called "emperipolesis" [86].

The relative importance of these structural alterations of the endothelium in the genesis of tumor edema has not been completely clarified. A quantitative study in glioblastomas [486] has recently revealed the quantitative importance of the formation of canaliculi and true breaks of the endothelial layer as compared with pinocytotic vesicles and fenestrations, which could be less frequent than expected.

An important pathogenetic role in the formation of vasogenic edema is played by the products of the degradation of phospholipids of the cell membranes and of arachidonic acid, which is the main polyunsaturated fatty acid in the brain and its tumors [411]. The liberation of arachidonic acid in cerebral tumors may be capable of triggering a series of events in the capillary walls by increasing their permeability and, therefore, increasing the amount of edema [787].

The action of permeability factors has also been demonstrated in the peritumoral area. Apart from prostaglandin E and thromboxane B_2 [489], other factors have been identified in the supernatant of cultures of C6 glioma cells [2067] and of human gliomas [308, 517]. The factors could be inhibited by dexamethasone. On this point of view there is no general agreement, because there is no doubt about the existence of structural changes in tumor blood vessels resulting in increased permeability. The same cannot be said with certainty for the peritumoral tissue.

The majority of studies has demonstrated a lack of change in blood vessel permeability in peritumoral tissue [1437, 225]. This is analogous to what occurs in other conditions which lead to cerebral edema, where the damage to the BBB is present only at the site of the lesion and not in the surrounding edematous tissue.

A 47% reduction of capillary permeability to sodium and urea has been observed in the cerebral peritumoral tissue in the rat [1626]. The reduction could be secondary to compression by the tumor on peritumor capillaries or an accumulation of tumor metabolites which inhibit the transcapillary transport of sodium and urea.

There are, on the contrary, observations that blood vessels in peritumoral position show open junctions and more vesicles than normal, thus appearing to be leaky. Ultrastructurally, they appear to be of immature type [3014].

It is possible that the tumor infiltration per se induces the increase of vessel permeability in the invaded tissue, perhaps through diffusible factors [2741]. This hypothesis is supported by the observation that in microvessels there are many more changes in the interendothelial junctions the greater the tumor infiltration is, even when capillaries are not directly surrounded by tumor cells. Experimental brain tumors have demonstrated many of the same abnormalities as human tumors [2437].

There is no complete agreement between various authors on the electrolyte composition of the cerebral edema fluid: reduction of the sodium content and increase in potassium in the brain [2304, 1210] or the opposite [1361]. The protein content is also not identical to that in serum. In edematous white matter, for example, the increase in γ-globulins occurs at a later time than the increase in albumin.

5.3.2 Morphological Changes and Sequelae

The increase in fluid content causes an increase in volume and weight of the brain, which leads to flattened gyri, narrowed sulci, and small ventricles. In vasogenic edema,

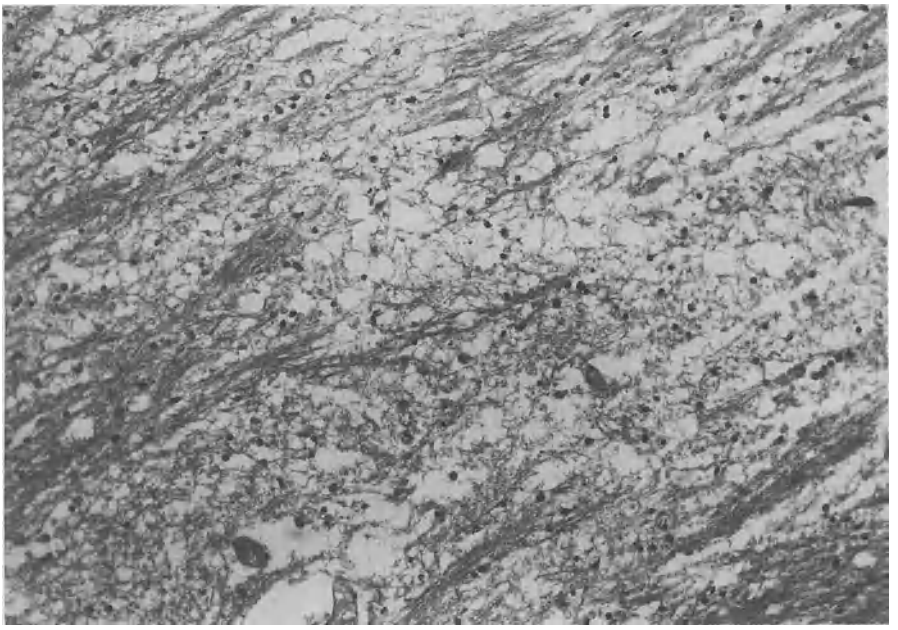


Fig.5.9. Peritumoral edema in the white matter; dissociation of myelin fibers and demyelination, Luxol Fast Blue B, ×200

the edema fluid collects mainly in the extracellular spaces between the white matter fibers. Even in the earlier phases, the dilatation of this space may be demonstrated at the ultrastructural level if the tissue is properly fixed [1137]. The use of electron dense tracers allows easier detection. Under worse conditions, edema is also apparent with conventional histologic examination as vacuoles of various dimension in the white matter and as dilatations of the perivascular and perineuronal spaces and dissociation of myelin sheaths (Fig.5.9). The preferential diffusion of the edema fluid in the white matter is due to the fact that it follows anatomical pathways of lesser resistance. The bundles of fibers in the white matter, thanks to the absence of demonstrable junctions between the myelin fibers, are easily dissociated for considerable distances and facilitate the diffusion of the edema fluid (Fig.5.10). On the contrary, the thick network of junctions in the cortex (synapses and junctions between glial cells) remarkably limits the progression of the edema.

The progression is not simply the result of passive diffusion but is related to active pressure [2304]. In fact, there is no difference in the speed of diffusion of molecules of different size. However, the speed of edema progression at around 10 mm/week [1210], which is inferior to that expected by simple diffusion, demonstrates that the main influence is an expression of the pressure exerted by the fluid coming out of the capillaries, rather than of the resistance of the tissue [1210]. At any rate, there is a gradient in the water content of the peritumoral white matter which decreases as the distance from the tumor increases. The edema fluid, finally, is in part drained into the ventricular system when the edema front reaches the walls of the ventricles [2304]; the serum proteins are

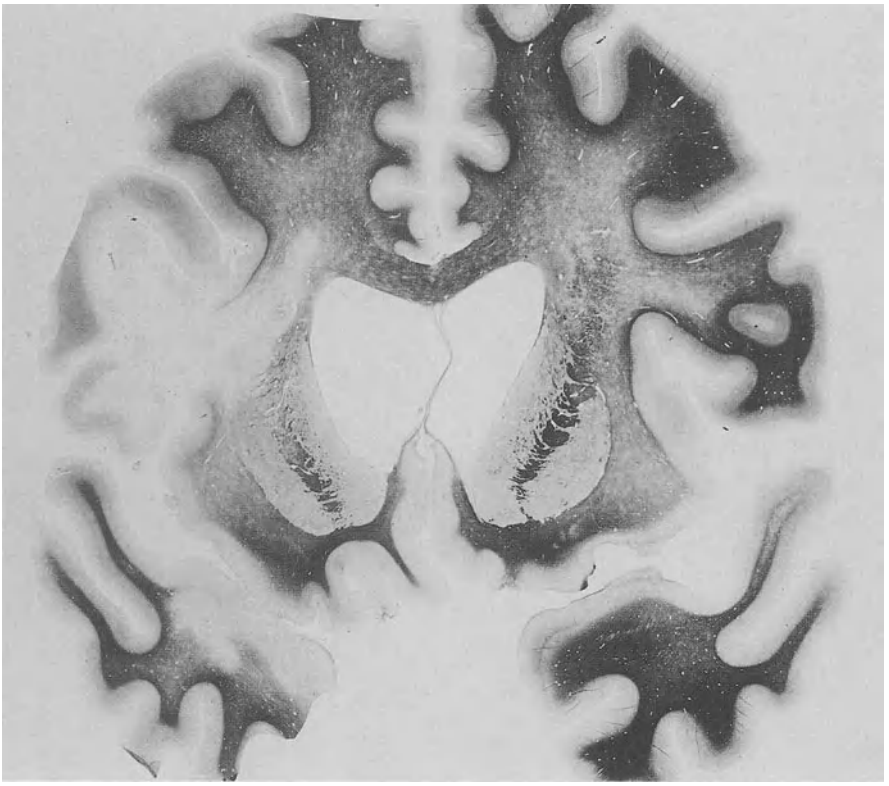


Fig.5.10. Peritumoral edema diffused through the white matter of both hemispheres with myelin loss, Luxol Fast Blue B

absorbed by astrocytes, macrophages, and even neurons, which transport them to the blood vessels, pia, or ependyma with a possibility of being discharged into the CSF [2276]. The persistence of the edema causes the appearance of serious tissue changes such as demyelination and reactive astrocytosis (Fig.5.11).

Cerebral edema may influence the blood vessel flow by reducing the perfusion pressure as a consequence of the increase in intracranial pressure, or by increasing vascular resistance by compressing the microcirculation [1210]. Even if there is no complete agreement between studies on tumor edema in man and under experimental conditions, it is, nevertheless, probable that cerebral edema causes a decrease in the regional blood flow [142] when it is accompanied by an increase in intracranial pressure.

Tumor-associated edema on CT scan is usually seen as a hypodense area surrounding the area of tumor enhancement. On MRI, it appears as a region of increased T2 signal outside the gadolinium enhanced area. When the enhancement is not present, for example in infiltrating or in low grade tumors, then it is very difficult to differentiate between infiltrated tissue and edema [614]. It must be taken into account that malignant cells can be found long distances away from the major tumor mass [2483, 1375, 332].

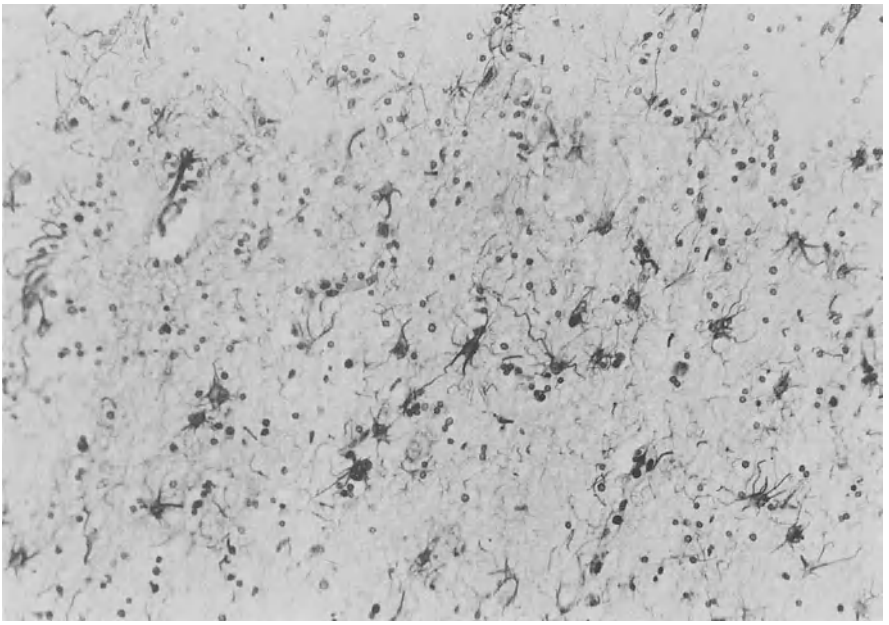


Fig.5.11. Fibrous gliosis in chronic edema, Holzer, ×300

Steroids are effective in reducing tumor-associated edema [2590], including that associated with inflammation [784], even though the exact mechanism is not known. Since they are not effective in all types of edema, one may conclude that they are not effective in all conditions under which the BBB is altered.

5.4 Calcifications

The old concept relating the presence of calcifications to the benign nature of a process has been surpassed and is today unacceptable. Multiple factors come into play in their production. The frequency of calcification in the different oncotypes varies greatly, being very low in some, high in others.

Calcifications may be detected by conventional radiology in a small percentage of cases; however, the percentage increases with computed tomography (CT) [2050], even though, according to some, the majority of calcifications seen on CT are also visible on plain X-ray films [984].

Magnetic resonance imaging (MRI) is even more sensitive, and calcifications appear as areas of signal attenuation because of the lack of mobile hydrogen [278, 3127]. However, calcifications are often not seen on MRI.

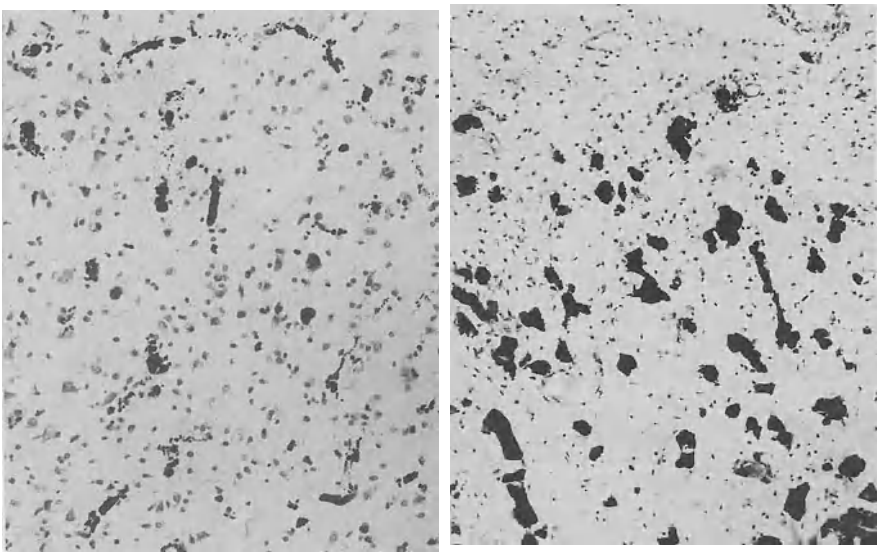


Fig.5.12. a Pseudocalcium-calcium (PCa-Ca) precipitations as fine granules on capillaries in an astrocytoma, H&E, ×200. **b** Broad precipitations on vessel walls in an ependymoma, cresyl violet, ×150 [2486]

From the morphological point of view, calcifications in gliomas are not dissimilar from those which are observed in the "symmetric, nonarteriosclerotic deposition of pseudocalcium-calcium" or in other calcifying conditions [721].

Fine granules may deposit on capillaries and subsequently become confluent, so as to form strings of beads or larger structures, giving the capillary network a coral-like appearance. This type of precipitation is more frequent in peritumoral tissue, especially around oligodendrogliomas or astrocytomas (Fig.5.12).

Precipitates may occur in the blood vessel wall both as granules, which subsequently become confluent, and as larger precipitates. The blood vessel wall may become impregnated, and ring calcifications may form. This type is particularly frequent in oligodendroglioma, in which a large part of the blood vessel network may undergo changes similar to those in Sturge-Weber disease (Fig.5.13a).

A last type is in the form of stratified, morular, and needlelike deposits, of different sizes and staining properties, apparently lying free in the tissue (Fig.5.13b). This type appears mostly within the tumor or in infiltrated cortical areas.

Calcific deposits are basophil, stain variously with cationic dyes depending on the intensity of mineralization, are metachromatic with toluidine blue, and are negative for lipid reactions. The histochemical behavior is not dissimilar from that described in the symmetric deposits of pseudocalcium-calcium [2481]. They are formed by an organic matrix and a mineral component. The former includes a protein-GAG complex, showing an extinction point at pH 2.6–3.1 and alcian blue positivity, as may be observed in Fahr's disease [2494, 2495]. The GAG may vary from one tumor to another or within the same tumor, depending on the stage in which the calcification occurs. This is well demonstrated with fluorochromization by acridine orange [2495].

The mineral component is very variable. Calcium salts are usually demonstrated with routine histochemical methods, while the presence of iron depends mostly on the stage of evolution of the

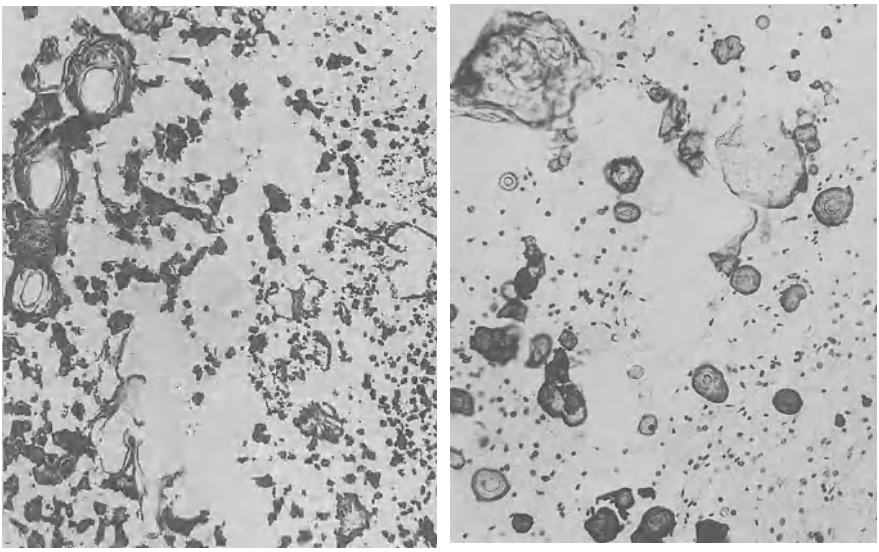


Fig.5.13a,b. Oligodendroglioma; **a** pCa-Ca deposits on the whole vascular network; **b** agatiform stratifications in large deposits, cresyl violet, ×100 [2486]

deposits and on their location in different cerebral areas. For example, the presence of iron is much easier to demonstrate in the first stages of calcification and in cerebral areas where it is normally present. In small deposits, minerals are more difficult to demonstrate than in large ones, even with the help of microchemical and microincineration methods.

Chemical analyses reveal the content of phosphates and carbonates, but the former clearly predominate [2481], as occurs in Fahr's disease, Sturge–Weber disease, and other conditions. Importantly, hydroxyapatite crystals are found on X-ray spectrography [2492] (Fig.5.14). Ca is found mainly as the phosphate form and the Ca/P ratio is identical on chemical analysis to that theoretically calculated for hydroxyapatite. Apart from Ca, numerous other minerals such as Fe, Na, Mg, Zn, Cu, and Pb are present, as shown by qualitative spectrography [2481]. In meningiomas, oligodendrogliomas, glioblastomas, and craniopharyngiomas, the elemental composition of the deposits seems to be characteristic of each type of tumor [672].

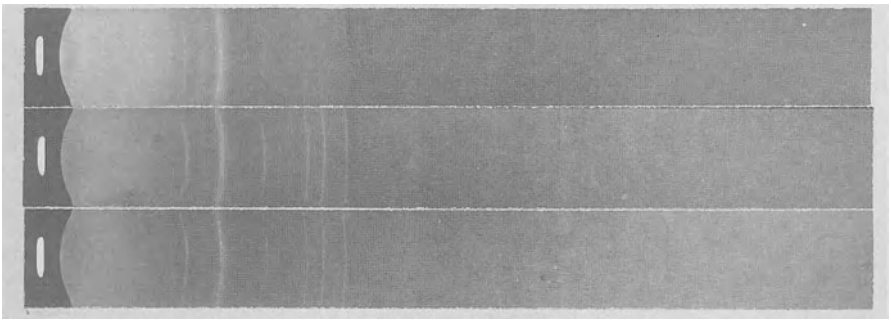


Fig.5.14a–c. Roentgen spectrographic analysis on **a** a bone fragment in a meningioma; **b** small and **c** large deposits in an oligodendroglioma. Apparatus Rx General Electric, type XRD3, [2492]

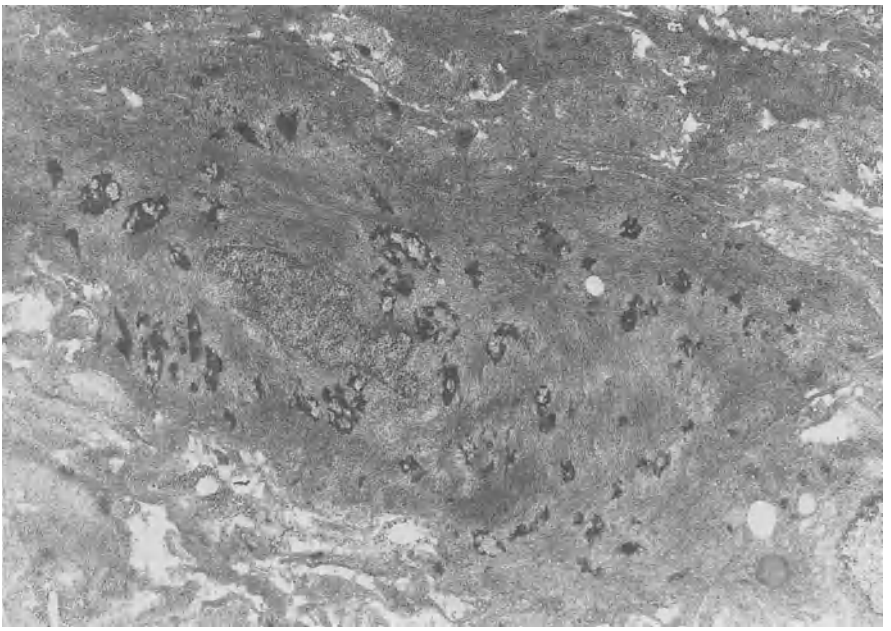


Fig.5.15. Ependymoma: intracellular microfoci of calcification with a heterogeneous structure, ×7000

In all the calcifying conditions studied, it has been found that the organic matrix is "thirsty" for Ca, because of the presence of GAG [2481]. The hypothesis is that calcification occurs following the principles which regulate that in cartilage. In strongly calcified concretions within cerebral tumors, reactions for GAG are more evident after demineralization, and the intensity of the calcification is greater where acid radicals are of the sulfate type [2481], so that the interaction between acid radicals and Ca is supported. Whether Ca is bound also to the amino groups of proteins cannot be established, even after microspectrophotometric infrared studies. It is, however, certain that as the process progresses, the concretions lose the organic matrix, and their mineral component increases. In fact, after demineralization of old, heavily calcified concretions, the intensity of histochemical reactions of the matrix is much less than in more recent, less mineralized deposits. The enlargement of concretions is mainly due to hydroxyapatite crystals which show a strong surface activity and a high degree of ionic exchange in vitro [717], so as to be able to adsorb Ca or other minerals.

Electron microscopy has provided interesting information. In nontumor calcifying processes, it has been observed that deposits are found in the basement membranes of blood vessels or just outside them [1029, 1930, 2002]. They may appear as minute granules in the cytoplasm of adventitial cells and sometimes in glial processes, so that a suspicion has been raised that pericytes participate in this process [1465]. In tumors, the findings of heterogeneous microfoci of calcification is common and usually associated with a fibrous hypertrophy (Fig.5.15).

5.5 Immune Response

Undoubtedly, the nature and the efficacy of the tissue response to the tumor reflects the capacity of circulating lymphocytes to mount an immune response. In patients with gli-

omas, it has been noted that there is a degree of cellular and humoral anergy [303, 1874], which is in direct relationship to the degree of malignancy [1734, 305]. In particular, in those with malignant gliomas, the number of γ-suppressor cells [899] and of OKT8+ lymphocyte subpopulations is high, whereas that of OKT4+ is low [1253]. The low mitogenic index of circulating T lymphocytes [2374] and the increase of the T suppressors would cause a defect in the normal T-lymphocyte response [2950].

Besides the finding of a defective cell-mediated immune system, signs of a local immune response consisting in the presence of mononuclear cell infiltrates are observed (Fig.5.16a). Since the first description of lymphoid infiltrates in astrocytomas [188], mononuclear infiltration has been the object of numerous studies. In autopsy material, the lymphocytic reaction considered as an expression of the immune response is marked in 30% of gliomas, modest in 28%, and absent in 42% [2320]. In malignant gemistocytic astrocytomas, lymphocytic perivascular cuffings are particularly abundant [2796]. Furthermore, a correlation has been reported between survival and the amount of lymphocytic infiltration in malignant gliomas [2121, 304]. However, the opposite or no correlation has also been found [2499, 2425]. The perivascular infiltrate, predominantly lymphocytic with rare plasma cells, is more frequent in less malignant areas and lacking in necrotic and hemorrhagic areas. Parenchymal infiltration is present in 29% of gliomas, mostly in glioblastomas [304].

Attempts to characterize the mononuclear cell subpopulations in the infiltrates have yielded contrasting results [3097]. A prevalence of B lymphocytes has been noted by some, but other authors [2716, 2950, 1942, 2119] have stressed the presence and sometimes the predominance of T lymphocytes, in particular of the subpopulation OKT8+ (suppressor/cytotoxic) [1146]. NK (natural killer) cells have also been isolated from malignant gliomas [1882] and are increased in number as compared with the peripheral blood [749]. It appears, therefore, that lymphocytes sensitized to glioma antigens escape from the circulation and gather in the tumor [2950], thanks also to the alteration of the BBB.

The type of local response revealed by the characterization of the subpopulations seems to indicate the presence of immunoregulatory factors. Lymphocytes infiltrating malignant gliomas have been isolated and cloned [1882]. The clones are capable in vitro of destroying allogenic and autologous cells to a greater extent than the peripheral blood lymphocytes in the same patients. However, their ability to clone is much lower than that of the circulating lymphocytes. It seems, therefore, that there is an accumulation of specific cytotoxic lymphocytes in the tumor, but their activity is limited by the presence of T-cell-suppressive factors. A suppressive action has been attributed to anticonvulsants, anti-inflammatory drugs, specific immunoglobulins and circulating immune complexes [2654, 889], and the close topographical relationships with tumor cells [1882]. Immunosuppressive factors have been found in glioma cyst fluid [1414] and in the serum of patients before operation [302]. A factor isolated from glioma cells in culture has been found to antagonize the effects of interleukins (IL) 1 and 2 [798]. It has been called "glioma-derived T cell suppressor factor," and it is able to suppress both the IL2-dependent T-cell proliferation and the generation of cytotoxic T cells in mixed lymphocyte cultures. It further suppresses lymphokine-activated killer (LAK) cell activity [1537] and is identical to transforming factors (TGF) β_2 [587, 235].

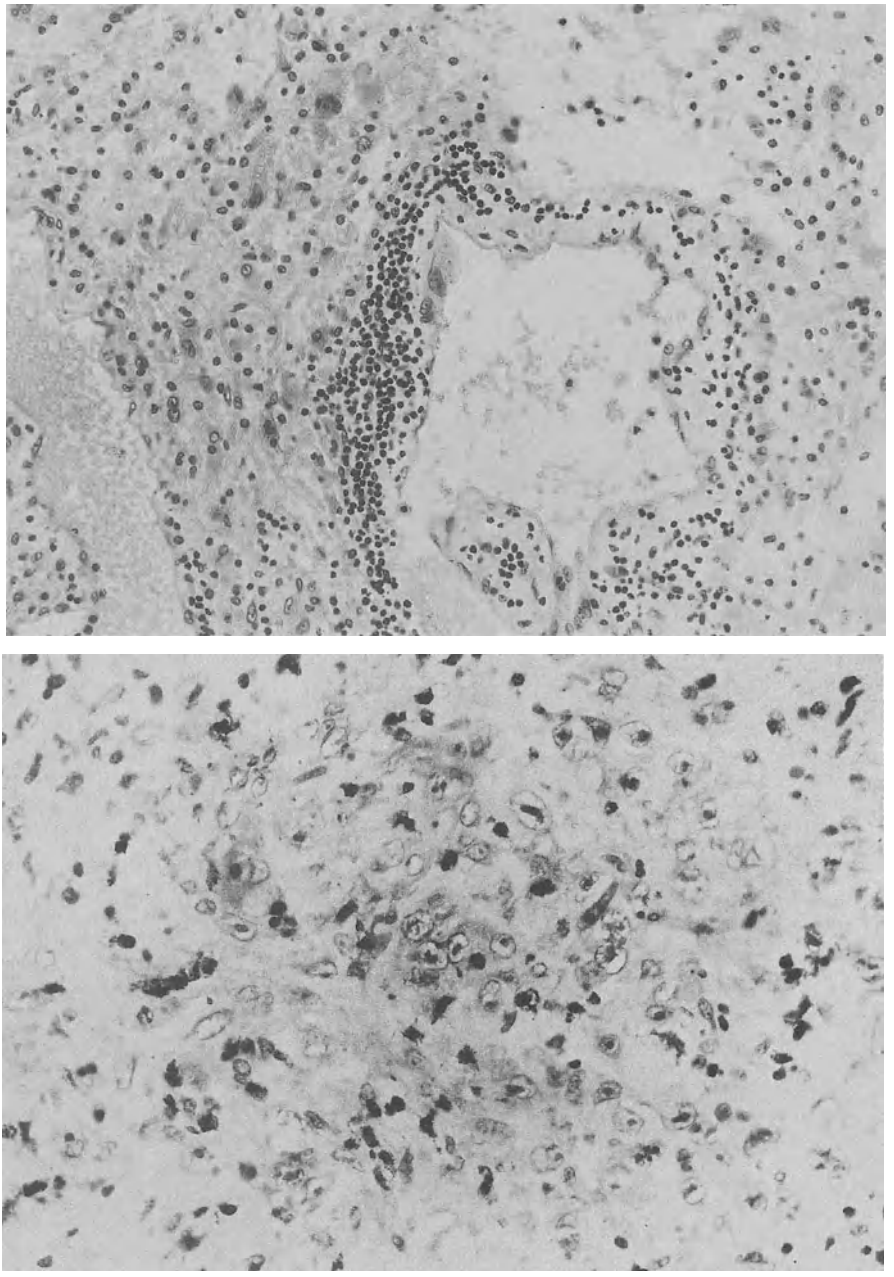


Fig.5.16. a Lymphocytic infiltrates in the vessel walls of a glioblastoma, H&E, ×300; **b** cerebral carcinomatous metastasis: macrophages are evident by immunostaining for lysozyme, PAP-DAB, ×400

Other mechanisms have been proposed to explain the escape of gliomas from the immune response: a defect in immunogenicity and the secretion of a mucopolysaccharide coat. The interaction of glioma cells in culture with a macromolecular factor produced by peripheral blood mononuclear cells increases the production of this protective coat [631].

The role of macrophages in humoral immunity is clear, but little is known in relation to gliomas. They represent part of the infiltrating cells within primary and secondary tumors (Fig.5.16b) with different percentage values in various studies, perhaps depending on the method used [3073, 1925, 735, 2371, 1146]. The entrance of macrophages into the tumor is essential to initiate the lymphocytic response and is due to the breakdown of the BBB. An alternative route is the transformation of microglia into macrophages, which may be triggered by the release of IL3 from astrocytes,an event which has been documented in culture [825].

Macrophages in malignant gliomas are present in necrotic areas, in tumor parenchyma, and at the borders with normal tissue. They express class II MHC antigens, a fact which led to the belief that they are involved in the immune response apart from phagocytosis [2371]. Glioma cells, reactive astrocytes, and cerebral endothelial cells also express a human leukocyte antigen (HLA-DR). Its expression is potentiated by stimulation of γ-interferon [900, 2201]. These cells are, therefore, able to present the antigen to lymphocytes [593].

In glioma patients, an autologous, humoral, nonspecific response against the tumor has been described. This response is not a direct one. In fact, even though B lymphocytes are present in gliomas, it is doubtful whether they produce glioma-specific antibodies which may participate in cytotoxic, cell-mediated complement-dependent or antibody-dependent reactions [1785, 66].

A modest antiglioma activity is present in the serum of patients, especially of these with low grade gliomas. This is probably related to a IgG or IgM immunoglobulin, but it is easily absorbed by platelets and other tumor cells [1488, 1785, 462].

6 Classification and Nosography of Neuroepithelial Tumors

A century has now elapsed since the first attempts to classify cerebral neoplasms systematically. The identification of new cellular elements in the nervous tissue, their histogenetic classification, the discovery of other morphological tumor features and the accruing of biological data have progressively led to the classifications being updated. This has been facilitated by the progress in neurosurgery and, more recently, by the introduction of molecular biology into neuro-oncology.

It is opportune to discuss the actual status of the classification and nomenclature of cerebral tumors, to provide some historical data, and to follow, even if in broad terms, the conceptual development which allowed the classifications to be devised. To deal with neuroectodermal tumor classifications means to describe their history. However, it is difficult to resist the temptation to classify the classifications. Diverse criteria, i.e., morphological, histogenetic, biological, and organogenetic, and often more criteria at the same time, inspired earlier classifications.

Even though attempts to identify cerebral neoplasms had already been made, only with Virchow in 1863 [2942] was a systematic classification begun. The identification of the neuroglia by the German pathologist was followed by the description of "gliomas," which he separated from the sarcomas and further subdivided into hard, soft, rich in cells, medullary, fibrotic, teleangectatic, and myxomatous. This parallelism between the description of particular cellular structures of the CNS and that of corresponding tumors was to last for several years. In fact, the description of "fibrillary cells" by Deiters [611] or "spider cells" by Jastrowitz [1291] was followed by the identification of the "spider cell gliomas" by Simon [2646]. The identification of blepharoplasts was followed by the description of ependymal tumors [1744], and so forth. The first classification inspired by unitary interpretative criteria was that of Pick and Bielschowsky in 1911[2197] who considered cerebral tumors as corresponding to the elements derived from the so-called undifferentiated neurogliocytes. These were considered to be multipotent elements from which neural, glial, and Schwann cells could arise. Along these lines, Ribbert [2311] perfected the systematics of cerebral tumors and thought of gliomas as being composed of glial cells. These tumors, in agreement with Cohnheim's theory [474], could have originated from residues of tissues which remained isolated during embryogenesis and arrested at different developmental stages. Thus, the foundations for future and more complete histogenetic classifications were lain. In relation to developmental stages, tumors were arranged by Ribbert from the most immature to the more mature as follows: spongioneuroblastoma, spongioblastoma, glioblastoma, glioma, and neuroblastoma. Contemporary to Ribbert, a histogenetically based classification of tumors was published by Strauss and Globus [2750]. For these authors, the elements of the cytogenesis of the neuroepithelium were in reciprocal relationship and were related to the tumors [944].

It has to be remarked that these schemes, like other ones thus far followed, were oriented toward purely morphological classification criteria, i.e., they were based on the similarity the tumoral elements have with elements in cytogenesis. This system was nevertheless useful and susceptible to being encompassed in a more ample evaluation of cerebral neoplasia which, by taking into account the important data provided by clinical practice, could pretend to have an accomplished biological meaning.

Great progress was brought about by the development of neurosurgery and was made possible by the close cooperation between pathologists, neurologists, and neurosurgeons. This collaboration reached its peak in the association of Bailey and Cushing in 1926 [112]. Bailey correlated the various tumor cell types with the stages of maturation of the corresponding normal elements, as defined by histologists [1145, 360]. He first distinguished 15 tumor types, reduced in 1932 to 10, which could be matched to the medullary epithelium or its derivatives. These were medulloblastoma, neuroepithelioma, glioblastoma multiforme (to include the spongioblastoma multiforme [112, 944] and the polymorphic glioma [2381], pinealoma, spongioblastoma (which included the unipolar spongioblastoma [112] and the polar spongioblastoma [2169]), astroblastoma, astrocytoma, ganglioneuroma, ependymoma, and oligodendroglioma. This classification [112, 113], therefore, provided a histogenetic foundation for the various tumor types, as summarized in Fig.6.1. With this classification, the authors also wanted to attribute a biological meaning to the diagnostic label, i.e., they wanted it to contain indications on survival, as inferred from clinical data, which were widely taken into consideration in the preparation of the definitive version.

According to survival criteria, Bailey [106] gave the following order of decreasing malignancy: medulloblastoma, neuroepithelioma, glioblastoma multiforme, pinealoma, ependymoma, astroblastoma, spongioblastoma, oligodendroglioma, ganglioneuroma, astrocytoma. Even if criticized and blamed for having stressed cytogenesis, which was not yet well understood, by creating even nonexistent elements such as the glioblast (to maintain in the system tumors such as the glioblastoma), this methodology of tumor classification represented, nonetheless, for the neurosurgeon and the neuropathologist an undoubted practical advantage, and therefore it was universally accepted.

Almost at the same time, another classification was developed by Roussy et al. [2381]. It was based on the similarity that tumor cells have with embryonal or mature elements and also took into account progressive or regressive events within the tumor. It comprised astrocytomas, fibrillary and nonfibrillary gliomas, glioblastomas, and spongioblastomas. Roussy, in fact, criticized the too exact identification of the tumor elements with the corresponding stages of maturation of the cells of the primitive epithelium used by Bailey, because he thought that the knowledge of the histogenesis of the CNS was still too fragmentary. In the atlas of Roussy and Oberling of 1931[2380] it is stressed that the classification was based only on the similarity of the tumors with embryonal tissues. The following tumor types were named: (1) gliomas: astrocytoma, oligodendroglioma, glioblastoma; (2) ependymochoroidal tumors: ependymocytoma, ependymoblastoma, ependymoglioma, plexus-papilloma; (3) ganglioneuromas; (4) neurospongiomas; (5) neuroepitheliomas.

Numerous other classifications were subsequently devised, including that of Penfield [2170], which was very close to that of Bailey and Cushing [112]. The names "piloid" astrocyte and "piloid" astrocytoma were introduced; the term piloid recalls the arrangement and the appearance of the isomorphous gliosis. The methodology of Bergstrand deserves special mention; he elaborated the surgical series of Olivecrona and accepted his subdivision into benign and malignant tumors [171, 172, 173]. Among the former, he included the fibrillary, the protoplasmic, and the gigantocellular astrocytoma and among the latter, the polymorphic, the fusiform, and the protoplasmic glioblastoma. The great merit of Bergstrand was, however, the separation of the cerebellar astrocytomas from the cerebral astrocytoma group; he called them "embryonal gliocytoma" and subsequently "glioneuroblastoma," to underline their malformative character. This distinction found later not only morphological, but also valid biological foundations.

In the classification of Hortega [1189, 1190], the distinction was made between "gliomas" deriving from the glia proper and the "paragliomas" deriving from the ependyma, choroid plexus, pineal body, and so forth. This distinction was later to be accepted by Zülch [3134]. According to Hortega, cells which develop from the medullary epithelium can give rise on the one hand to gliomas, through the glioblast or "stem cells", and on the other to paragliomas. The different glial types

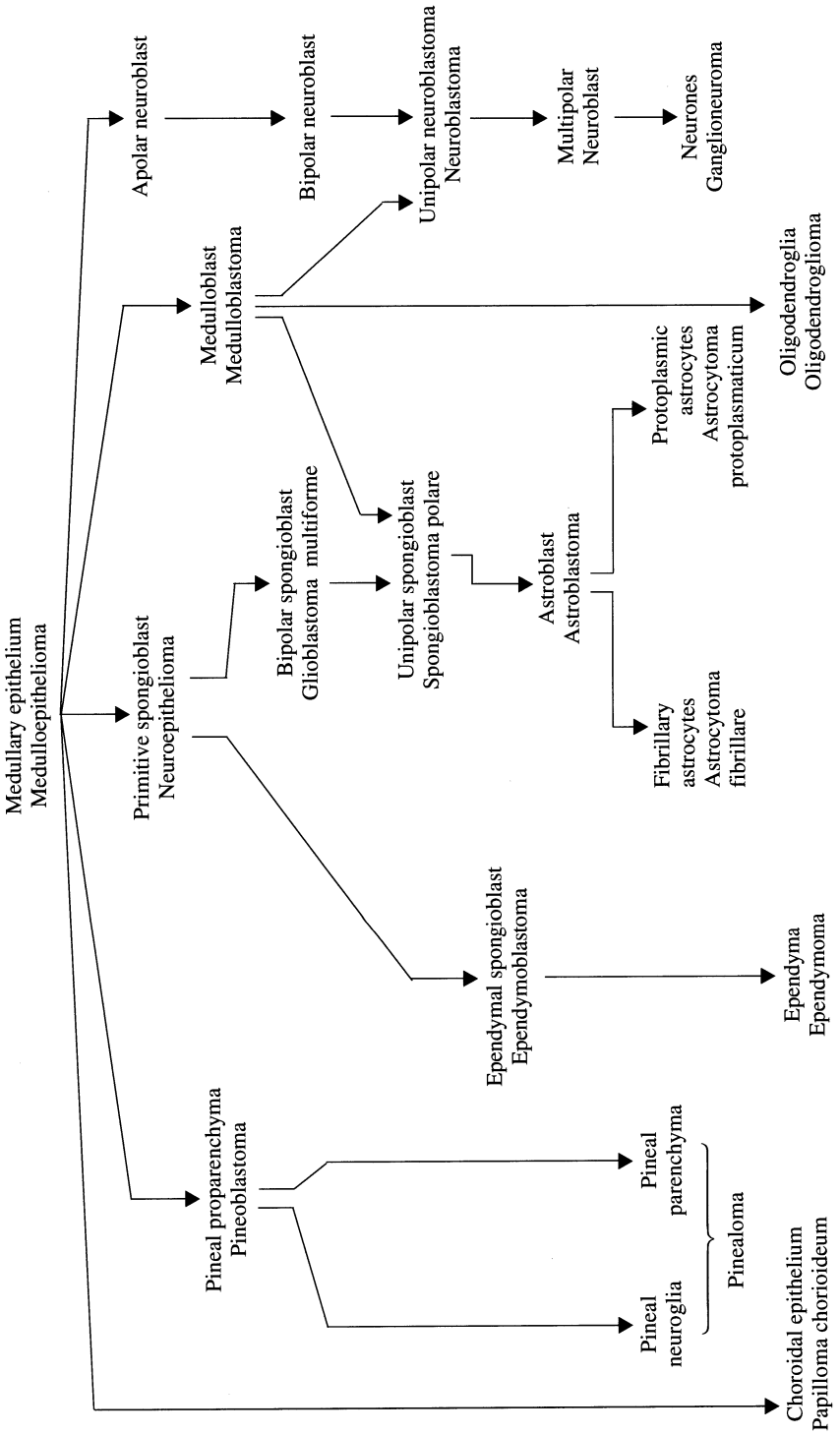


Fig. 6.1. Bailey's classification

and, therefore, the different glial tumors, among which there could be transitional forms, would derive, in fact, from the glioblast. His classification was purely histogenetic and reflected the fact that he belonged to a school primarily interested in histology, particularly investigations with metal impregnation techniques. The tissue architecture was not sufficiently taken into account, and biological clinical data were almost lacking, so that there was a strong discrepancy between many tumor groups and their respective prognosis. Hortega's classification is, accordingly, biologically based, difficult to interpret, and at variance with contemporary or immediately subsequent classifications. The diagnostic label given to a tumor after transferal into another biologically based classification system indicated a completely different tumor. For example, according to Hortega the term astroblastoma indicated a group of tumors with differing biological behavior. These tumors, therefore, were or will need to be placed individually under other names in classifications which had, or will have, taken biological data into account.

In the cerebral tumor system elaborated by Scherer [2475, 2477], the histogenetic classification had no meaning except for mature tumors, such as oligodendroglioma and astrocytoma. For other oncotypes, the cytological diagnosis was not useful to identify the elements of origin or to establish how these would have differentiated. Furthermore, the elements of the matrix were themselves tumor cells, i.e., modified cells. He underscored most of all the architecture of the tumor, the stroma, and tumor growth and distinguished, within the neoplasia proper, secondary and tertiary structures. Scherer's system was more a principle than a true tumor classification, and the conclusions reached on prognosis were not fully consistent with clinical observations. The most important thing to be recalled is that, according to Scherer, there are no circumscribed astrocytomas; they all have a diffuse type of growth, and the majority undergo dedifferentiation toward glioblastoma. There would, therefore, be "primary" and "secondary" glioblastomas derived from astrocytomas, through a process which today is called anaplasia.

Recognizing the great importance of anaplasia in the cytology of gliomas, Cox [506] proposed to classify them into tumors of adult tissue (astrocytoma, oligodendroglioma, ependymoma, pinealoma, and ganglioneuroma), anaplastic forms (glioblastoma multiforme), transitional tumors (astroblastoma, polar spongioblastoma), medulloblastomas, and rare tumors of the medullary epithelium and neuroepithelium. The classification of Chiovenda [428], which was very complex because of the large numbers of subdivisions, belongs to this period. Chiovenda recognized four groups of tumors: gliomas, neuromas (formed by neural cells), glioneuromas, and pinealomas. Gliomas were either typical or atypical. The former encompassed astrocytic, ependymal, and choroidal forms which could be mature or immature. The latter comprised glioblastomas belonging to diverse types. Various glial oncotypes were, therefore, distributed in this framework.

Extending the concept of anaplasia, limited to the glioblastoma by Roussy et al. [2381] and Cox [506], Kernhoan et al. [1405] proposed a new classification of cerebral tumors, applying to them the principle of grading introduced by Broders [292, 293] for the epitheliomas and then extended by the Mayo Clinic to tumors in general. The different types of tumors did not develop from tissues at different stages of maturation but instead through a process of anaplasia which would come into play in cerebral ontogenesis. For example, in their system of "grading" one passes through increasing degrees of anaplasia from the protoplasmic and fibrillary astrocytoma, through the astroblastoma, to the glioblastoma. In Fig.6.2 this scheme is fully reproduced. This classification, by rejecting the histogenetic basis, is maximally simplified, also because some tumors, such as polar spongioblastoma and neuroepithelioma, are excluded. This classification offered several advantages at the practical neurosurgical level for which it was specifically designed. A new principle of systematization of cerebral tumors is thus introduced, borrowed from nonneurological pathology where it has led to good results, and applied to a tissue with a complex cell composition such as the nervous tissue.

New	Old, with new in parentheses
Astrocytoma, grades 1–4	Astrocytoma (astrocytoma, grade 1) Astroblastoma (astrocytoma, grade 2) Polar spongioblastoma (obsolete) Glioblastoma multiforme (astrocytoma, grades 3 and 4)
Ependymoma, grades 1–4	Ependymoma (ependymoma, grade 1) Ependymoblastoma (ependymoma, grades 2–4) Neuroepithelioma (obsolete) Medulloepithelioma (ependymoma, grade 4)
Oligodendroglioma, grades 1–4	Oligodendroglioma (oligodendroglioma, grade 1) Oligodendroblastoma (oligodendroglioma, grades 2–4)
Neuroastrocytoma, grades 1–4	Neurocytoma Ganglioneuroma Gangliocytoma Ganglioglioma } (Neuroastrocytoma, grade 1) Neuroblastoma Spongioneuroblastoma Glioneuroblastoma and others } (Neuroastrocytoma, grades 2–4)
Medulloblastoma	Medulloblastoma

Fig. 6.2. Kernohan's classification

The scheme of Kernohan et al. [1405] has been accused of not taking into account the regressive cellular changes which can produce a polymorphous picture, without changing the grade of malignancy. Diverse morphological aspects may be present in different areas, without the general biological behavior of the tumor being affected. If the "grading" is applied to a small biopsy fragment, the prognosis indicated by the diagnostic label may be wrong [3134]. The principle of "grading" could only be applied to autopsy material, when the entire neoplasm is examined, because anaplasia may be the result of a local phenomenon of lesser prognostic importance [2415]. The possibility that a tumor may be diagnosed as an astrocytoma on biopsy and as a glioblastoma at autopsy does not escape anybody's attention. On the contrary, in many glioblastomas it is not possible to find any sign uncovering their evolution from a more differentiated tumor. These tumors, therefore, must have had such a character since the onset (primitive glioblastomas of [2477]).

In many ways similar to the classification of Kernohan et al. [1405] is that designed with exclusively practical intent by Ringertz [2325]. Three grades, instead of four, are used (benign, intermediate, and glioblastoma) and applied to astrocytomas, ependymomas, and oligodendrogliomas. It is, however, to be stressed that the number of glioblastomas to be considered as originating from

ependymomas and oligodendrogliomas is certainly less than could be deduced on the basis of their frequency. In this regard, it is important to highlight that anaplasia may proceed such as to erase any trace of the preceding tumor and, therefore, hamper the identification of the secondary origin of the glioblastoma. Even evaluating a glioblastoma as an anaplastic tumor originating from more differentiated tumors, the Swedish author is against abolishing such a term in the classification, as occurs in the scheme of Kernohan et al.

Another biomorphologic classification distinguished tumors deriving from parenchymal cells which form the CNS (oligodendroglia, astroglia, ependyma, and neural cells) from those deriving from cells of the adjacent organs (pineal cells and choroid epithelium) and from embryonal germs (neuroblastomas and medulloblastomas) [367].

In more recent years, the most accepted classifications have been those of Zülch [3134] and of Russell and Rubinstein [2415].

The classification of Zülch [2415] stems from that of Bailey and Cushing conceived not as an absolute dogma, but as a useful, working hypothesis. The tumors categorized by the American authors are maintained as biological entities, independent of their histogenetic problems. The intermediate aspects, the variations in type and so forth, are considered as variants which are specific for each group. Particular importance is attributed to the regressive events as capable of modifying the morphology of a tumor; because of this they are considered as specific manifestations of the tumor. It has to be stressed that in this classification there are a certain number of nonclassifiable tumors. Adhering in part to the concept of Hortega, Zülch distinguishes neuroepithelial tumors into medulloblastomas, gliomas, paragliomas, and gangliocytomas. The medulloblastomas are undifferentiated tumors; the gliomas, paragliomas, and gangliocytomas are differentiated. Among the anaplastic tumors are the glioblastoma and, perhaps, the ependymoma and the anaplastic pinealoma.

The subdivision adopted by Russell and Rubinstein [2415, 2420] also appears to stem from that of Bailey and Cushing, with whom they share the concept of tumor types in which the cells recapitulate the stages of glial embryogenesis. This concept is, however, accepted only if the variations in shape and other cellular features are not indicative of an anaplastic process, which is notably frequent. Medulloblastoma is no longer a separate undifferentiated tumor but, instead, is encompassed within the tumors of the neuronal series because of the prevailing neuronal differentiation. In the classification of Zülch [3134], the medulloepithelioma does not exist as a tumor entity, and the majority of neoplasms containing neuroepithelial structures fall into the group of ependymomas, with which they share the same biological behavior. If medulloblastoma is considered as a tumor of the neuroblastic series [2750, 2415, 2420], there is a place for a medullo- or a neuroepithelioma which would be the true undifferentiated tumor originating from the "indifferent" cells of Schaper [2467]. In particular, the existence of the medulloepithelioma, reaffirmed by Globus and Cares [942], emphasized by many authors [1293, 88, 2473, 2455] as the more primitive multipotential tumor of the CNS. The number of cases published is scanty; however, the importance of this oncotype in the relationship between tumors and cytogenesis is so high that it must be retained in the classification.

A second point of discrepancy between the two classifications is represented by the position of the polar spongioblastoma. Whilst for Zülch [3134] it is a benign tumor arising from the subependymal glia and, therefore, always in relation with the ventricles and characteristically containing Rosenthal's fibers, for Russell and Rubinstein [2415, 2420] it is a rare and primitive malignant tumor. The problem is still a semantic one.

With the term "spongioblastoma" Russell and Rubinstein refer to the spongioblasts of the cytogenesis. These are very immature elements, and therefore the corresponding tumor must have adequate characteristics of immaturity and malignancy. In effect, the tumor alluded to is malignant and immature, but it is extremely rare. Zülch, on the contrary, does not refer to the cytogenesis but to the resemblance of spongioblastoma cells to spongioblasts and employs the term to indicate a vast group of tumors, usually benign, including the so-called cerebellar astrocytoma, which in the nomenclature of Russell and Rubinstein are included among the pilocytic astrocytomas [3141]. The cerebellar spongioblastoma of Zülch is to be identified with all the types of cerebellar astrocytomas of Russell and Rubinstein. There are, however, no doubts about the biological behavior of this neoplasm. It is obvious that Rosenthal's fibers, thought by Zülch to be characteristic of spongioblastomas, are found by the other authors in astrocytomas.

Another point of controversy is the astroblastoma, not recognized by Zülch [3134] in the histogenetic sense [112] as a tumor entity, but as a feature which occurs in malignant gliomas and is therefore very close to glioblastoma. For Russell and Rubinstein [2415, 2420], on the contrary, it is a tumor per se.

The most important problem remains that of the glioblastoma. Zülch considers it a separate tumor, rarely originating from a preexisting astrocytoma [2821], in contrast with previous views [1405, 2325]. The possibility of anaplasia and the dedifferentiation of astrocytomas are satisfied with the creation of a group of malignant astrocytomas. By contrast, based on previous concepts [2477, 2325], Russell and Rubinstein discuss whether the category of glioblastoma should be maintained, as there is so much evidence for its origin following dedifferentiation of an astrocytoma; their anaplastic astrocytoma represents an astrocytoma in which the dedifferentiation may lead to glioblastoma.

Amongst the ependymal tumors, Russell and Rubinstein also accept subependymoma, arising from the subependymal layers and formed by a proliferation of subependymal astrocytes. The term subependymoma was coined by Scheinker [2468] to indicate already known and variously named tumors, which were subsequently renamed. The existence of such a tumor was denied by Zülch, according to whom it would be an ependymoma with pressure atrophy or a variant of spongioblastoma.

At the bottom of the debate on classification there are not only conceptual but also semantic problems. Certainly, both the creation of new names for tumors which were previously included under other labels and the keeping of old names for tumors which instead have acquired a new position have contributed to the polymorphism of the nomenclature.

A symposium on the classification of cerebral tumors was held in Cologne in 1962 with a long discussion on nomenclature. A scheme elaborated in 1958 by the Union Internationalis Contra Cancrum (UICC) as a basis for discussion was presented [1054]. In this symposium, the three main classifications were confronted, i.e., Kernohan et al., Zülch, and Russell and Rubinstein. The "grading" scheme according to Kernohan et al. was defended [2460]. Since the principles of Cohnheim [474] and Ribbert [2311] underlying the recent histogenetic classifications are no longer tenable, it is likely that tumors arise because of some disturbance of the adult cell. Several examples of tumors produced by external agents support this concept. The "grading" system is based, in fact, on the deviation of cells from the normal cytotypes, i.e., on the degree of dedifferentiation present and not on the possibility that, in the development of the tumor, the cells gradually become more malignant, as is erroneously thought. The grade with which a tumor is labeled depends on the time when cells are struck by the cancerous deviation. The naming according to grades does not imply a clinical judgment but refers only to cell metabolism, and the use of four grades is not qualitatively different from that of three grades, widely applied by everyone, when the terms semibe-

nign, semimalignant, and intermediate are introduced. Finally, the criticism that the "grading" system provides a diagnosis-prognosis derived from very small tumor fragments while considering the inhomogeneity of several brain tumors was applied by Sayre to any examination of this type, independently of the classification scheme followed.

In 1979 the WHO (World Health Organization) published a classification based on the work of various groups [3137] which provided a compromise between that of Zülch and that of Russell and Rubinstein. The position of each oncotype in relation to the degree of malignancy was also indicated. This new classification was not unanimously accepted and several criticisms were made, especially in the new systematization of the degrees of malignancy. Glioblastoma, for example, was kept separate from astrocytic tumors and put into the group of poorly differentiated and embryonal tumors. Astroblastoma was maintained as a variant of astrocytoma, in spite of its recognition as a separate entity [1228, 1156].

In the years which followed, a remarkable amount of data has been produced in the different fields of neuro-oncology: immunohistochemical demonstration of new antigenic expression in tumors with their relationship to cytogenesis, molecular biology revelations with their putative relationship to pathogenesis, identification of new tumor subgroups on the ground of statistical studies of survival (on which topic many contributions accumulated [921, 3059, 2009, 470, 856, 1944, 2517, 2523]) and identification of new tumor entities. As examples, the problem of primitive neuroectodermal tumors (PNET) [2355, 157], pineal tumors [1074], polar spongioblastoma, and many others regarding meningiomas [1390] required a new consensus on classification.

The problem of PNET can be regarded as paradigmatic. The term was first introduced by Hart and Earle in 1973 [1069] to label 23 tumors which could not be classified into any of the known categories and were characterized by undifferentiation, malignancy, circumscription, cyst formation, and appearance in young subjects. In the past decade, studies [158, 2353, 2356] again suggested grouping together tumors composed of undifferentiated neuroectodermal cells, with or without foci of differentiation, occurring in the CNS of children or young adults in different locations.

All further descriptions [2134, 237, 1494, 675, 862] indicated one or more differentiations. Rorke [2353] proposed a scheme based on the concept that these tumors, first of all medulloblastoma, derived from the neoplastic transformation of primitive neuroepithelial cells, undifferentiated but capable of differentiating along neuronal, glial and ependymal lines. Subsequently, a modification of the WHO classification was proposed in order to include the group of PNET which was composed of medulloblastoma, neuroblastoma, pinealoblastoma, and ependymoblastoma [2356].

The most important question is whether or not the use of the term PNET is a simplified and more reliable tool to categorize embryonal tumors. Undoubtedly, it is an attempt to define tumors not easily classifiable, because of their uncertain nature by means of descriptive instruments instead of referring to the "cells of origin" [2355]. However, if only undifferentiated tumors are considered, the problem is practically restricted to medulloblastoma. Becker and Hinton [158] found 112 medulloblastomas in a series of 127 undifferentiated tumors. In our series, 112 out of 117 were found [2519]. In order to avoid confusion, since the term medulloblastoma is used too much by clinicians, it has been proposed to limit the term PNET to supratentorial tumors [2855].

The next question is whether medulloblastoma is a tumor specific to the cerebellum or a primitive undifferentiated tumor, together with similar supratentorial tumors of the pineal region and of the spinal cord, independently of the nature, uniformity, or multiplicity of the primitive undifferentiated cells [2356].

Several objections have been made to the PNET categorization. First, since the undifferentiated nature of the cells is emphasized, the system might accept cells that are simply unidentifiable and thus become a category of undiagnosed tumors; second, it includes heterogeneous and noncomparable tumors; and, third, it does not take anaplasia into due consideration [2393]. As anaplasia is a progressive phenomenon, it could be responsible for the undifferentiated appearance of a tumor. Medulloblastoma could, for example, be the anaplastic end stage of an astrocytoma [1966, 2405, 2540]. Not only it is difficult to distinguish between embryonic and anaplastic tumors, but the maturation of an undifferentiated tumor could also go unrecognized [132, 761, 1112]. Application of the PNET system might largely depend on the interpretation of the cell forms, and thus it might be impossible to obtain uniform diagnoses from different examiners. A better knowledge of the embryological origin is required; reliable prognostic evaluations cannot be made on the basis of the histological results as a similar morphology does not imply a similar biology [1851].

Very recently, a panel of well-defined and extensively characterized Mabs was used on a series of pediatric brain tumors: In one third, both neuronal and glial differentiation was present [1914], as were positive neuroendocrine markers [983]. These observations support the PNET concept, even though 35 out of the 37 cases studied were located in the posterior fossa, i.e., they were medulloblastomas. However, it has been proposed that, in order to distinguish primitive cells showing differentiation from undifferentiated primitive cells, the former should be called "neuroectodermal cells" committed to neuronal, astrocytic, or ependymal differentiation. Molecular biology data reported deletions on 17q or 17p or *myc* amplification [196, 2254]; the neural and neuroendocrine protein gene product 9.5 isolated from human brain [1268] has been demonstrated in 21 tumors [1066] even though they were obtained from posterior fossa tumors, i.e., medulloblastomas. Still other immunohistochemical findings are available concurring to define characteristics of PNET. In some cases different cytokeratin proteins, together with S-100 protein and vimentin, were expressed, indicating a wide range of differentiation patterns in PNET of early infancy [1004A]. Other investigations showed that whereas astrocytomas and ependymomas are positive for nerve growth factor receptor (NGFR), only few PNET are positive, these being the ones with astroglial differentiation [115A]. A systematic immunohistochemical study of ontogenesis and of PNET demonstrated that in these tumors a certain recapitulation of the ontogenetic development of differentiation is present [1445B].

The use of the term PNET has practical and theoretical meanings. From the practical point of view, it indicates tumors with various kinds of differentiation and with a variable amount of cells which appear undifferentiated [2355]. From the theoretical point of view, the problem of the existence of a common, primitive, undifferentiated tumor cell (or cells) is of paramount importance, even though the meaning of the term "primitive" has not been further specified [157, 2355]. The concept of PNET is based on a criticism of the cytogenetic scheme of embryonal neuroepithelial tumors, because of the impossibility of predicting the differentiating potential or of establishing the ancestry of primitive neuroepithelial cells in a tumor by current morphologic techniques [980, 2355]. It is also based on the observation that tumors are composed of primitive neuroepithelial cells whose differentiation does not necessarily follow normal schemes [2355].

Perhaps a definitive system of classification, taking into account all these points of view, is not possible. Classifying cerebral tumors also means making a histological diagnosis and recognizing histological prognostic factors. There are a number of limiting factors, one of which is the reproducibility of the histological diagnosis. Within the confines of the Childhood Brain Tumor Consortium (CBTC), for example, the reproducibility of the systematization in the diagnostic classes of the WHO has been evaluated. The Px, or conditional probability of agreement between different neuropathologists, has been found to vary for various tumors. The pilocytic astrocytoma, ependymoma, medulloblastoma, and astrocytoma have lower values, and the use of a single category of "astrocytoma" to include the fibrillary and protoplasmic varieties is recommended. It is also suggested that the criteria of anaplasia in astrocytomas and ependymomas be redefined [424]. Another point of great difficulty is to establish a grading system which could also take into account clinical and therapeutic parameters while satisfying at the

same time the clinical necessities [577, 567, 330A]. Advances in antigenic expression analysis and molecular biology oblige us to leave the matter of classification open. However, for the present, after meetings held in Houston (1988) and Zürich (1990), a new version of the WHO classification has been presented [1443]. In principle, its suggestions are followed in the present book.

7 The Concept of Malignancy: Anaplasia, Cell Proliferation, Metastasis

7.1 General Considerations

In intracranial tumors the concept of malignancy has a clinical and a biological sense. Contrary to tumors in other organs, intracranial tumors grow within a closed space whose only reserve depends upon shifts in the CSF. The brain and the spinal cord are formed by different structures composed of cells in various stages of differentiation: They are, therefore, inhomogeneous from an anatomical and functional point of view. Whilst some cerebral structures may withstand severe damage for a long time without the life of the patient being compromised, others cannot tolerate, even for a short time, minimal damage. A tumor, therefore, may be "malignant" and lead to a fatal outcome solely on the basis of its location. Given the same histological appearance, an astrocytoma of the aqueduct will be more "malignant" than a similar astrocytoma in the hemisphere. The criteria of operability also play a role, so that an astrocytoma of the third ventricle may be more "malignant" than an analogous tumor of the cerebellar hemisphere.

The concept of biological malignancy refers instead to the proliferating potential of the neoplastic cells which conditions the histological and other features of the tumor, rapid infiltrative and destructive growth, recurrence after surgical removal, and metastasis as for tumors in other organs. The histological signs of malignancy depend on the genuine growth potential of the tumor.

The cellular appearances of neuroepithelial tumors in some way correspond to those shown by the normal stages of neurocytogenesis up to the final differentiation step. Concepts such as dedifferentiation, anaplasia, and cellular atypia were often expressed in the older literature. Atypia was meant to express the taking on by tumor cells of morphological and metabolic properties no longer reconcilable with the stages of cytogenesis, either of the same series to which tumor cells belong or of other series. The concept of anaplasia was related instead to dedifferentiation, which meant the loss of morphological molecular characteristics typical of that grade of differentiation and a return to the characteristics of earlier stages. Alternatively [3122] anaplasia meant simply the process by which cells failed to differentiate, never reaching morphological maturation. In practice, atypia should follow anaplasia.

Many of the morphological structural features of glial tumors, such as the malignant transformation of astrocytomas, may be described dynamically along the lines of cellular dedifferentiation. The foundations of the different "grading" systems [1405, 2325] are still valid if cell dedifferentiation is considered in relation to the neoplasm as a whole.

The histological signs indicative of malignancy are nuclear polymorphism, immature appearance of the cells, absence of one or more features of differentiation, alteration of the nucleocytoplasmic and nucleolo-nuclear ratios, nuclear hyperchromasia, formation of giant or polynucleated cells, presence of mitoses (especially if atypical), regressive events such as necrosis and stromal changes. None of these characters may be considered by itself as indicative of malignancy, since any of them may be found in nonmalignant tumor conditions or even in pathological nontumor conditions as a secondary nature.

The divergence of opinions regarding the DNA content of neoplastic cells and the meaning of nuclear hyperchromatism, which were much debated topics in the past, no longer exists, even though the ploidy and the frequency of mitoses remain important diagnostic characteristics. The morphology of a tumor represents the result of a series of hierarchical biological events. The prognostic value of a malignant histological phenotype must be confirmed by a statistical analysis of survival.

In human pathology, there are no systematic observations on the early stages of development of brain tumors, only reports of neoplasms occasionally found at autopsy [1236]. However, by considering the frequency of the different oncotypes in adults and children, and their mode of growth, and by comparing them to known experimental models, especially those obtainable with nitrosourea derivatives, general trends may be identified.

Fetal neuroepithelial cells in the latest stages of development may be the target of neoplastic transformation [2406, 2393], as are neuroepithelial cells of the five additional loci where neurocytogenesis also occurs in postnatal life [1637], i.e., the subependymal zone, the astrocytes and oligodendrocytes during myelinogenesis, the external granular layer of the cerebellum, the fascia dentata of the hippocampus, and the molecular subpial layer of the cerebral cortex.

Neoplastic transformation may occur in successive steps as the target cells differentiate and migrate. As a consequence of this displacement, the tumor may "arise" at sites away from that of the first transforming event [2406]. The essential factor is that the target cell must still be capable of multiplying at the time the transforming event occurs [2406]. The "neoplastic vulnerability" of neuroepithelial cells varies according to a series of factors: the existence of a reserve population of stem cells, the ability of already differentiated cells to reenter the cell cycle, the number of cells in cycle at risk at a given time, the time period during which a given cell population remains in the cycle and its state of differentiation [2396]. Taking into account that the neuroepithelial cells struck by the neoplastic transformation continue to differentiate, and that differentiated tumors may undergo anaplasia, the formal pathogenesis of gliomas must be discussed in terms of the bipolarity differentiation/ dedifferentiation.

Astrocytomas can be considered an example of differentiation after transformation. An interesting observation has been made on this. The majority of astrocytoma cells are GFAP-positive but negative for A2B5 and galactocerebroside (GC) antibodies. This combination would indicate an origin from type 1 astrocytes. Few tumors, and only those of low grade malignancy, contain A2B5- and GC-positive cells [217]. Once malignancy arises, the already mentioned typical histological signs appear.

Contrary to what occurs in other organs, the number of CNS cells susceptible to neoplastic transformation in adult life is minimal, and these cells usually have a low

turnover. Therefore, even though a tumor may arise from the neoplastic transformation of neuroepithelial cells in adult life, most tumors derive from the transformation of neuroepithelial cells during embryonal morphogenesis. One must also consider that the differentiation of transformed neuroepithelial cells does not necessarily follow normal schemes: Specific characteristics of a certain normal cell type may be expressed by transformed cells following alternative avenues of differentiation. An example may be the expression of GFAP in the plexus papilloma [2396] or the development of striated muscle fibers in medulloblastoma; thus, differentiation could be metaplastic or heteroplastic.

The more precocious the cytogenetic stage at which transformation occurs, the more numerous the lines of differentiation which the tumor may express. A typical example of this is medulloepithelioma [2473, 2455]. On the other hand, the shorter the susceptible cytogenetic phase or the lower the susceptibility to transformation, the rarer the related tumor. An example of this is also the very rare medulloepithelioma, which represents the neoplastic counterpart of the earliest and shortest development stage. Cerebral neuroblastoma could correspond to a longer late stage, but it is also rare because when neuroblasts migrate they no longer replicate, and thus the tumor can differentiate in only one direction. The greater frequency of peripheral neuroblastoma would be due to the longer period of migration and proliferation of the cells of the sympathetic system. Desmoplastic ganglioglioma has been given as an example of a rare tumor, because the vulnerability of its corresponding embryonal elements is limited in time [2396]. Tumors like medulloblastoma and gliomas in general, whose corresponding embryonal cell counterparts have a long period of vulnerability, are more frequent. The precursor cells of medulloblastoma remain a long time in a mitotically active phase and are located primarily in the external granular layer of the cerebellum. For gliomas, the long period of vulnerability is due to the persistency of glial cell turnover during adult life.

The main difficulty, especially with gliomas, is represented by the relationship between benign and malignant forms. Glioblastoma is considered the end result of progressive anaplasia in astrocytoma. The cells go from the nonproliferative to the proliferative pool, the growth fraction increases, and signs of increased proliferation, such as a high number of mitoses and high cell density appear. Angiogenesis and necroses take place, with all the known histological consequences.

The neoplastic transformation is a multistep process which occurs in stages. Morphologically, through anaplasia, tumor progression proceeds to the final malignant features of the neoplasm as commonly seen in biopsies and at autopsy. It may be defined as a series of consecutive alterations of multiple units: growth rate, invasive capacity, ability to grow freely in body fluids and independently of hormones [805]. Subclones replace the predecessors. The pathology may be interpreted as the result of a dynamic continuum in which the most important characteristic is selection by competition [2539, 1445].

Molecular biology now provides much detail, but it is not yet clear whether the new data have to be considered on the pathogenetic slope of tumor progression or as a simple servo-mechanism of cell functions and aspects. Changes such as translocation, amplification, gene rearrangement, and point mutation have been widely studied and interpreted. Voluminous information is also available on the cooperation between oncogenes in neoplastic transformation, on transforming growth factors [524, 1227], and on

the tumor suppressor genes [1782, 216]. Progressive stages of malignancy are supposed to be associated with a series of molecular events, among which specific somatic losses of heterozygosity predominate. Glioblastoma, for example, could be a common terminus reached by some cellular subtypes through a common molecular pathway [477]. A scheme can be constructed in which the loss of different chromosomes (17p, 13, and 22) occurs both in early and advanced tumors, whereas the loss of chromosome 10 is restricted to glioblastoma. It seems that a gene inactivation on chromosome 10 could be effective in the development of glioblastoma [207].

All the molecular biology data are also interpretable in morphological-diagnostic terms. In the diagnostic field few molecular biology applications are today available, in particular concerning the amplification of EGF.R [2292, 3071, 207]. In this field, we have to rely upon the rules deriving from the concept of anaplasia. This is today interpreted as the result of genotypic heterogeneity, a consequence of the genetic instability of tumor populations and of the progressive increase of the mutation rate, conditioning a phenotypic heterogeneity. Anaplasia may also be considered either as a maturation arrest [3122] or as an accelerated growth of already differentiating cells [354]. This concept interlocks with that of "stem cells" whose existence has been postulated but as yet not demonstrated. They do not need to be the same as those of cytogenesis. Independently of their identification with "primitive, undifferentiated" cells and of their capability to express differentiation antigens, which is a crucial point in neuro-oncology, it is sufficient that they can re-enter the proliferative cycle, as seems possible for astrocytes and oligodendrocytes [1705]. On the morphological level, cellular atypia, which is not necessarily present, is the first consequence of anaplasia.

Cell heterogeneity has been documented by karyotypic analysis, [1768, 2603], cytophotometry, flow cytometry [1197], and comparison between established cell lines [206]. It remains to be established whether all the phenotypic variations are also genetic, and how or whether they depend on epigenetic factors [204, 2406].

With the occurrence of anaplasia, the growth fraction increases [1196] because cells are transferred to the proliferative pool leading to a series of phenomena characterized by an increase in cell density, mitotic index, and labeling indices such as those obtained with BUdR or Ki-67. These events are a direct consequence of the increase of the growth fraction, while other overestimated features such as nuclear polymorphism, cellular monstrosity, and in part also necrosis are indirect consequences.

The increase in number of mitoses and cell density may, however, be a phenomenon circumscribed within the tumor, at times easily missed in the histological examination, so that beginning anaplasia may go unrecognized.

An example of anaplasia by cell heterogeneity is given by expression of GFAP, the characteristic marker of astrocytic differentiation [580, 251], evaluated as an element of heterogeneity [1321]. In gliomas, it is found in all cells with fibrillogenic capacity, and its expression is inversely correlated with the degree of anaplasia [712, 2903, 2923]. GFAP is lacking in too primitive and in anaplastic cells. It has to be emphasized that the small hyperchromatic cells, which proliferate rapidly [1196] and are responsible for tumor invasion and growth in glioblastoma [914], are GFAP negative [2923]. The appearance of anaplasia in astrocytoma and the active cell proliferation in glioblastoma are sustained by the progressive increase of a cell population rich in mitoses, with isomorphous nuclei and negative for GFAP [2515, 1536] (Figs.7.1–7.3).

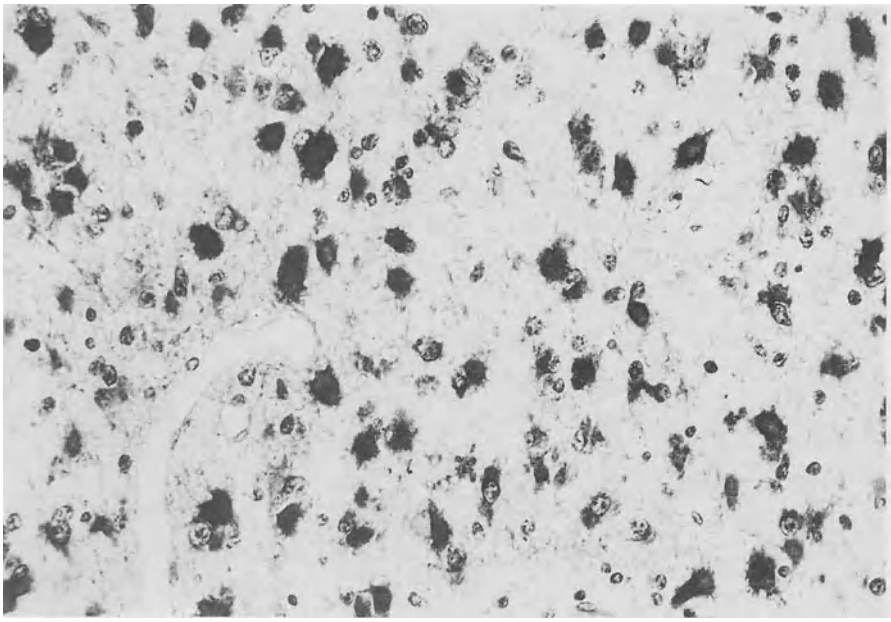


Fig.7.1. Astrocytoma: all cells express GFAP, PAP-DAB, ×400 [2484]

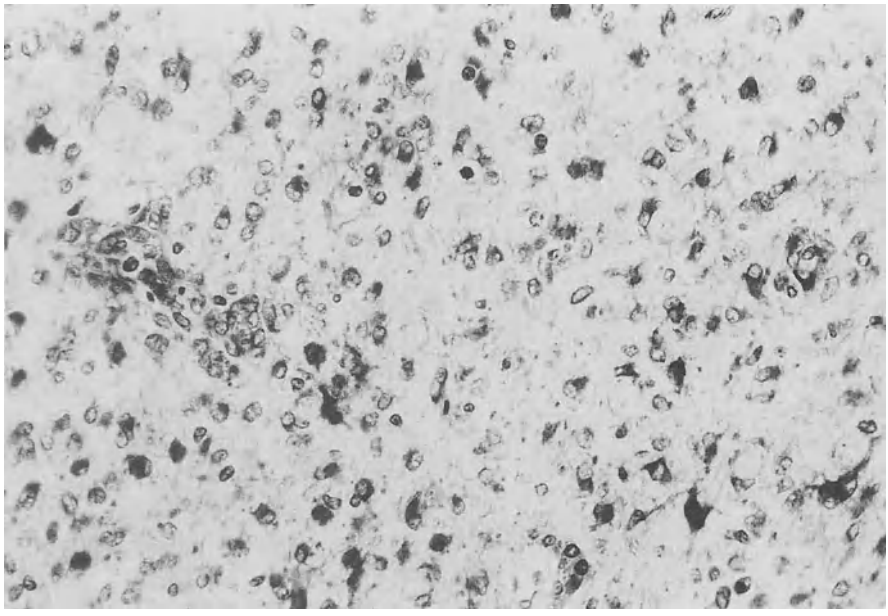


Fig.7.2. Anaplastic astrocytoma; some cells still express GFAP, but many are negative and mitoses are present, PAP-DAB, ×400 [2515]

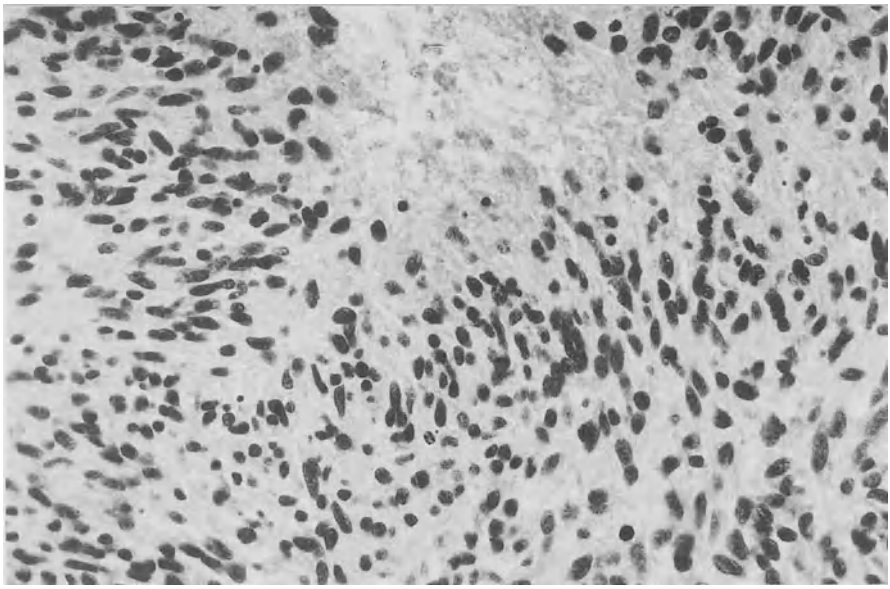


Fig.7.3. Glioblastoma: in the proliferating area no cell expresses GFAP, PAP-DAB, ×400

The recognition of the malignant transformation in vivo is of paramount importance. It is a matter of everyday debate, especially after the introduction of new imaging techniques such as CT, MRI, and stereotactic biopsies. Practically speaking, the most common problem encountered in histological diagnosis concerns the degree of malignancy. It could be related to a surgical sampling error, for example, in small specimens taken by stereotaxis. In this regard, the importance of imaging in the interpretation of the histological findings must be stressed. It is also possible that malignant transformation can occur after the histological diagnosis has been made. Since anaplasia may be a localized and mild rather than a generalized and intense phenomenon [2419], it may be missed both histologically and by neuroimaging; it may be detected only when it reaches a certain extension and intensity.

7.2 Cell Kinetics

The growth fraction, number of mitoses, nuclear polymorphism, and nuclear hyperchromatism are all indicators of the proliferative capacity of a tumor. In the past, they were discussed in relation to the so-called supernormal load of tumor cell nuclear DNA. The classic A and B cells of Caspersson and Santesson (1942) [389], representing the extreme degrees of chromaticity, must be remembered. The nuclear DNA content immediately after cell division is diploid, while in the S phase of the cycle it is tetraploid. One

must remember, however, that many nondividing cells, and even normal ones, have a heteroploid DNA content. Some CNS cells have a tetraploid content [1576, 1575].

The cytophotometric analysis of DNA is not reliable enough to evaluate minimal differences. Flow cytophotometry, based on the intensity of fluorescence emitted by a dye bound to the DNA [2906], is preferable. It has been demonstrated that the quantity of DNA is very variable in malignant gliomas where, beside diploid cells, there are many aneuploid or polyploid ones and many in S phase, while in benign tumors there are few cells in S phase, and the DNA content is more constant [819, 1201, 1364]. Obviously, the variations from one region to another of the same tumor are much greater in malignant tumors [1201]. On the basis of the DNA content, the various classes of cells have been found to be clonogenic [1203], and the variations genetic [1197]. Questions remain about whether clonogenic cell populations in culture correspond to the tumor cell populations in vivo [1197].

Flow cytophotometry may also be applied to tissues fixed and embedded in paraffin [1092, 1093]: Diploid elements prevail in differentiated gliomas, and aneuploid ones in malignant tumors [917], although the percentage of the latter cells is not high [788].

An old and simple method to evaluate the cell kinetics of tumors is the mitotic count, but it is a restrictive procedure. First of all, the M phase represents only a minimal part of the cell cycle, and second in histological sections only metaphase and anaphase are observable. Furthermore, during slow fixation, mitoses may disappear from tissues because they reach completion or because they are technically not observable [398]. However, the higher the mitotic index the greater its value.

Undoubtedly, it has been the development of autoradiographic techniques which permitted a more reliable definition of precise concepts such as the growth fraction (GF), doubling time of the cell population (T_d), and cell loss (CLF). The GF corresponds to the proliferating pool of cells/total cell population [1866]. The factor CLF has been calculated to be equal to $1-(T_p/T_d)$, where T_p is the potential doubling time [2718].

Autoradiography is carried out with the administration in vivo or in vitro of [^{3}H]thymidine with or without the addition of mitotic inhibitors [2879]. The labeling index (LI) is the proportion of labeled cells. Over the years, fundamental contributions have been added [1317, 423, 1543, 855, 1199, 1202], revealing the LI to be high and greatly variable in glioblastomas (5%–15%), low in well differentiated gliomas (1%), and intermediate in anaplastic astrocytomas (4%). These figures have been found to correlate with the survival data [1199]. The duration of the S phase (T_s) has, in contrast, been noted to be constant (7–13 h), so that the turnover time (T_s/LI $\times 100$) is a few days in malignant gliomas and about 2 months in astrocytomas. Calculation of the doubling time of a malignant glioma must obviously take into account the cell loss. Nevertheless, the autoradiographic method has not been exempt from criticism, some of which have even questioned its validity. In glioblastomas, for example, low values of LI have been found which do not correlate with survival [258]. The passage of [^{3}H]thymidine through the blood vessels is one of these limiting factors, as are the extent vascularization of individual tumor areas and the possibility that thymidine binds to other substances within the tissue [1915].

More recently, a monoclonal antibody binding to DNA which incorporated BrdU has been produced [995]. BrdU, a nonradioactive analogue of thymidine, may be administered in vivo with less damage than [^{3}H]thymidine (Fig.7.4a). The antibody labels

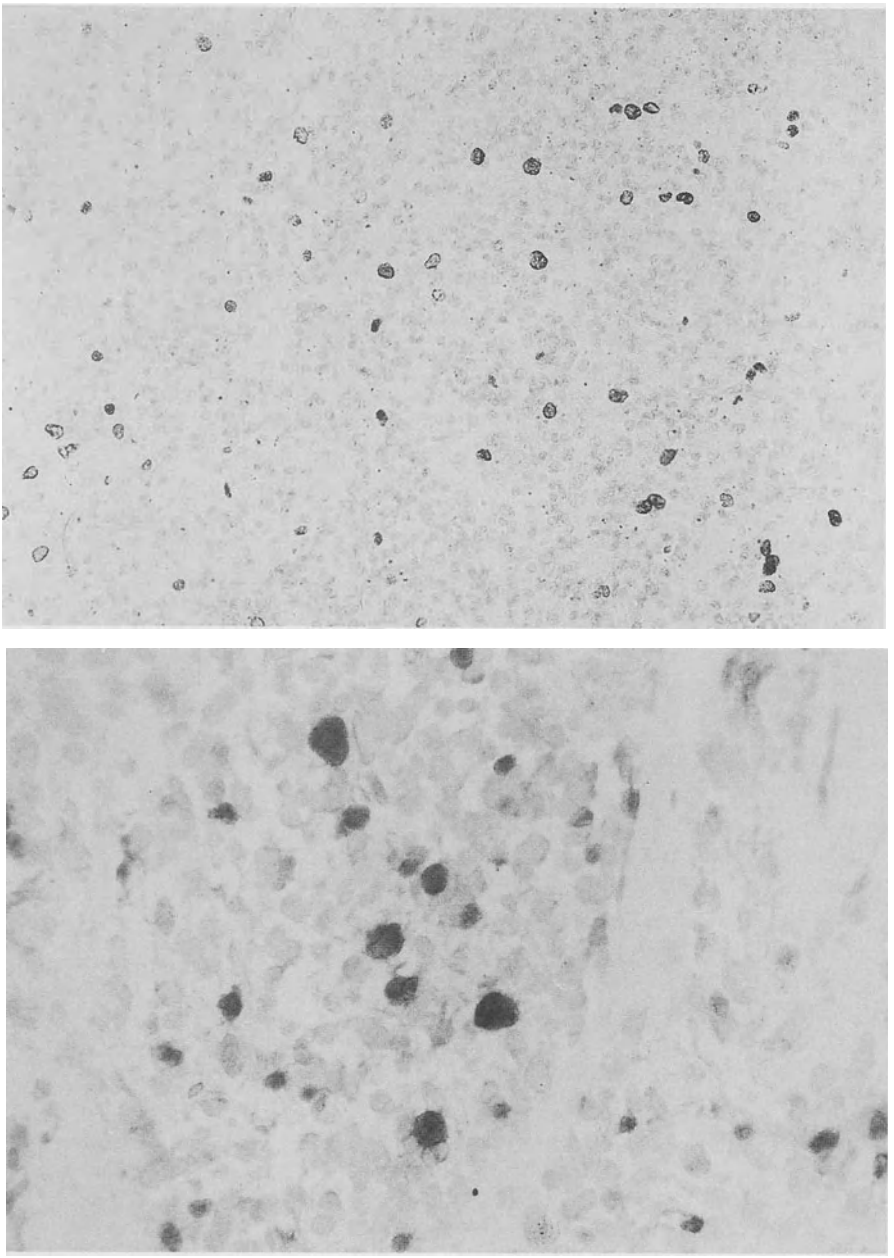


Fig.7.4. a Labeled cells in an ENU induced tumor after in vivo administration of BrdU, anti-BrdU, PAP-DAB, ×400. **b** Human glioblastoma; cells labeled with Ki-67 (Courtesy of Dr. F. Giangaspero, University of Bologna)

DNA in the S phase, and it may be studied both in sections and with flow cytometry [1989]. The LI reflects the proliferative potential of tumors and correlates with survival [1208]. A good correlation has been found between data obtained by the examination of sections and those of flow cytometry [1990]. Tumors with similar histological features may have different proliferative potentials [1205, 1208], and a high LI may indicate a shorter recurrence interval in astrocytomas [1207], ependymomas [1990], and meningiomas [430, 854, 1264]. A good correlation between BrdU LI and a histological grading system has been found [1548A].

A method which may eliminate errors due to the variable vascularization of the tumor, avoids damage to the DNA with subsequent teratogenic effects [1204], and is of easier practical application is in vitro incubation of fragments of tumor tissue with BrdU [1937]. The method has given good results, similar to those obtained with other methods. However, due to the heterogeneity of malignant gliomas, it is advantageous to consider as representative of the tumor the area with the highest LI instead of making an average of the various areas [1937]. However, the possibility has been envisaged that an in vitro method entails the danger of overlabeling.

Undoubtedly, the BrdU method represents a good prognostic tool. Some limiting factors, however, must be taken into account such as the passage of the BBB, the diffusion of the antibody in the tissue, and the intensity of the immunohistochemical reaction. These factors could influence the results both positively and negatively, apart from the sampling errors common to all methods.

As far as the correlation with survival is concerned, it has not yet been ascertained whether the LI with BrdU represents a better prognostic factor than tumor morphology, since no studies with multivariate analysis have compared it with histological, biological, and clinical factors.

Recently, the development of the monoclonal antibody Ki-67 has opened up new avenues [897]. It recognizes a nuclear antigen present in all phases of the cell cycle, except G_0 [898]. In brain tumors, the number of cells labeled correlates with histological malignancy (Fig.7.4b) [338], even if the absolute values may vary from one study to another [918], as in glioblastoma [606]. The method proved to be reliable and statistically significant through quantitative assessment, with differences in the LI among different malignant glioma [2255]. It has also been applied with success to stereotactic biopsies of gliomas [2097] and has demonstrated the presence of a high LI in recurrent or anaplastic meningiomas [2346]. A good correlation has been found comparing the in vitro administration of BrdU with Ki-67 [1937]. A nonlinear relationship between Ki-67 LI and mitotic index (MI) was found in gliomas of different grades and meningiomas, which can be explained by the variability of cell cycle times [2564A].

Another antigen, p105, which is associated with proliferation has been tried. It is found in interchromatinic granules and is increased in proliferating cells [460, 461], but it does not seem to be useful for prognosis [788].

Another way to evaluate the proliferation potential of brain tumors is the visualization of nucleolar organizer regions (NOR) by the silver staining method. This demonstrates nonhistone proteins associated with NOR, which are sites of genes transcribing to ribosomal RNA. Their increased number and reduced size are considered signs of malignancy [621]. A study has been performed comparing the BrdU LI, Ki-67 LI, MI, and mean number of Ag-NOR/nucleus. A statistical correlation was not found among

the different LI, probably because of technical difficulties in recognizing single Ag-NOR within nucleoli, especially in high-grade tumors [1738]. In another study [2211], the results were quite the opposite: The mean number of Ag-NOR per cell paralleled the degree of histopathological malignancy in gliomas. A relationship was also found between Ag-NOR and BrdU LI and survival, lending reliability to the method. Usually, Ag-NOR are studied on paraffin sections. Smear imprints seem to have some advantages over paraffin sections, rendering Ag-NOR more readily identifiable [2409]. With this method [1338], a close relationship was found with Ki-67 LI, and thus Ag-NOR technique may be considered suitable for estimating the proliferative potential of brain tumors, especially in stereotaxic biopsies. The immunohistochemical demonstration of proliferating cell nuclear antigen (PCNA), auxiliary protein of DNA polymerase delta, seems to be a new possibility as proliferation marker of brain tumors [33A, 1694A].

7.3 Metastasis

Distant dissemination in the rest of the body (metastasis) is different from seeding within the CNS via the CSF. The former is a rare event for brain tumors. For a number of years the occurrence of well documented examples of blood borne metastases of gliomas was a matter of debate. Beside completely negative positions [3057, 3134], others used less restrictive criteria in the documentation of cases [523, 2415]. The absence of lymphatic vessels in the CNS, the protection of large veins, the collapse of small veins, the impossibility of growth of neural tissue elements in other tissues, and the short survival of patients with malignant gliomas were reasons given to explain the absence of metastases [3048]. Criteria were developed on the basis of which the reported cases could be accepted. These were [3008] (a) the histologically demonstrable presence of a neuroepithelial tumor in the CNS; (b) concomitant and relative clinical symptoms; (c) histological characteristics of the metastases similar to those of the primitive tumor; (d) negative autopsy findings for tumors in other organs. An analysis of the literature up to 1961 made with these criteria led to the identification of 81 cases, but not all of them were considered to be acceptable [1639]. There were no doubts, for example, of metastases to bone from medulloblastoma; and to cervical and supraclavicular lymph nodes and lung from ependymomas and glioblastoma [742, 2486]. Metastases were also found for mesodermal tumors, such as meningiomas and sarcomas.

The old considerations on the absence of remote metastases [3048] have been demonstrated to be unfounded. Even though there are no true lymphatics in the CNS, a CSF lymphatic drainage system exists, both under normal conditions and during increased intraventricular pressure [1834]. The veins may be invaded by the tumor [1948], and the tumor cells may grow extracranially. It has, in fact, been demonstrated that autotransplants of anaplastic astrocytoma in subcutaneous tissue may grow successfully with a morphology similar to that of the original tumor [145]. It is, however, obvious that, due to the inexpansibility of the cranium, a brain tumor cannot reach the same mass as an extracranial tumor without being fatal, and this limits the possibility of metastases [46]. There are, however, exceptions facilitated by craniotomies, which favor the diffusion to soft tissues and hence to lymph nodes [2419], even though some maintain that this is not essential [65, 277].

Until late 1985, 282 metastatic cases had been reported. Forty per cent were in children, mostly medulloblastomas, followed by astrocytic tumors, ependymomas, and meningeal tumors. In the adult, astrocytic tumors prevailed, followed by meningeal tumors, medulloblastomas, and ependymomas [1166]. Medulloblastoma metastasizes to bone, bone marrow, lymph nodes and, less frequently, to lung, pleura, liver, and breast. Glioblastoma and ependymoma metastasize to the lungs, less often to bone, pleura, and liver. Meningiomas metastasize to lung and pleura, less often to lymph nodes, liver, and bone.

Metastasis is not always accompanied by local recurrence, and there are even cases in which the primitive tumor was not found at autopsy [1448].

With the employment of CSF shunts, cases of metastasis have increased. Of the 282 cases of metastases mentioned above, 34 had a shunt, and 33 of these were in children [1166]. However, with the exception of malignant pineal tumors, this is not universally accepted. The use of a Millipore filter in these shunts seems to have reduced the possibility of metastasis [2133].

The relatively high incidence of extracranial metastases in children can also be explained by their present longer survival due to the improved treatment, and by immunodepression following chemotherapy [674].

The rarity of glioma metastases had also been explained by their growth along the lines of lesser resistance, with a tendency to infiltrate the perivascular spaces rather than penetrate the blood vessels. This was supported by experimental studies [3122, 2010]. Collagen IV studies demonstrated that the endothelial cells, rather than the basement membrane, form a barrier to tumor infiltration. The possibility that tumor cells may enter the blood vessels from the perivascular space [1535] is not generally accepted [1135, 3014]. Vessel penetration, dissemination through the systemic circulation, passage of the cells into the target organ, and the formation of micro- and macrometastases with neovascularization form the steps of the entire process [1673].

Seeding via the CSF is, on the contrary, frequent enough. Metastases may be near or distant to the primitive tumor and single, multiple, or diffuse, as in the "secondary meningeal sarcomatosis." Apart from medulloblastoma, which more frequently than other tumors gives rise to diffuse dissemination, the neuroepithelial neoplasms usually seed along the CSF routes [3134]. Spinal metastases can be found in all neuroepithelial tumors with the exception of astrocytoma [3134]. In ependymomas, for example, the percentage of subarachnoid metastases is high, especially if the tumor is in contact with the CSF pathways. Metastases have even been found from tumors primarily located in the region of the cauda equina [1826]. These latter are tumors which are repeatedly surgically treated, with long survival and massive local recurrence.

Very rarely, the metastasis produces clinical signs before the primary tumor, or its symptoms are so dominant as to require surgical intervention first [450, 2771].

Under the name of "meningeal gliomatosis" are included gliomas with diffuse dissemination to the meninges. The 42 tumors described by Polmeteer and Kernohan (1947)[2218] were subdivided thus: 20 medulloblastomas, 6 glioblastomas, 5 ependymomas, 5 oligodendrogliomas, 3 astrocytomas, 2 retinoblastomas and 1 pinealoma.

Leptomeningeal diffusion is particularly frequent for neuroepithelial tumors in children, where it may occur in 10%–20% of cases [73, 2106]. It has been found in 43% of malignant gliomas, in 27% of medulloblastomas, and in 15% of germ cell tumors. These

figures are greater than those found in adults [2888]. Recently, the number of cases with meningeal gliomatosis in children has increased further, probably due to the improved survival of neuroepithelial tumors after craniospinal radiotherapy. It has been calculated to occur in 50% of medulloblastomas and in malignant gliomas [2109]. Studies in progress tend to see the process of diffusion as regulated by mechanisms of exfoliation, adherence, and cell conglutination [1804].

7.4 Expansion and Invasiveness

Brain tumors grow by expansion or infiltration. Expansion may or may not be accompanied by encapsulation. Neurinomas, pinealomas, teratomas, and meningiomas are fully or partially encapsulated; the capsule, in these cases, does not continue over the dura and fails to prevent invasion of the meninges. Angioblastomas, choroid plexus papillomas, and ependymomas are not encapsulated. They push aside the nervous tissue, which may undergo atrophy and gliosis. In ependymomas, for example, there may be a distinct border between the tumor and the nervous tissue, but this does not preclude infiltration elsewhere. This is true also for oligodendrogliomas (Fig.7.5a). Pineal region tumors, particularly germinomas and pinealoblastomas, grow over the lamina quadrigemina but eventually invade the posterior part of the third ventricle and reach the intermediate commissure, or even the foramina of Monro. The thalami are pushed aside, the posterior part of the corpus callosum upwards, and the vermis downwards and backwards. All these structures may be infiltrated as well.

Growth by infiltration is typical of gliomas but is also observed in other tumors. It may be circumscribed or diffuse [368]. Local and circumscribed infiltration is typical of cerebellar and midline astrocytomas, oligodendrogliomas, and glioblastomas, whereas diffuse infiltration is associated with astrocytomas, glioblastomas, medulloblastomas, oligodendrogliomas (Fig.7.5b), and malignant lymphomas. The limits of the tumor cannot always be established histologically, since its cells are intermixed with normal and reactive cells. Infiltrative growth in one place does not exclude sharp edges of the tumor in other areas.

The spreading capacity of neuroepithelial tumors is largely due to their growth potential and invasive behavior. Invasiveness depends upon many factors, among which are certain biological properties. In vitro studies have shown that the fibrinolytic activity [3113, 1129], phagocytic activity of glioma cells [2052], and high migratory capacity [2221, 1082] are important with regard to invasiveness [1552].

In relation to the invasion capacity of neoplastic cells, some characteristics, such as migration and adherence [1450, 2408] have to be taken into account. For example, the cellular proliferation may be influenced by many proteins of the extracellular matrix [29]. These are especially involved in the interaction between tumor cells and host tissue [1661]. Observations on experimental tumors demonstrate that tumor invasion is related to the synthesis and degradation of proteins of the extracellular matrix [2407].

However, though the biology of tumor invasion remains largely unknown [2975], it has been compared with angiogenesis, with which it shares such characteristics as a

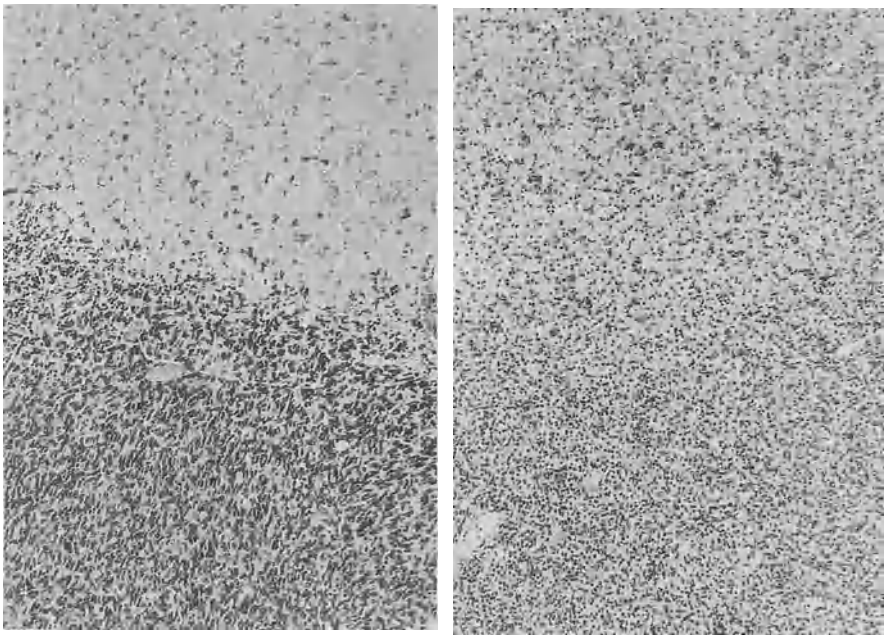


Fig.7.5a,b. Anaplastic oligodendroglioma: **a** clear-cut delimitation of the tumor, H&E, ×200; **b** progressive infiltration of the cortex, H&E, ×200 [2484]

high copper content [3120]. In the 9L gliosarcoma cell line transplanted into the rat, a copper-poor diet and penicillamine treatment inhibit pseudopodial protrusion [280]. It is clear that invasiveness and infiltration are not identical, and that the latter is not a synonym for malignancy. It should be pointed out that the idea that expansion is typical of benign, and infiltration of malignant tumors would imply that diffuse astrocytomas are malignant, as once believed [2477]. The main difference between the spread of slowly growing hemispheric and malignant gliomas is that the former are often diffuse, with no sharp demarcation, whereas the latter grow both by expansion and infiltration.

The way a tumor spreads is greatly influenced by the existing structures and by the general anatomy of the structure in which growth takes place. If a tumor grows in a ventricle, i.e., ependymoma, plexus papilloma, or medulloblastoma, or reaches it from the parenchyma, as oligodendroglioma, glioblastoma, and germinoma often do, the cavity may be filled. This has with regard, for example, to intraventricular ependymoma been called "plastic" ependymoma.

Growth out of the ventricle is exemplified by the passage of ependymoma from the fourth ventricle to the subarachnoid spaces through the foramina of Luschka. A tumor may also spread from one cavity to another. Pineal tumors, for example, pass from the third ventricle to the lateral ventricles through the foramina of Monro. A tumor can reach the subependymal layers and grow into them, with or without protrusion into the cavity. It may also spread into the ventricular system and the subarachnoid space (Fig.7.6).

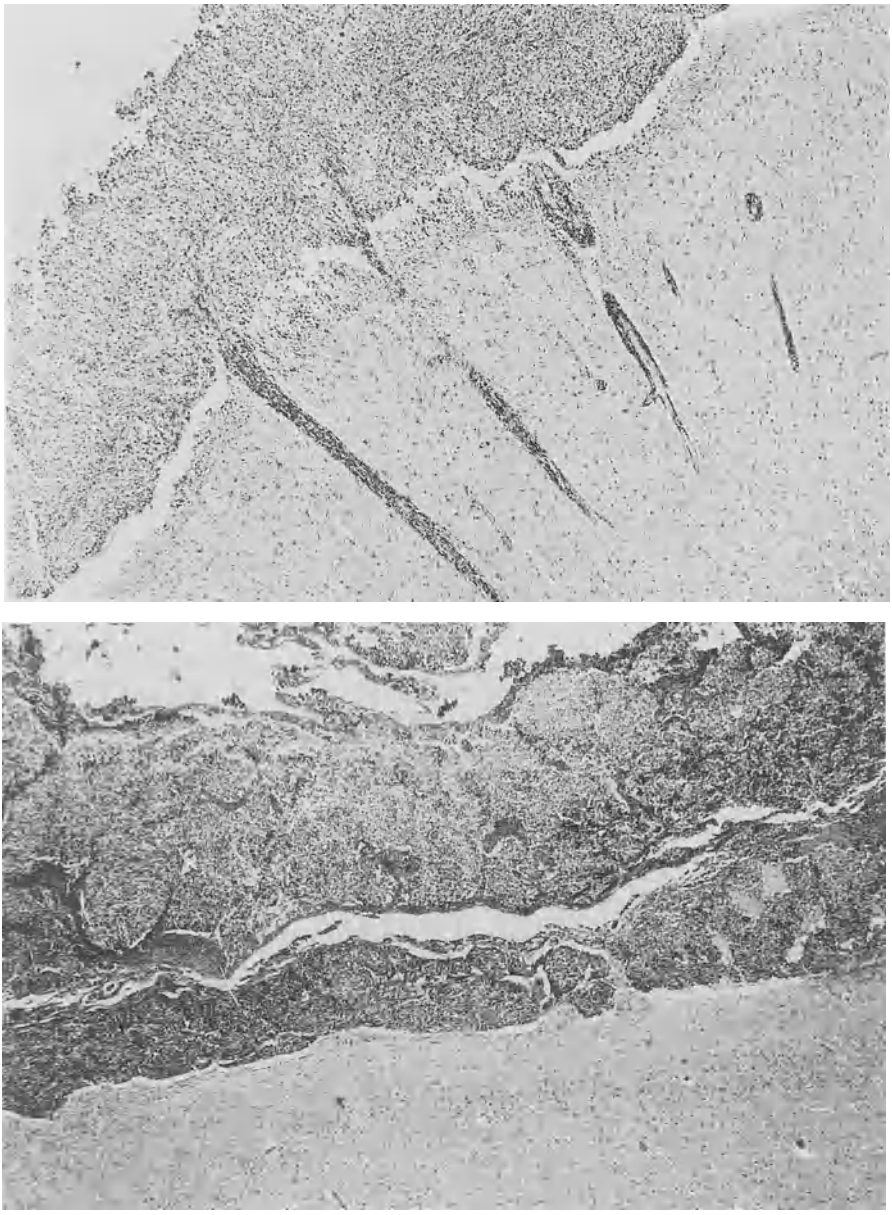


Fig.7.6. a Subarachnoid seeding of a glioblastoma with reinvasion of the cortex, H&E, ×150; **b** proliferation of an oligodendroglioma in the subarachnoid space, H&E, ×150

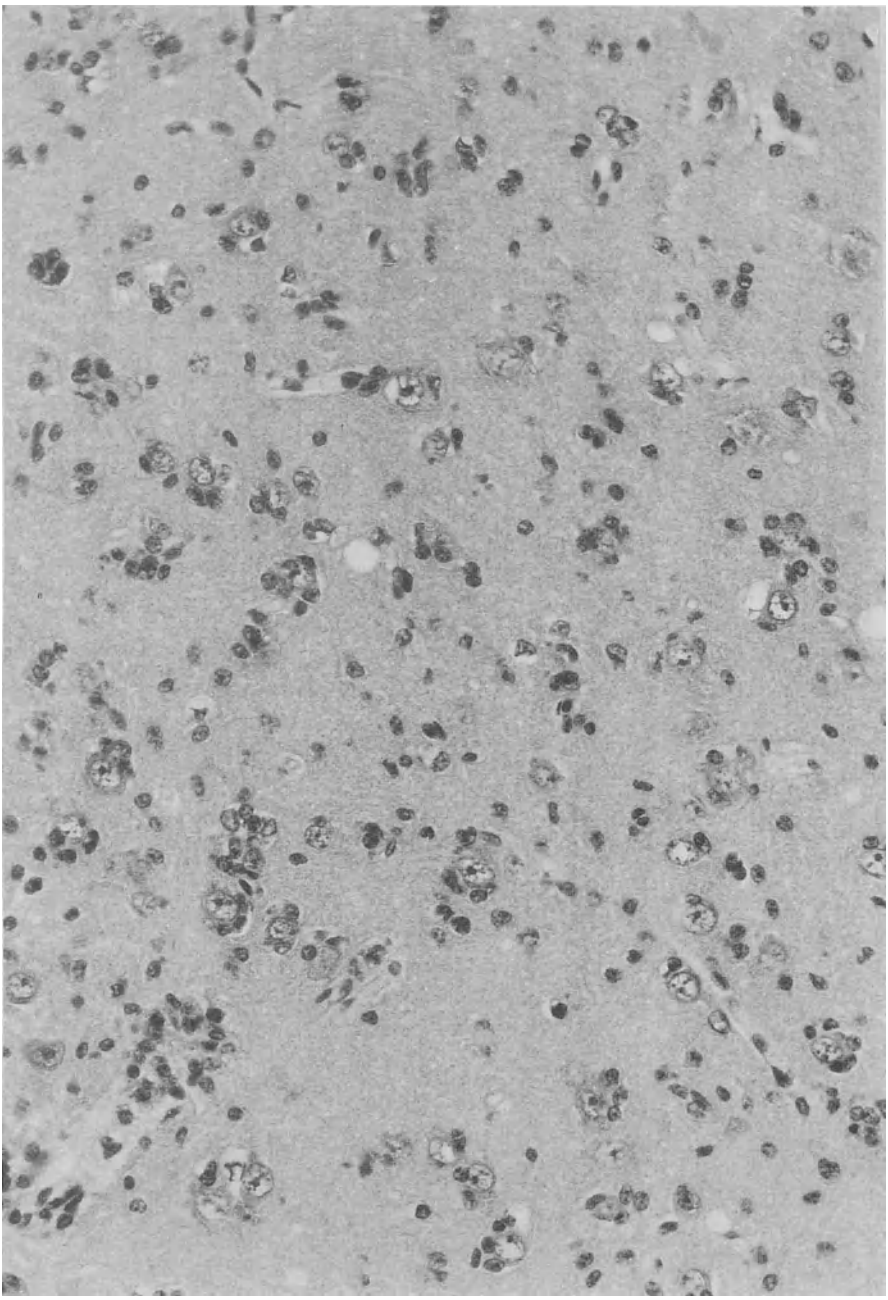


Fig.7.7. Perineuronal satellitosis in an oligodendroglioma, H&E, ×300

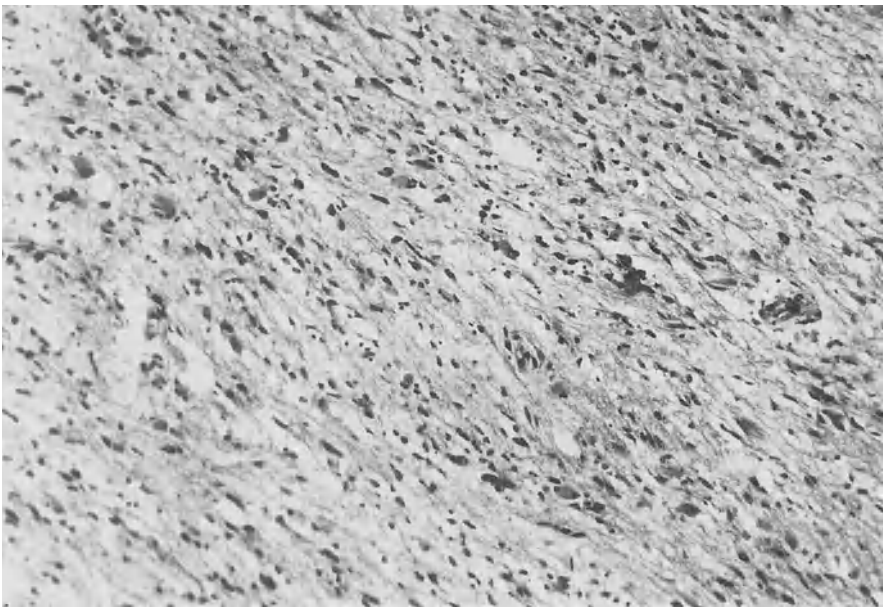


Fig.7.8. Spreading of a glioblastoma into the corpus callosum, H&E, ×200 [2484]

If tumor cells find their way into the CSF, metastasis can be retrograde as well as along the spinal cord. Medulloblastoma, ependymoma and glioblastoma are mainly responsible for this kind of colonization. Metastases can be found on the arachnoid, among the posterior roots, and in the cauda region. These observations have guided the strategy of radiotherapy which is applied to the entire neuraxis in cases of medulloblastoma and ependymoma.

A tumor can also spread in the cortex and along its outer surfaces. A glioma growing from the white matter to the cortex has several pathways which it may follow: invasion of the cortical layers, thus creating the appearance of satellitosis (Fig.7.7), although the neurons themselves may remain visible for a long time; crossing the pia and giving rise to subpial and leptomeningeal growths, from which the cortex itself may be reinvaded; expansion into the leptomeninges resulting in meningeal gliomatosis [2218], leaving the gyri either normal or invaded, as seen when oligodendrogliomas infiltrate convolutions and give them a "hypertrophic" appearance. As they pass from one convolution to another, the tumor produces "garlands" by forcing a passage through the cortex in the same way as a fungus.

One of the main routes along which hemispheric gliomas spread are the fiber tracts, i.e., the corona radiata, internal capsule, corpus callosum (Fig.7.8), and anterior commissure [1805]. Gliomas have typical sites of origin, which become less recognizable during tumor growth. The spreading pattern depends on the location and is schematically predictable [368]. Progression is both in the ipsilateral hemisphere and through the corpus callosum to the opposite side, giving rise to the classic picture of a "butterfly" tumor.

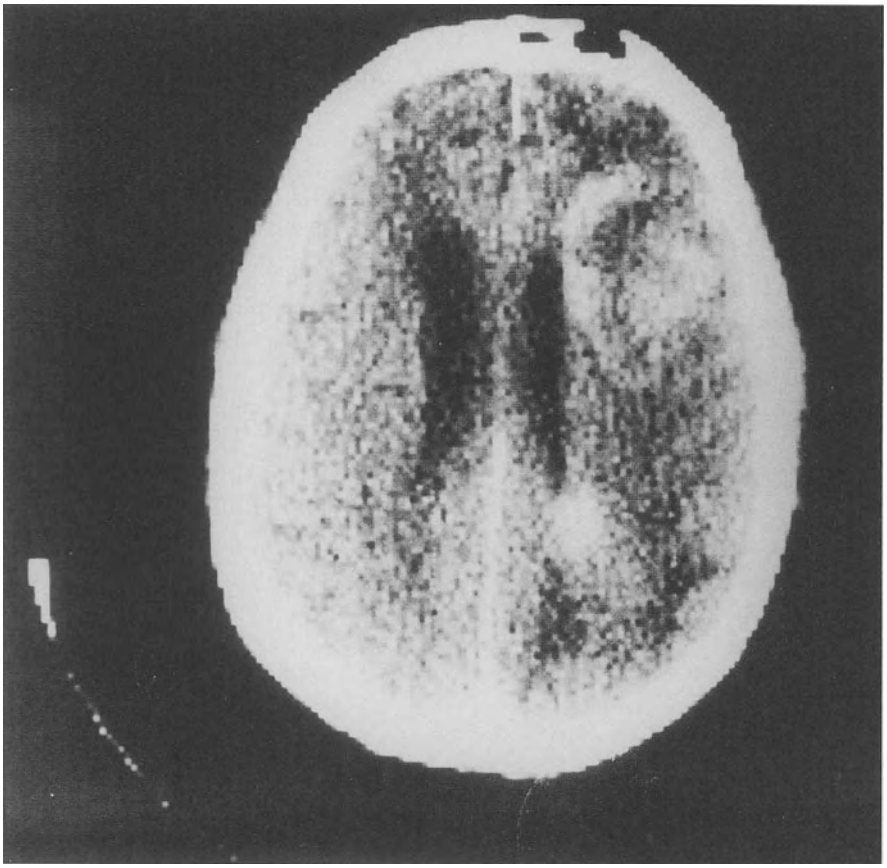


Fig.7.9. Apparent multicentric growth on CT scan

Histologically, elongated cells are observed among the myelin fibers. They acquire a pilocytic or spongioblastic appearance, since their growth pattern is greatly influenced by the existing fiber plane. It is often difficult to determine whether they represent a primary or a secondary architecture. When the cell density is low, it is even difficult to recognize the advancing tumor. This growth pattern is shared by glioblastomas and different types of hemispheric and midline pilocytic astrocytomas.

Malignant gliomas very often present as multicentric growths (Fig.9.14) or as a multicentric malignant transformation of a diffuse astrocytoma. The first possibility raises serious difficulties in the differential diagnosis of metastasis by CT scan (Fig.7.9). The multifocality of a tumor is an event difficult to prove since in most cases it is merely apparent. The multiple foci may be connected by thin strips of tumor involving commissures or septa, such as the septum pellucidum. In other cases, multifocality may be mimicked by diffusion through the CSF followed by reimplantation. The second possibility is that an astrocytomatous proliferation, not detectable by CT, may connect all the foci visible on CT into a single large, tumor [1650]. This situation is of great importance when it is necessary to establish the extent of a tumor by CT so that an appropriate radiotherapy strategy may be chosen [2483, 332].

8 Descriptive Epidemiology of Primary Nervous System Tumors

8.1 General Data

8.1.1 Mortality

Data pertaining to the mortality of patients with primary CNS tumors are readily available, as many countries have published the standardized data collected through death certificates. Comparison between mortality rates (number of deaths/100,000 inhabitants per year) of various countries in the periods 1951–1958 [958] and 1967–1973 [102,103] has shown a persistent geographic variability and a clear tendency to increase with time. The annual age-adjusted rates for the period 1951–1958 varied from 1.1 (Mexico) to 6.8 (Israel), while for the period 1967–1973 they varied between 4.2 (Chile) and 10.0 (Federal Republic of Germany). For the majority of countries the increment in mortality rates was about 40%, although it was over 100% in some. The increments were lower and of the same magnitude in countries with high health standards before 1958 (United Kingdom, USA, and Canada). The increase in mortality with time was found to be particularly high (from 5.3 to 16.1) when white Americans between 60 and 64 years born in 1880 and 1910 respectively were compared, whilst in younger subjects this increment was not found [223]. This observation led to the belief that the increment in mortality over time for CNS tumors is mostly related to improvements, variable from country to country, in the social/health systems, diagnostic facilities, and data collection.

Mortality is higher in males than females. Still referring to the 1963–1973 period, it has been noted that the mortality rate was about 7.5/100,000 for males vs. 5.58/100,000 for females [2551]. In Italy, the values were, respectively, 4.86 vs. 3.66 in 1956 and 6.76 vs. 4.92 in 1978 [582]. The mortality curve in relation to age demonstrates a modest peak in infancy, followed by a higher peak in adults [958, 1542]. The mortality for CNS tumors was higher in whites than in other races [1542].

8.1.2 Incidence

Data on the incidence of primary CNS tumors collected in tumor registries from 30 different populations through the UICC relating to the 1968–1977 period [103] reveal many analogies with mortality data. There was, in fact, marked geographic variability: the incidence rates adjusted for age (number of new cases/100,000 per year) varied from 1.5 (Singapore) to 9.1–10.0 (Israel and Sweden). The values were high, with minor variations in time, for countries with a high socioeconomic status and generally higher in

males (male/female ratio = 1.3). The increase in incidence with time has clearly been lower than the increase in mortality. There had even been a decrease in one third of the countries.

The race differences heavily influenced the incidence ratio. In multiracial communities, such as the USA, for example, the incidence was constantly higher for whites than for Indians and blacks. For a given race, instead, there were no differences between natives and immigrants from other countries. Differences in ethnic origin may also be important: Within the Israeli population, the incidence of malignant primary tumors varied between 14.3 for Hebrews born in Europe or America to 9.5 for those born in Israel.

8.2 Epidemiology of Intracranial Tumors

Data relating to the epidemiology of intracranial tumors alone are of two types: those based on hospital series (neurosurgical and neuropathological) and those based on population studies. The first type arises from carefully collected series as for the classification of tumors but are often "selective," i.e., influenced by the specialization of various centers. The second has the advantage of deriving from studies in which the frequency was calculated for the whole population "at risk" but was often limited by a less accurate histological diagnosis, because these included nonhistologically verified cases. The frequency of cerebral tumors found in autopsy series is about 1.2%–1.4% [2486].

The incidence ratio of primary intracranial tumors varied from 4/100,000 in Iowa, USA [1039] to 14.7/100,000 in Rochester, Minnesota, USA [62, 1539]. These enormous differences are in part artifactual and reflect the diversity in the definition and in the methods of case ascertainment. Some studies do not consider tumors of the pituitary gland [471] or include spinal tumors [126]. In general, higher values are related to more accurate case ascertainments, as found in isolated small populations with little mobility and high health care standards like the Faroe Islands or Rochester [1314, 1539]. They can be found also in more recent studies using CT in the diagnosis [793, 2768]. The particularly elevated values found in Rochester are for the most part due to the inclusion of cases diagnosed only at autopsy [2549]. If these are excluded, the maximum frequency descends from 14.7 to 8.2, a value which is superimposable on the average reported from the USA [2969]. In large studies carried out in Connecticut [2553] and Rochester [62], the increase in incidence over time was attributed to better case detection. Italian data vary from 8.4 or 8.5 in the Trento and Bolzano provinces [1696, 1688] to 9.2 in the province of Varese [2313].

8.2.1 Histological Type

The distribution according to histological types of primary intracranial tumors overlaps uniformly (with few exceptions) in population studies and clinicopathological series. Gliomas rank highest (40%–67%), almost always representing more than half of all tu-

mors, followed by meningiomas (9%–27%), on average about 20%, and then pituitary adenomas (7.6%–14%) [2969, 2551]. An exception is the Rochester study [1539], in which meningiomas (40%) were more frequent than gliomas (35%). However, if only cases diagnosed ante mortem are considered, the percentages are closer to those of other studies. The interest which neurosurgeons and neuropathologists have for particular oncotypes has led to a higher frequency of some tumors in some series, as in the case of pituitary adenomas for Cushing [1935] and meningiomas for Olivecrona [1967]. Particular distributions are probably influenced by genetic-racial and/or environmental factors as, for example, the high frequency of acoustic neurinomas in India [565] or of pineal tumors in Japan [68].

Within the glioma series, the most frequent oncotype is glioblastoma (more than half), followed by astrocytoma and ependymoma. The incidence rate values vary from 2.1 to 7.1/100,000, with a tendency to higher values between 4 and 6 in more recent studies [1102, 1341, 2448, 1101, 1623]. Within the subtypes of gliomas [2550], the following figures were reported: for astrocytoma 0.52 in males and 0.34 in females, for glioblastoma 2.07 and 1.51, and for ependymoma 0.08 and 0.07, respectively. From the brain tumor registry of Japan, gliomas represent 28.9%. The oncotype distribution is astrocytoma 43.1%, medulloblastoma 7.3%, glioblastoma 26.6%, oligodendroglioma 6.1%, ependymoma 6.3%, and plexus-papilloma 1.2% [2046].

8.2.2 Age

Many studies demonstrate a first incidence peak in infancy, with a subsequent, more marked, peak in the decade 55–65 years, followed by a decrease, especially after the age of 70 years. In the Manitoba Canadian epidemiological study [2768], the incidence was 4.2/100,000 in the 0–4 year group, and 27.2/100,000 in the 60–69 year group. The only exception was reported in the Rochester study [1539], where the incidence was found to continue to increase even after the age of 65 and 70 years. This finding was relevant only for gliomas and meningiomas diagnosed at autopsy. It is possible [2969] that when studies based on routine CT scans become available, the incidence curves for age may become closer to those of the Rochester study. Even today, they have reduced the number of undiagnosed tumors in vivo, especially in the elderly. A bimodal shape of incidence curves for age, similar to that of intracranial tumors globally considered, has been observed for gliomas, but with different shapes for different oncotypes. Well-differentiated astrocytomas and ependymomas account for the peak of gliomas in the infantile age, and in adults their incidence shows a relatively flat and regular curve. The incidence of glioblastomas, relatively rare in the younger age group, follows a steeply ascending curve from 30 years onwards, with a nadir around the age of 65 years. Oligodendrogliomas occur fairly constantly at all ages, with a slight predilection for middle age.

Brain tumors in childhood (0–15 years), considered as a separate group, have an incidence of 2.2–2.5/100,000, varying between 1.0 and 5.0/100,000 [2554, 953, 2140, 2233, 1568]. The incidence is always inferior to that of tumors in adult age. The peak incidence is between 3 and 9 years of age [1628]. There is no qualitative difference in oncotypes as compared with adults.

As the renewing reserve cells, the neuroepithelial cells are scarce and the turnover of glia is low in the adult CNS, it may be thought that the majority of gliomas originate because of neoplastic transformation of neuroepithelial cells during development. It follows that there is no difference between tumors of adult and embryonal type, as encountered in other organs [2396]. Very enlightening in this respect is the application of the concept of the "window vulnerability," [2396] referred to in Chap. 7.

Cerebral tumors are very rare in the first 2 months of life and account for 1.5% of all brain tumors in infancy [2453, 1324]. They are thought of as congenital and considered certain, probable, or possible (see Chap. 2). In the first year of life, brain tumors become more frequent, 7.7% [1324], and their oncotype composition also changes. The most frequent are astrocytomas, followed by medulloblastomas, ependymomas, and plexus papillomas [2257, 1036A, 83A]. Supratentorial locations and neuroepithelial tumors (89%) also prevail. Cerebellar astrocytomas are less frequent than in infancy. The hemispheric astrocytomas are mostly benign, glioblastoma being almost unknown, with the exception of some series [2432]. Metastases are rare and generally limited to the adrenal carcinoma.

The incidence of oncotypes in relation to site is different from that in adults. While in the adult there is a clear predilection for the anterior rather than posterior parts of the brain, especially for gliomas [2419], in infancy the predilection tends to be reversed, with 50% of tumors in the posterior fossa, more or less equally subdivided into medulloblastomas and astrocytomas. Only 12%–25% of tumors, mostly gliomas and ependymomas, develop in the cerebral hemispheres. Astrocytomas are generally the most common oncotype: The incidence in Connecticut is 0.81/100,000 [647]. Meningiomas, oligodendrogliomas, and pituitary adenomas are rare.

In a Japanese series [2445], brain tumors globally represent 14.9% of all tumors. Gliomas represent 60.6%, followed by craniopharyngiomas with 12.5%, other congenital tumors with 5% and pineal region tumors with 8.5%. Among neuroepithelial tumors, astrocytomas are the most frequent (27.3%), followed by ependymomas (14.8%). While tumors such as astrocytoma and ependymoma are clearly more frequent in infancy, others such as glioblastoma and anaplastic astrocytoma are less frequent.

It is important to remember that tumors in infancy have a wide range of features, depending on different factors: The ability of fetal cells to differentiate; the effects of anaplasia, which may appear later as an expression of tumor progression; the possibility of aberrant or heteroplastic differentiation, especially in embryonal tumors; the fact that the neoplastic differentiation has wider limits than normal [2396].

8.2.3 Sex

The incidence of intracranial tumors is slightly higher in males than in females: 8.5 and 7.9/100,000, respectively in the USA [2969]. Gliomas clearly prevail in males, while meningiomas and pituitary adenomas are more common in females. For example, in the Manitoba Canadian study [2768] the incidence data were as follows: 4.2 vs. 2.7 for malignant gliomas, 1.3 vs. 0.8 for differentiated gliomas, 1.5 vs. 3.1 for meningiomas, and 1.4 vs. 2.1 for pituitary adenomas.

8.2.4 Race

The incidence of all intracranial tumors and of individual oncotypes is higher in whites than in blacks [746, 2236, 1502, 329, 2925]. All types of glioma are more frequent in whites. Data obtained from the Georgia Tumor Registry (USA) showed a white/black ratio of 2.3:1 [1852]. The maximum difference in frequency appears to occur for oligodendrogliomas. The relative frequency of the oncotypes is different: In black people, gliomas are less frequent, but meningiomas and pituitary adenomas are relatively more frequent. In infantile tumors the male/female ratio is different for medulloblastomas [329].

8.3 Epidemiology of Intraspinal Tumors

Data regarding the epidemiology of spinal tumors are relatively scarce. They are less frequent than intracranial ones with a ratio varying between 9:1 and 15:1 [2452]. The incidence of spinal tumors varies from 0.9 [1609] to 2.5/100,000 [1538], with more frequent values between 1.2 and 1.3 [458, 2176, 41, 2452, 793]. The distribution of the histological types in broadly different population studies such as in Iceland [1016], Israel [1609], and Rochester [2452] is similar: neurinomas and neurofibromas (26%–38%), meningiomas (13%–28%), and gliomas (11%–13%) encompassing astrocytomas and ependymomas. In infancy, spinal tumors are less frequent than in the adult: 11% vs. 20.8% [41]. The composition of oncotypes is also different: Meningiomas and neurinomas are rare, and the congenital and sarcomatous tumors are more frequent.

9 Astrocytic Tumors

9.1 Nosological Problems

Astrocytic tumors were originally subdivided into fibrillary and protoplasmic types [112, 113]. The gigantocellular and pseudopapillary types, identifiable with astroblastoma, were subsequently added [2380], so that five varieties were definitely recognized [3134]: fibrillary, protoplasmic, gigantocellular, astroblastoma, and the malignant variant. Still stemming from the original classification [112, 113], another nomenclature was used for these tumors, with the introduction of the pilocytic and gemistocytic varieties [2170, 709]. The term pilocytic derives from the Greek word for"hair" and indicates the elongated and bipolar aspect of the cells. The term gemistocytic refers to cells which in the German nomenclature were described as "gemästete Zellen" from the Greek word γεμίζω for "to stuff". On the basis of this subdivision and with the introduction of the concept of anaplasia, expressed by the "grading" system [1405], astrocytomas were subdivided into protoplasmic, fibrillary, pilocytic, gemistocytic, and anaplastic [2415 , 2419].

Pilocytic astrocytomas are characterized by elongated and bipolar elements and are subdivided into "adult" and "juvenile" types according to their firm or loose texture. This scheme differs from that of Zülch as in the latter, astrocytomas with a pilocytic aspect are included in the fibrillary variant when they are situated in the cerebral hemispheres and in the spongioblastoma group when they are paraventricular or cerebellar. Zülch (1956) [3134] conceived of the spongioblastoma group as an all-encompassing one to which most of the midline gliomas belong, i.e., the spongioblastoma of the chiasm, hypothalamus, brainstem and aqueduct, cerebellum, fourth ventricle, and some of the "Stiftgliome" of the spinal cord. They have a common origin from the subependymal glia and share the presence of Rosenthal's fibers, which are characteristic of subependymal glia in neoplastic, degenerative, and inflammatory processes. Earlier studies of anatomical systematics and cytoarchitectonics have interpreted spongioblastomas as typical tumors of the dorso-lateral prechordal sheet. Their main location is, therefore, the neural tube equally in its dorsal and basal part, spinal cord, medulla oblongata, pons, quadrigeminal plate, cerebellum, thalamus, hypothalamus, chiasm, and optic nerve. Typical subependymal spongioblastomas are then found at different points of the ventricular wall and could originate from the allocortex, hence from the olfactory cortex, cingulate gyrus, hippocampus, indusium griseum, corpus callosum, splenium, and fornix.

The endless debate started when the term spongioblastoma, which indicated a malignant glial tumor, was replaced by glioblastoma [112]. The former remained to indicate a group of benign tumors characterized by elongated cells resembling the spongio-

blasts of cytogenesis [2380, 1189] and mainly located in the region of the optic nerve, chiasm, and hypothalamus. These tumors were called spongioblastomas by some [3134] and piloid [709] and pilocytic astrocytomas [2415] by others. The latter authors reserved the term "spongioblastoma" to designate a rare tumor with malignant behavior whose cells resembled the primitive spongioblasts of cytogenesis (see Chap. 15).

The recent classification of the WHO [1443] subdivides astrocytic tumors as follows:

1. Astrocytoma
   Variants: fibrillary, protoplasmic, gemistocytic, or mixed
2. Anaplastic (malignant) astrocytoma
3. Glioblastoma
   Variants: giant cell glioblastoma, gliosarcoma
4. Pilocytic astrocytoma
5. Pleomorphic xanthoastrocytoma
6. Subependymal giant cell astrocytoma (usually in association with tuberous sclerosis)

In the present book, astrocytomas are described on the basis of their histological features and location. Fibrillary, protoplasmic, gemistocytic, pilocytic, and anaplastic variants of astrocytoma will be considered. Very often, however, a clearcut distinction between them is difficult, especially between the fibrillary and the protoplasmic variants.

9.2 Astrocytic Tumors of the Cerebral Hemispheres

9.2.1 Astrocytomas

Astrocytomas appear especially in the third and four decades of life and are in the main frontal, parietal, and temporal. They represent 25%–30% of all hemispheric gliomas. In our series, they represent 24.5% of gliomas and 11.3% of all intracranial tumors.

9.2.1.1 Fibrillary Variant

The tumor is firm, grayish-white, and difficult to distinguish from the surrounding tissue. Usually solid, it can occasionally include cysts of various dimensions. It is found in the white matter (Fig.9.1).

The tumor is composed of astrocytic elements with delicate processes, well demonstrated especially with silver impregnation methods, PTAH, and GFAP (Fig.9.2). The nuclei are round or oval, isomorphous, but sometimes of variable size and chromatin content so as to appear polymorphic, especially in the peripheral zones. Mitoses are rare. The cell density is low but most often higher than that of the white matter; sometimes it is quite difficult to recognize the tumor edge even microscopically. The cells are regularly distributed, but in some cases they are arranged in particular patterns such as the "stepladder" one; alternatively, they may infiltrate the cortex, forming perineuronal satellitosis.

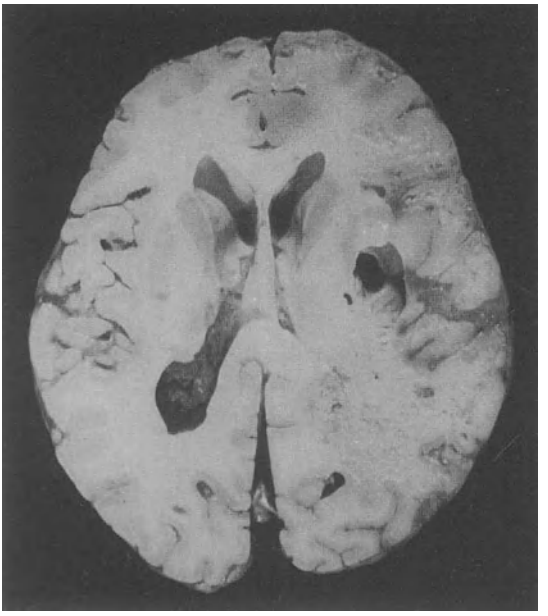


Fig.9.1. Hemispheric cystic astrocytoma

The most important regressive event is represented by fluidification with microcyst formation. Calcifications are found in 15% of cases [2486].

Blood vessels are scarce and of small caliber and no evidence of either neovascularization or endothelial hyperplasia is present.

The differential diagnosis includes normal tissue, reactive gliosis, anaplastic astrocytoma, and oligodendroglioma. The tumor is usually distinguishable from reactive gliosis because reactive astrocytes are scarcer and more regularly distributed and feature larger processes more intensely positive for GFAP. General criteria are available for the distinction between tumoral and reactive astrocytes [678], but they cannot be considered as absolute. For example, the occurrence of mitoses is inconclusive because they can be found in reactive astrocytes as well [2514]. The criteria for the distinction between fibrillary and anaplastic astrocytoma will be set forth later. Fibrillary astrocytoma is distinguished from oligodendroglioma by the presence of a fibrillary background, the aspect of the nuclei, the absence of the cytoplasmic "halo" around the nucleus, the type and distribution of blood vessels, and the lower frequency of calcifications.

9.2.1.2 Protoplasmic Variant

The protoplasmatic variant is mostly found in the cortex and originates from astrocytes of the central cortical layers. The tumor has ill-defined borders (Fig.9.3) and a homogeneous aspect, is grayish-white or pinkish, and often contains small or large cysts. The cells show eosinophilic and GFAP-positive cytoplasm with short processes and round

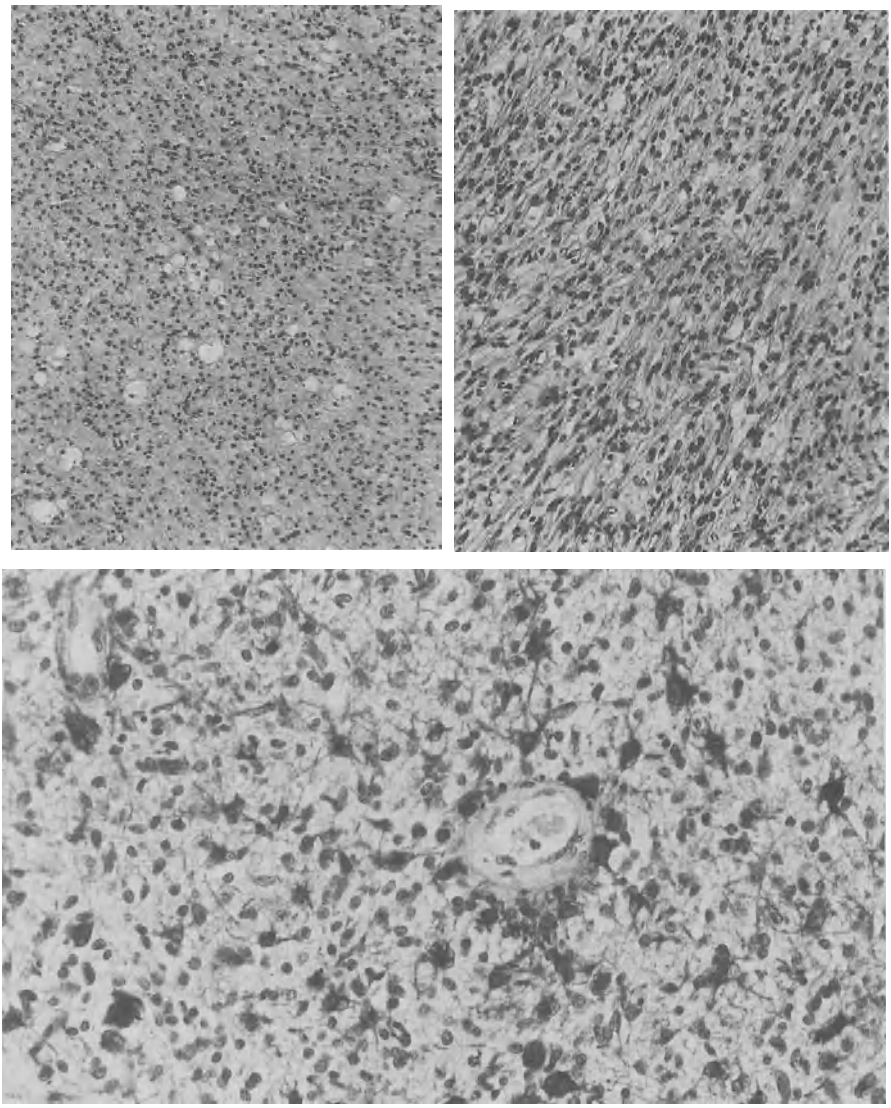


Fig.9.2a–c. Fibrillary astrocytoma, various aspects, H&E: **a** ×200, **b** ×300. **c** GFAP-positive reaction in many processes, PAP-DAB, ×400 [2518]

or oval nuclei (Fig.9.4a). Typically, numerous microcysts, which may be confluent, occur (Fig.9.4b). Only rarely is the histological picture pure, and both protoplasmic and fibrillary astrocytes are often present.

9.2.1.3 Gemistocytic Variant

The gemistocytic variant is characterized by large cells with expanded and eosinophilic cytoplasm provided with numerous, very short processes (Fig.9.5a), variably GFAP-

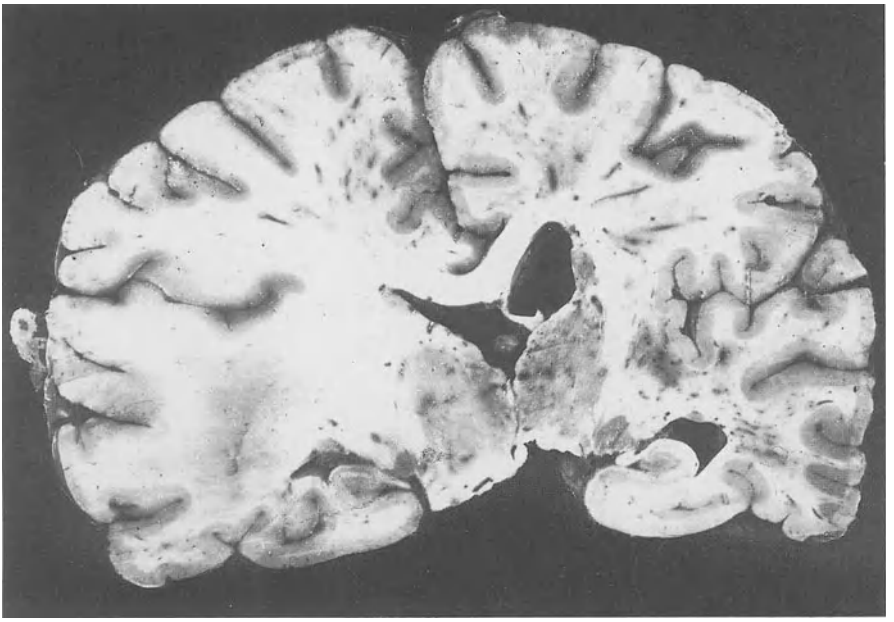


Fig.9.3. Temporoparietal protoplasmatic astrocytoma, with ill-defined borders

positive (Fig.9.5b). The nucleus is dark and peripherally situated. The gemistocytic appearance rarely involves the whole tumor; often it occurs focally in otherwise fibrillary or protoplasmic astrocytomas. Perivascular lymphoplasmacellular infiltrates are more common than in other types of astrocytoma (Fig.9.6a). Macrophages and CD8+ lymphocytes have been found in some astrocytomas [2372].

9.2.1.4 Pilocytic Variant

The pilocytic variant is composed of elongated, bipolar cells with long wavy processes often organized in parallel bundles, which take characteristic shapes on longitudinal or transverse section (Fig.9.6b). The same applies to the nuclei which can, therefore, show an oval or a round shape. Rosenthal's fibers and often calcifications are present. This pilocytic appearance is more characteristically found in gliomas of the midline and of the cerebellum, being identifiable with the spongioblastoma of Zülch (1956) [3134], but it can also be found in gliomas of the cerebral hemispheres. They can be distinguished nto "juvenile" and "adult" types (see Sect. 9.3.5.4). The juvenile pilocytic tumors are more frequent in the younger age group.

From time to time, mostly in the neurosurgical literature, series of cases usually with the characteristic histological features described above and generally associated with long survival are reported [2528, 454, 2122].

In all types of astrocytoma, IF can be seen under the electron microscope and marked by immunogold procedures with GFAP and vimentin antibodies (Fig.9.7). The two antigens colocalize.

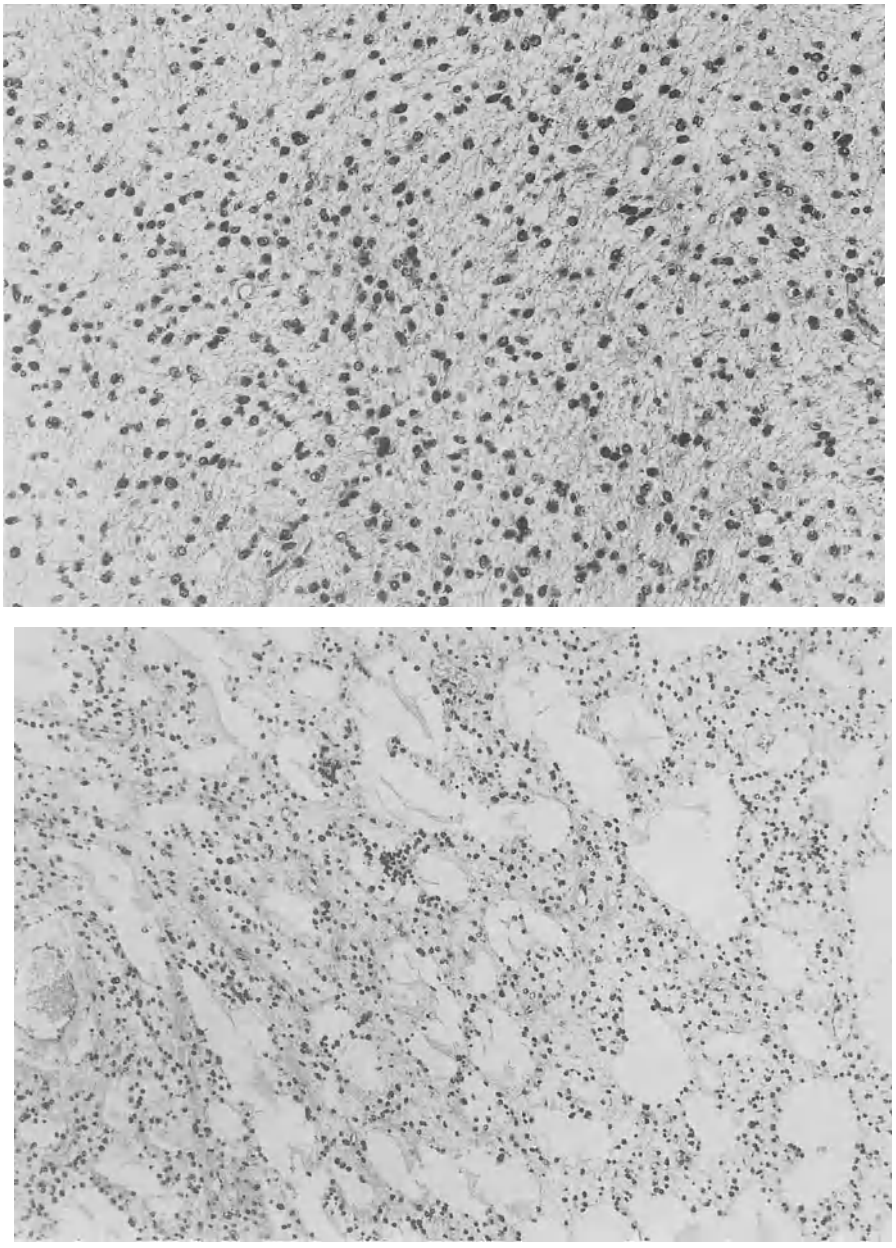


Fig.9.4a,b. Protoplasmic astrocytoma: **a** low cell density, round nuclei, and short processes, H&E, ×300; **b** formation of microcysts, H&E, ×150

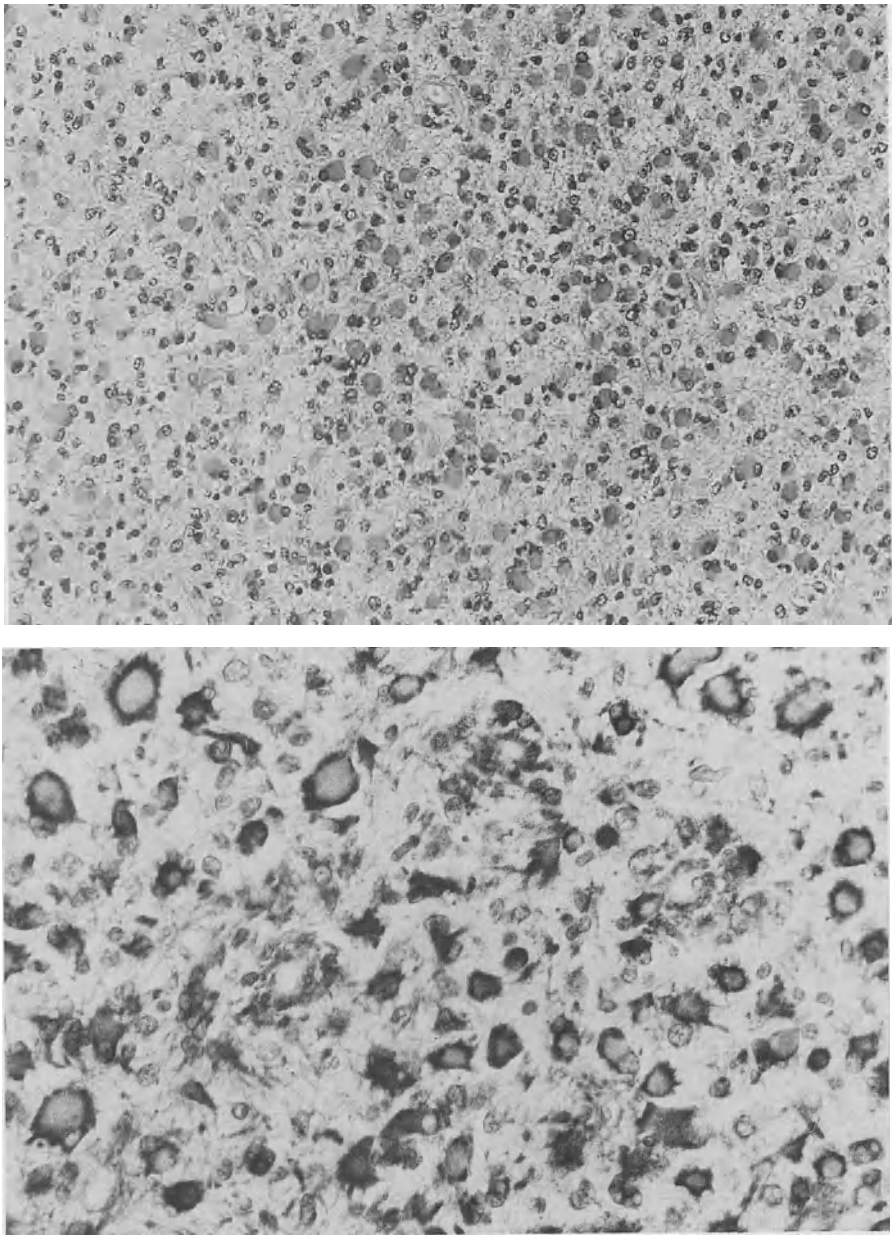


Fig.9.5. Gemistocytic astrocytoma: **a** expanded cytoplasms, H&E, ×300; **b** GFAP-positive cytoplasm PAP-DAB, ×400 [2515]

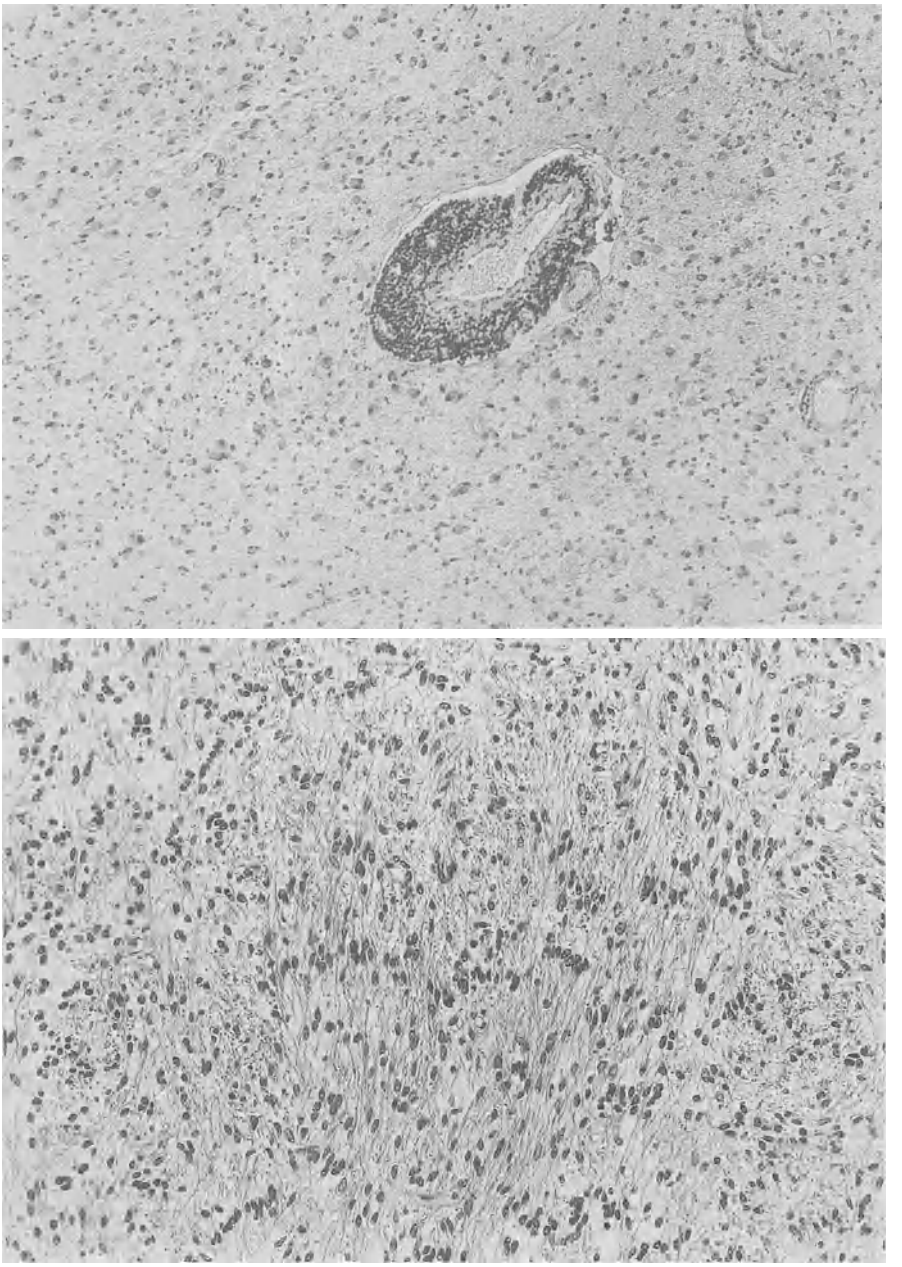


Fig.9.6. a Gemistocytic astrocytoma: perivascular lymphocytic infiltrate, H&E, ×200. **b** Pilocytic astrocytoma: elongated, bipolar cells are organized in bundles, H&E, ×200

Fig.9.7. Double immunogold staining for GFAP (small granules) and vimentin (large granules) in an astrocytoma, ×50 000

9.2.1.5 Anaplastic Variant

This neoplastic histotype represents the anaplastic transformation of an astrocytoma without reaching the extreme degrees of anaplasia seen in the glioblastoma, which are represented mainly by large areas of necrosis and prominent vascular disarrays. Since it represents the transformation of an astrocytoma, it often shares its macroscopic characteristics and location. It usually appears in slightly older patients than the other variants. The macroscopic aspect is intermediate between those of astrocytoma and glioblastoma (Fig.9.8).

The histological characteristics of anaplasia may be present diffusely within the tumor or be circumscribed and focal. They are represented by greater cellular density and nuclear polymorphism, more frequent mitoses, and less evident astrocytic features (Fig.9.9). The pattern of GFAP production is characteristic: As the extent of anaplasia increases, more and more GFAP-negative cells and mitoses appear, consistent with the concept that anaplasia depends on the genotypic and phenotypic tumor heterogeneity (Fig.7.2).

Compared with other astrocytomas, this tumor is more infiltrating and shows a greater tendency to invade the cortex and the subpial region. It is a matter of debate whether stromal changes, such as an increase in blood vessels and early endothelial hyperplasia (Fig.9.10a), as well as the occurrence of few, small, circumscribed necroses (Fig.9.10b), still indicate an anaplastic astrocytoma or already to the picture of glioblastoma. This is extremely important from the practical point of view, when the recogni-

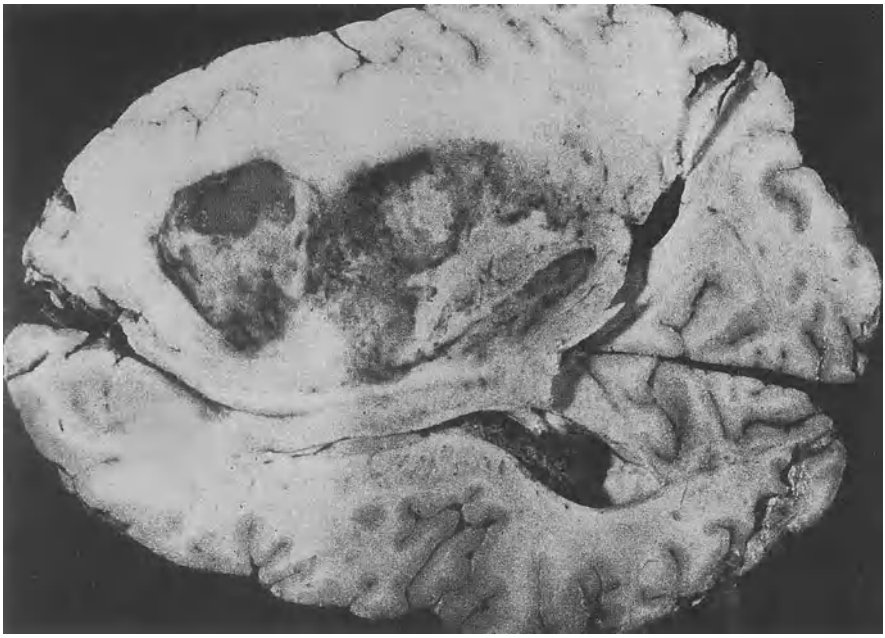


Fig.9.8. Hemispheric anaplastic astrocytoma

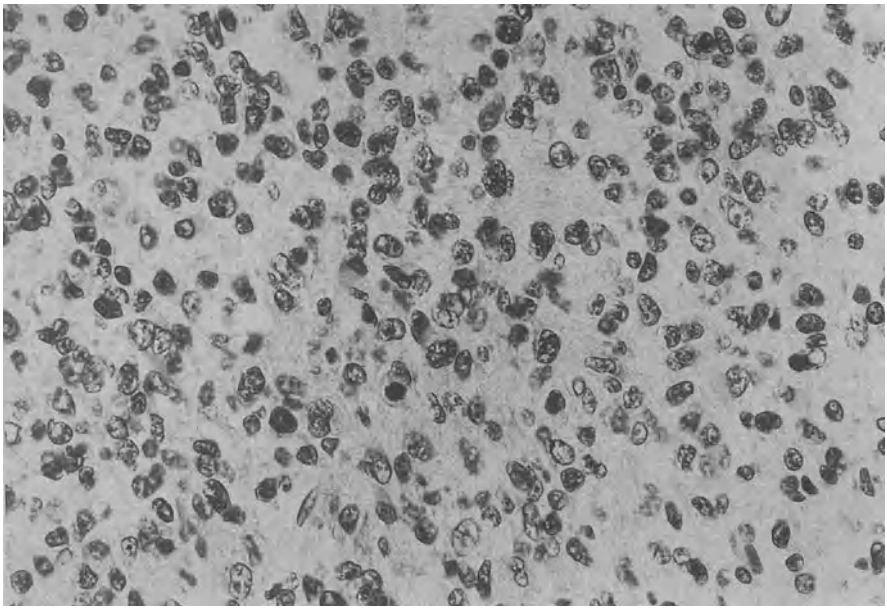


Fig.9.9. Anaplastic astrocytoma: increased cell density, less evident astrocytic features and more frequent mitoses, H&E, ×400

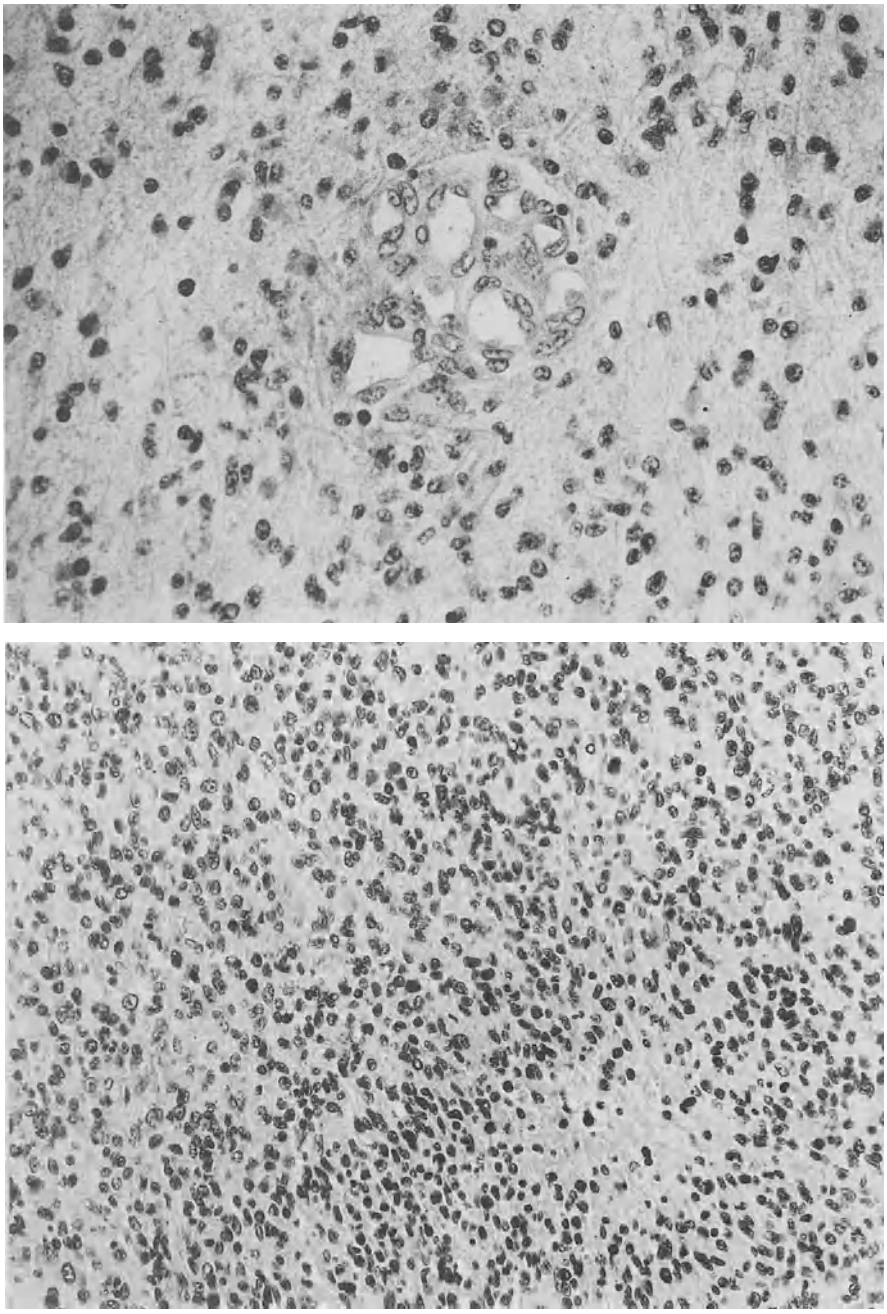


Fig.9.10a,b. Anaplastic astrocytoma: **a** early endothelial hyperplasia, H&E, ×300; **b** small circumscribed necrosis, H&E, ×200

tion of the variant has to be made on small biopsy samples. In the opinion of many authors, only large and extensive necroses with pronounced vessel changes are indicative of glioblastoma. In our experience [2517], early endothelial hyperplasia and isolated small necroses are still compatible with the diagnosis of anaplastic astrocytoma.

Since anaplasia can be a focal event and because of the extreme heterogeneity of malignant gliomas, incomplete sampling at surgery may account for the diagnosis of astrocytoma instead of anaplastic astrocytoma and of anaplastic astrocytoma instead of glioblastoma. The diagnosis of anaplastic astrocytoma on surgical material is more frequently made than in autopsy material. Since anaplasia is an evolving phenomenon, it could be that a tumor appearing originally as an anaplastic astrocytoma becomes transformed into a glioblastoma in time [2502]. As the two oncotypes have different survival rates they must be kept distinct, and the differential diagnosis has to be made.

9.2.1.6 Prognosis and Treatment of Hemispheric Astrocytomas

The hemispheric astrocytoma has an extremely variable clinical course due to the potential appearance of malignant transformation. Survival varies from 5 to 15 years down to figures which are very close to that for glioblastoma. The well-differentiated astrocytoma may undergo anaplastic changes, as is well known, but the time when these appear is not predictable, even though the general opinion is that they more frequently arise within the first years after diagnosis. It is then necessary to identify histological prognostic factors. The possibility of malignant transformation over time, however, renders the prognosis of well-differentiated astrocytomas constantly *sub judice*. This influences the therapeutic strategy.

The most important problem is that of recognizing the malignant transformation. First of all, there may be a surgical sampling error, because of the focal appearance of anaplasia, especially when the diagnosis is made on very small specimens. Secondly, some histological or cytological signs may be differently interpreted from the prognostic point of view: For example, nuclear polymorphism may be overestimated. The histological heterogeneity of gliomas has been found to be high [2149]. For this reason, the greater the amount of tissue examined, the more reliable the diagnosis.

Whilst no significant prognostic differences between fibrillary and protoplasmic astrocytomas have been observed, it is known that the gemistocytic variety bears a shorter survival rate due to the more frequent coexistence of signs of anaplasia [2419, 2517]. It has been observed that the presence of more than 60% gemistocytes in a fibrillary astrocytoma has the same poor prognostic significance as anaplastic astrocytoma [1509]. The study of the prognostic significance of individual histological factors in astrocytomas demonstrated that cell density (low or medium), nuclear polymorphism (absent or moderate), number of blood vessels, lymphoplasmacellular perivascular infiltrates, and presence of a limited number of mitoses (<5 per 10 high power fields, HPF) do not seem to influence survival [2517]. A low mitotic count was already recognized as not excluding the possibility of long survival [708]. On the contrary, a negative correlation with survival has been found for cases containing blood vessels of variable caliber [2517]. This variability, however, could be indicative of "sampling error," i.e., of the existence of anaplastic areas in parts of the tumor which were not removed.

Utilizing the LI obtained with BUdR, it has been observed that the 3-year survival is significantly greater for cases with a LI below 1% [1207]. A positive correlation has

also been found between the BUdR LI and the recurrence-free interval [843]. The macroscopic presence of cysts seems to be related to a better prognosis [951, 708, 1686].

Clinical factors correlated with longer survival are young age, long duration of preoperative symptoms, epileptic fits at onset, absence of important pre- and, especially, postoperative neurological signs [3005, 1589, 2198]. The uptake of contrast material on preoperative CT scanning would seem to be a prognostically independent factor: The astrocytomas which take up the contrast medium have a worse prognosis [2198]. In some of these cases, it could be a sampling error in an anaplastic astrocytoma.

Astrocytomas are associated with long survival if anaplastic changes do not occur: 26%–36% survive to 5 years and 10%–20% to 10 years. Cases surviving for between 10 and 30 years are on record [574, 3003, 990, 1844, 2566, 876], even in the absence of any therapy [708]. In a series of 461 patients the 15-year survival was 15% [2617].

As has been said, the duration of survival can be abruptly shortened by malignant transformation. The frequency of this event is not exactly known; however, except for a few cases [1686, 2198], the percentage of astrocytomas showing signs of anaplasia at reoperation for recurrence or at autopsy is high in the many series reported and varies from 49% to 85% [1778, 1589, 2688, 2930]. The risk of malignant transformation seems to be greater in the first 5 years after surgery [2688]. From the clinical standpoint, it would be very important to be able to detect the tumor areas which are undergoing anaplastic transformation; the results which are being acquired with fluorodeoxyglucose positron emission tomography (FDG-PET) seem encouraging [808].

Anaplastic astrocytoma has a worse prognosis than the well-differentiated one. The recognition of anaplasia is theoretically very easy, but practically it is still a controversial issue. In our experience, a mitosis count >5 per 10 HPF, cell density >800 nuclei/HPF, and endothelial hyperplasia are the fundamental elements for its identification in the group of astrocytomas. A standardized evaluation of nuclear atypia, necrosis, mitoses, and endothelial proliferations leads to a good correspondence with survival [569, 1418]. Once anaplasia is established, circumscribed or diffused, parenchymal only or also stromal, it cannot be further graded if evaluated in multivariate analysis [2517] (Fig.9.11). The prognostic importance of single histological factors in anaplastic astrocytomas has been highlighted by some studies [337, 856, 2687]. Whilst endothelial proliferation is constantly associated with a worse prognosis, cellular density, nuclear polymorphism, number of mitoses, and perivascular lymphoplasmacellular infiltrates seem to be of poorer prognostic significance [2687]. Others [856] have noted that a high number of mitoses entails a shortening of survival. Analysis of the DNA pattern added to that of other histological features could perhaps contribute to identifying cases with a more aggressive behavior [488].

Young age and a high performance status of the patients are clinical factors unanimously recognized as entailing a better prognosis. A complete response instead of a partial one as judged by CT scan after radiochemotherapy is predictive of longer survival [1972].

Surgery is the first and basic diagnostic and therapeutic approach in astrocytomas [1633, 951, 3005, 1589, 2688]. There is little doubt about the surgical treatment of large and symptomatic astrocytomas. When one is dealing with young adult patients with a negative neurological examination, a clinical history of epileptic seizures, and a small hypodense lesion without enhancement after injecting contrast medium, the choice of

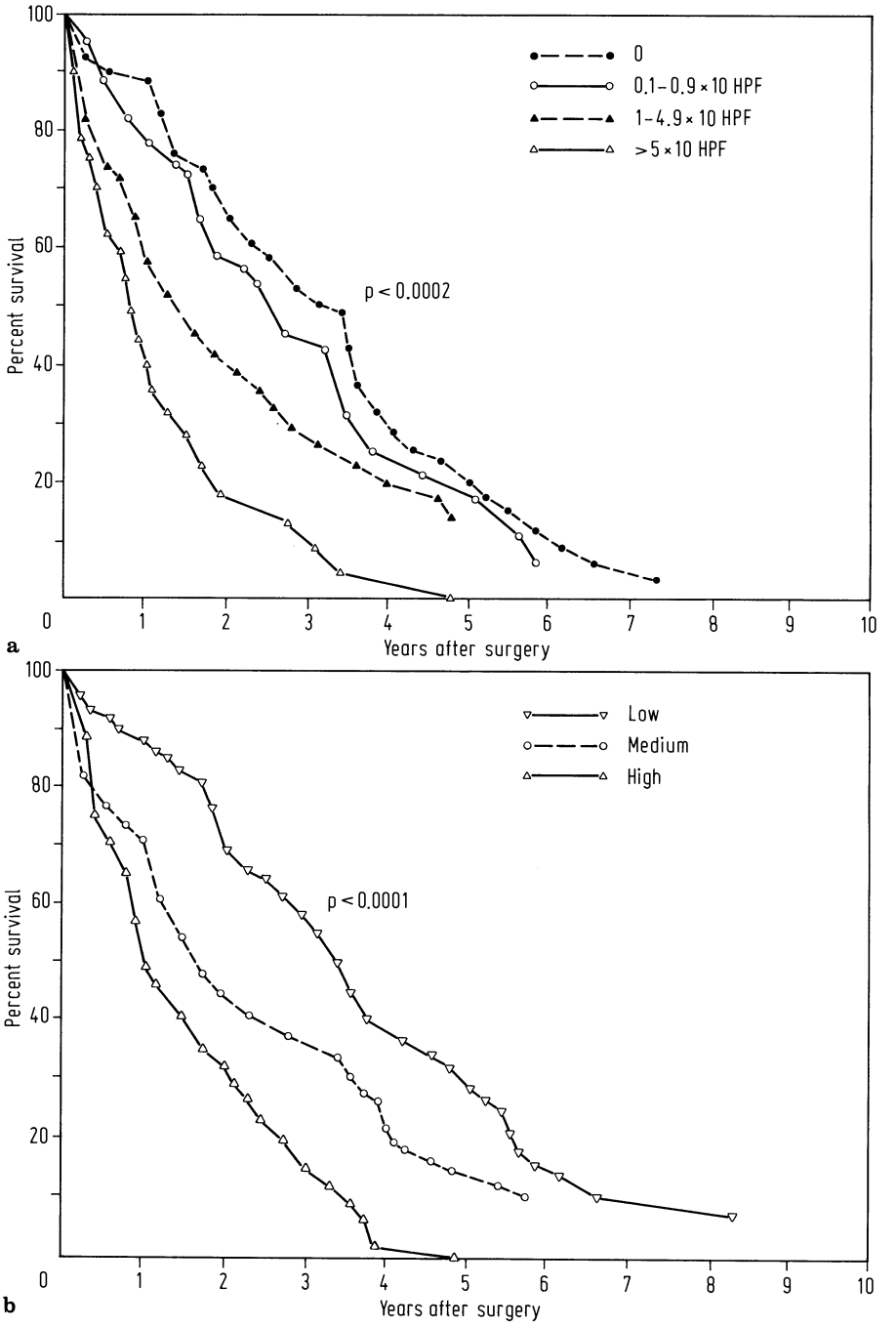
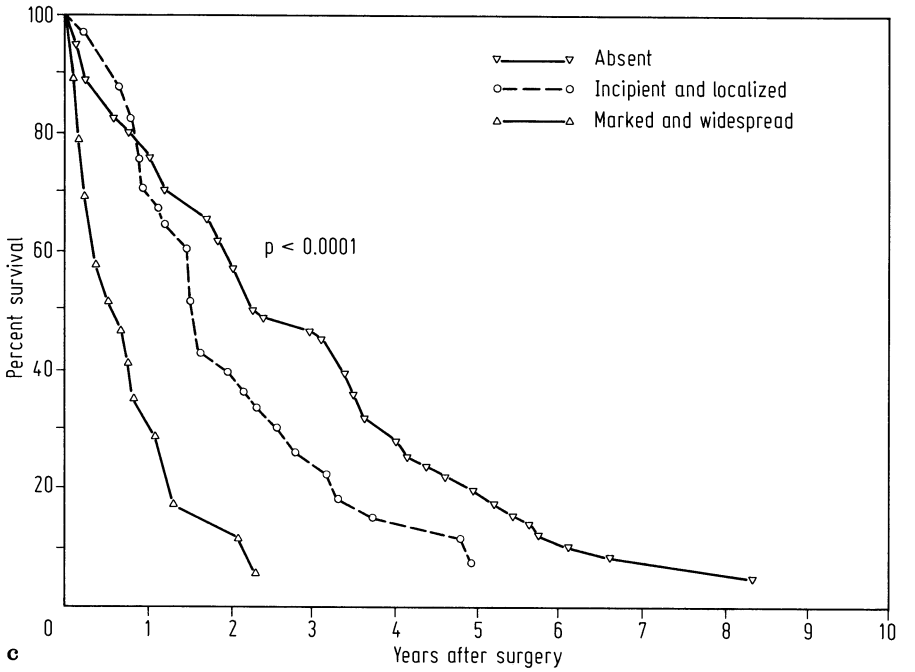
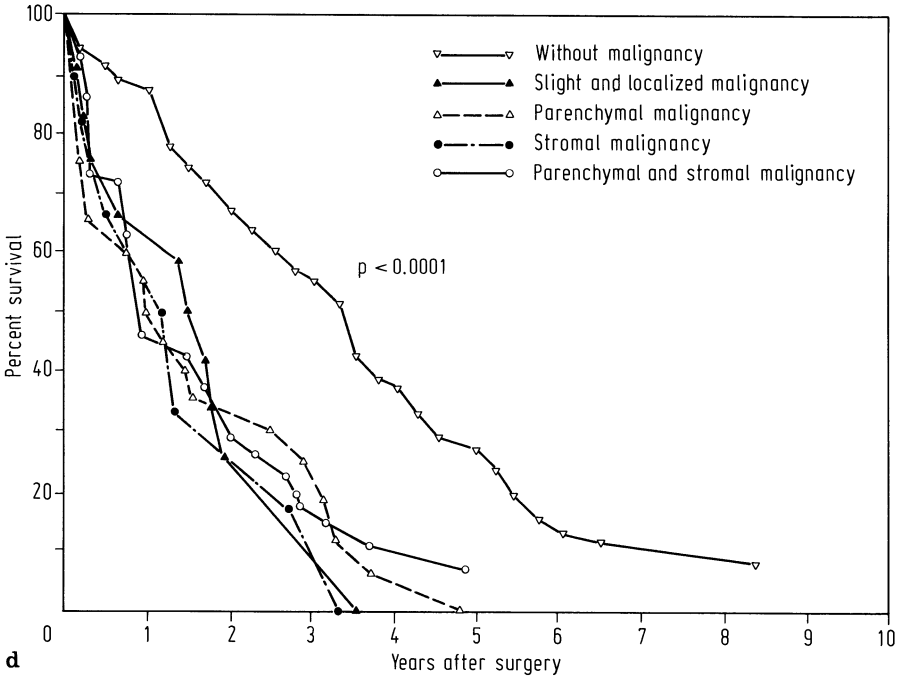


Fig.9.11a–d. Hemispheric astrocytoma; survival by **a** number of mitoses per 10 high power fields (HPF); **b** cell density; **c** endothelial hyperplasia; **d** different patterns of malignancy


Absent
Incipient and localized
Marked and widespread
p < 0.0001
Percent survival
Years after surgery

c


Without malignancy
Slight and localized malignancy
Parenchymal malignancy
Stromal malignancy
Parenchymal and stromal malignancy
p < 0.0001
Percent survival
Years after surgery

d

treatment is controversial. Often, they are well-differentiated astrocytomas, slowly growing, which may have a very long survival even without any therapy. In many cases, conservative treatment with anti-epileptic drugs is adopted, keeping more aggressive approaches in case of clinical worsening [355].

Other data seem to contradict such plans [1921]. A significant correlation has been found between survival and extention of surgical removal with a 50%–60% survival rate at 5 years after macroscopically total removal [1589, 2198, 2688]. All these studies are limited, however, by their retrospective nature, and prospective studies are not yet available.

A possible rationale for removing as much tumor as possible could be given by kinetics data [1198], which suggest that well-differentiated astrocytomas are mainly composed of cells which are not in cycle, and that passage from the "nonproliferating" to the "proliferating" pool is very limited.

Another point in favor of surgery is the necessity to ascertain the histological diagnosis and to discover signs of malignancy indicating adjuvant therapies. It must be stressed that 30% of anaplastic astrocytomas are hypodense on a CT scan [410], and often the histological signs of anaplasia are minimal and localized [2517]; the risk is that they may go undiscovered in a simple biopsy.

When hypodense tumors cannot be approached by surgery either because of their location (basal ganglia, thalamus–hypothalamus, pineal region, brain stem) or their small dimensions, the histological diagnosis may be made on stereotactic biopsy material. The diagnosis of oncotype can be obtained in 80% of cases, provided that specimens are taken by multiple tracks, permitting tumor mapping [67, 2094]. It is more difficult to recognize the malignancy grade. This procedure has also been proposed for the removal of the tumor itself, with encouraging results, provided that it is circumscribed and of small dimensions [1373].

From their kinetic and biological characteristics, there is no neuroradiobiological rationale for the external radiotherapy of differentiated astrocytomas, save sterilizing possible anaplastic foci in the remaining portions [2510] or delaying or diminishing the incidence of malignant transformation [1921].

There is no unquestionable demonstration of the efficacy of postoperative radiotherapy. The only available data on the usefulness of irradiating well-differentiated astrocytomas come from retrospective studies. The survival of patients biopsied or treated surgically by partial removal is improved by radiotherapy [1607, 1921], especially with high doses (53–55 Gy) to the tumor volume [2616], whereas radiotherapy does not seem to improve survival after total removal [2198]. In cases with extensive removal, if postoperative radiotherapy is not performed, a follow-up with CT and MRI must be done, and according to the result, reoperation and/or irradiation carried out. The controversy concerning whether to irradiate well-differentiated hemispheric astrocytomas or not will remain until ongoing prospective studies take into account the role of the various approaches [2617, 1354A].

The prognosis of pilocytic hemispheric astrocytomas is relatively good. Recently, 30 patients with the cystic paraventricular form have been described, with an average age of 22 years. The tumors were characterized by Rosenthal's fibers, microcysts, and calcifications. A mean survival of 6.95 years for males and 5.17 years for females was observed, but many patients were still alive at the time of the last follow up [454]. In an-

other series of 51 patients, with a mean age of 18 years, the tumors were mainly cystic, temporoparietal, with a mean survival of 17 years [2122]. Following complete or incomplete excision, 80% or more survive 10 years [875, 2617]. If pilocytic astrocytoma is totally removed, the patient usually should not be irradiated.

The therapeutic efficacy of interstitial irradiation with ^{192}Ir and ^{125}I is well documented as an alternative to surgical removal for lesions less than 3 cm in diameter or located in highly functional areas [2782, 178, 1971, 2095]. Its neuroradiobiological rationale is unopposable: the administration of a high radiation dose, specifically cytocidal for tumor cells, without damaging the adjacent normal nervous tissue. The same rationale is exploited by recent procedures of radiosurgery, whose results are under evaluation [480].

In anaplastic astrocytomas, macroscopically total surgical removal leads to a lower morbidity and longer survival than incomplete resections.

In patients with anaplastic astrocytomas receiving postoperative radiotherapy, surgical removal leads to better survival as compared with biopsy alone [2008], but the importance of the extent of removal, whether total or partial, is still unclear [2016]. Postoperative radiotherapy improves the prognosis significantly compared with surgical removal alone [876, 2687]. Reoperation for recurrence may be useful, but only in selected cases [52, 1068]. The median survival after surgery plus high dose radiotherapy (which gives the best results) of patients with anaplastic astrocytomas (with or without chemotherapy) is around 28 months [2009], with 62% at 18 months [2009], 38%–50% at 24 months, and 18%–20% at 5 years [1607].

A complete response instead of a partial one after radiochemotherapy, as judged by a CT scan, is predictive of longer survival [1972].

Patients with anaplastic astrocytomas, because of the better survival, are more exposed to the risk of damage from aggressive therapies, such as neutrons [1581], the radiosensitizer misonidazole [624], and intracarotid carmustine (BCNU) [2607].

For other therapeutic problems, see Sect. 9.2.2.12.

9.2.2 Glioblastoma Multiforme

9.2.2.1 General Considerations

Glioblastoma multiforme represents the extreme malignant variant of astrocytic tumors. Among neuroectodermal neoplasias, glioblastoma is the malignant tumor par excellence. Its nosological position has been discussed for a long time, especially as a form distinct from anaplastic astrocytoma. A short historical overview of the problem must be given.

Bailey and Cushing [113] named glioblastoma the malignant glioma, which earlier was labeled spongioblastoma multiforme [112, 2750], to distinguish it from the uni- and bipolar spongioblastomas. This new nomenclature was generally accepted, even though it faced opposition, especially because glioblasts were not well recognized in histogenesis.

Because of its various morphological aspects, this tumor was classified in different ways. For example, Bergstrand (1933) [172] distinguished three groups corresponding

to three different aspects: multiforme, fusiform, and protoplasmic. Busch and Christensen (1947) [347] instead preferred the subdivision into angionecrotic, multicellular, and magnocellular types.

The nosological position of this tumor was overturned with the classification of Kernohan et al. [1405], who abolished it as a tumor entity and put it in the group of grade 4 astrocytomas. There is no doubt that glioblastomas arise through a process of anaplasia from astrocytomas, but it cannot be said that this is an absolute rule. Sometimes, no sign indicating the preexistence of an astrocytoma is found. Therefore, the necessity of retaining glioblastoma as a tumor entity was emphasized even considering anaplasia [2325, 2415] and that it can develop so rapidly as to erase any trace of a preceding astrocytoma.

A powerful contribution to the problem of the relationships between astrocytoma and glioblastoma was brought by Scherer [2477]. He distinguished the rarer primary glioblastomas and the more frequent secondary glioblastomas, derived from astrocytomas. This point of view later found wide consensus [1109] and the concept was extended to other oncotypes, so that glioblastoma was thought to represent the final malignant pathway common to astrocytomas, oligodendrogliomas, and also ependymomas [2325, 1109].

9.2.2.2 Frequency, Age, Site

Glioblastoma is the most frequent neuroepithelial tumor. Its peak of frequency is in the fifth and sixth decades of life, and there is a slight male predilection [2486, 1296, 2970, 3138]. It is very rare in patients below 30 years of age. Glioblastomas represent, in the personal series, 68.4% of all gliomas and 31.6% of all intracranial tumors.

This tumor is located mainly in the white matter of the cerebral hemispheres, and its sites of predilection are: frontolateral, -dorsal, and -basal; temporolateral and -medial; parietodorsal and -lateral; occipitodorsal; basal ganglia; thalamus; corpus callosum [3134]. During tumor growth, such locations may obviously merge. For example, a glioblastoma of the basal ganglia is often also temporal; a frontal one may invade and cross the corpus callosum, expanding in the opposite hemisphere as a "butterfly" tumor. Temporal tumors diffuse more easily anteroposteriorly.

Diffusion may be facilitated in the white matter by long fiber tracts such as longitudinal fasciculi, uncinate fasciculus, corona radiata, and optic radiation. Tumors which invade the internal capsule tend to grow deeply, whilst the thalamic ones do not usually go beyond the internal capsule [1805]. It has to be noted that often the infiltration of a fasciculus is only noted microscopically [2483]. The cerebellar location is very rare (see Sect. 9.3.5).

The greater frequency in males suggested a possible hormone dependence of the tumor. This would be consistent with what has been observed in spontaneous murine gliomas [815] and with steroid receptors [2214]. Experiments on a cell line of human glioblastoma transplanted into athymic mice demonstrated that cell growth is facilitated in males and that androgenic receptors are found mainly in males [2931]. Glucocorticoid and especially androgen receptors have been demonstrated to be present in glioblastoma, more frequently in females than in males [2130].

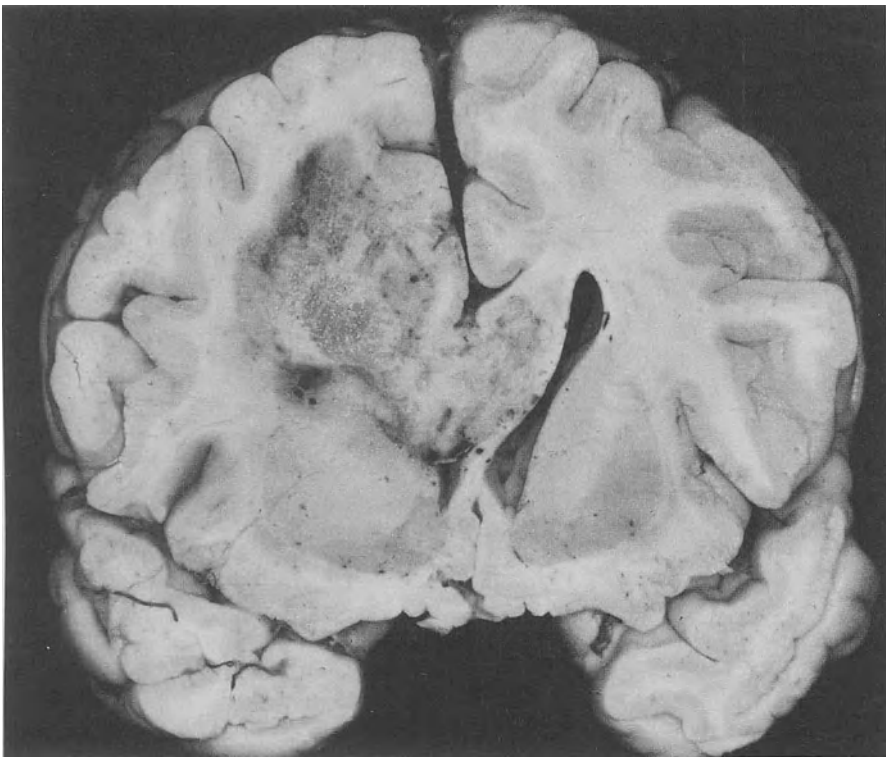


Fig.9.12. Glioblastoma invading the corpus callosum

9.2.2.3 Macroscopic Appearance

In general, the tumor features a large expanding mass infiltrating the white and gray matter (Figs.9.12–9.14). On the cut surface the color varies depending on the regressive events which have occurred: from reddish to bluish or from gray to yellow due to necroses. Very often, small cysts are visible. The consistency may vary from creamy in necrotic areas to hard in scarred ones. The tumor may not be seen on the cortical surface, but the gyri may be widened, swollen, or reddish due to small hemorrhages.

Glioblastoma is not uncommonly multicentric (Fig.9.15), but sometimes the multicentricity is only apparent because macroscopically visible proliferation centers are actually connected by tumor proliferations which are only microscopically detectable.

9.2.2.4 Microscopic Appearance

In all the reports, glioblastoma is presented as the most polymorphous glioma [3134, 2415,2417, 2486, 343], and its astrocytic character is not always diffusely present. Generally, there is a marked cellular density and nuclear pleomorphism (Fig.9.16a). Besides areas of packed cells with almost isomorphous nuclei, there are others showing monstrous nuclei, multinucleated cells, and intranuclear inclusions (Fig.9.16b). The cyto-

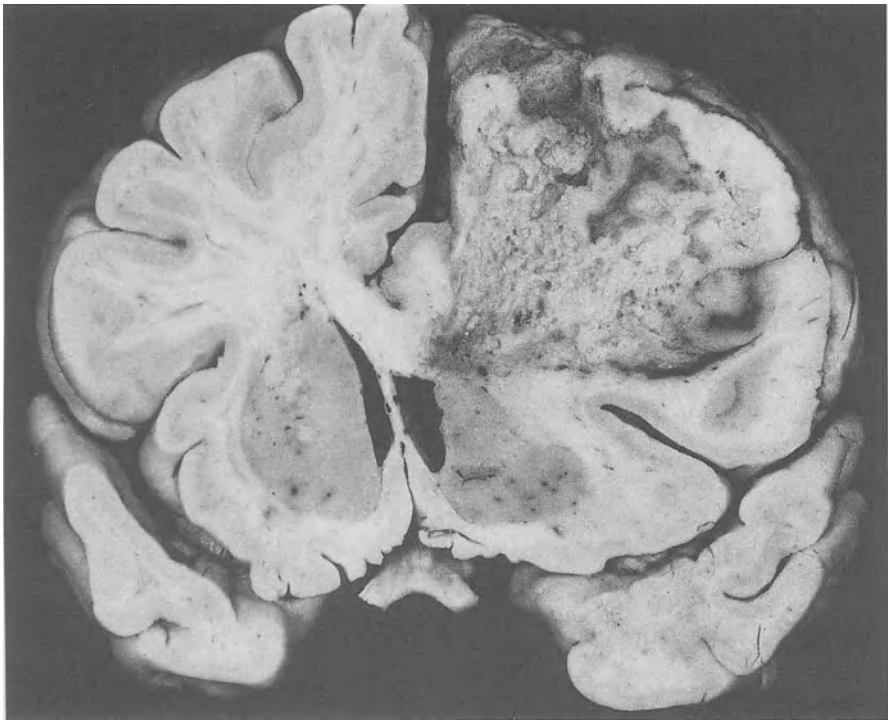


Fig.9.13. Frontal glioblastoma

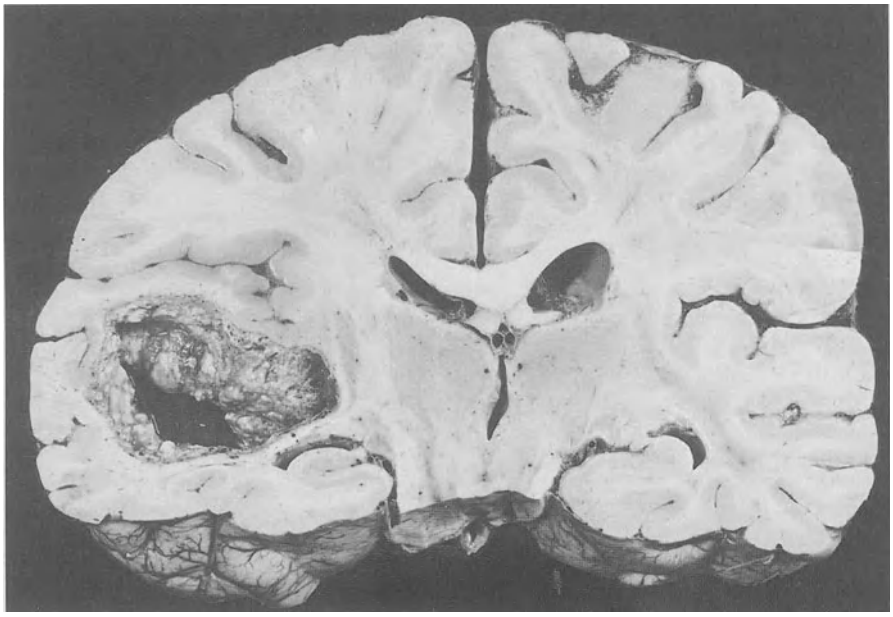


Fig.9.14. Temporal glioblastoma

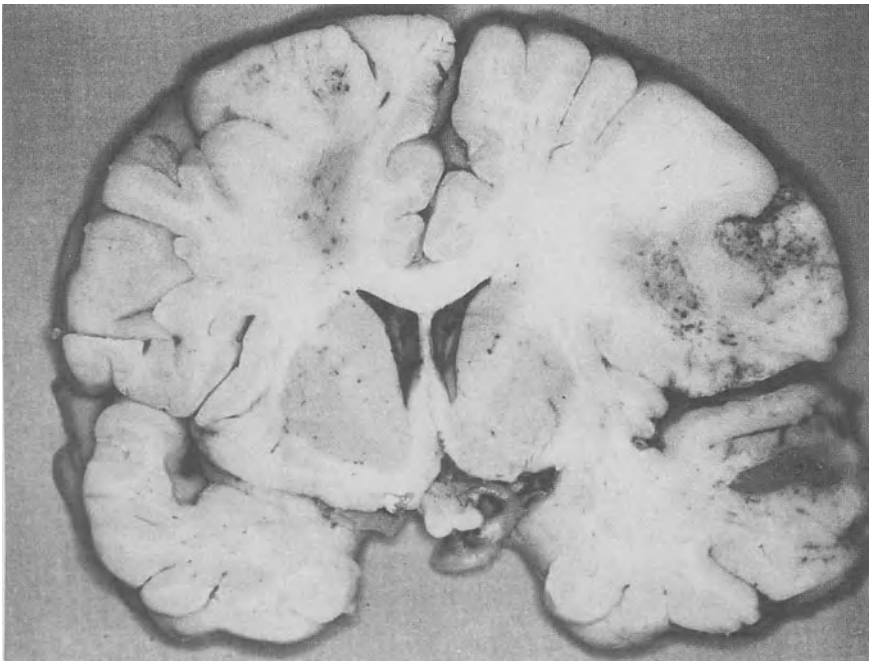


Fig.9.15. Multicentric glioblastoma

plasm can be of different sizes, round, elongated, and variably GFAP-positive or negative. Mitoses are very abundant, prevailing in the less polymorphous and in the more densely cellular areas.

The highly proliferating areas are characterized by densely packed cells with scanty cytoplasm, mostly GFAP-negative [581, 332, 2515], and show many mitoses. These areas are especially evident in cortical invasion (Fig.9.17). Necroses are a characteristic feature of glioblastoma. They may be extensive and centrally located (Fig.9.18) and of medium size with partial palisades or small with complete pseudo-palisades (Fig.9.19a). The latter may be numerous and sinuous in shape. Whilst the former are in general caused by the occlusion of blood vessels by thrombosis, the latter derive from highly packed proliferating growth centers without an adequate blood vessel supply [2508, 2521]. Large necroses are the fundamental element which distinguishes glioblastoma from anaplastic astrocytoma.

Another typical feature of glioblastoma is represented by the abundant blood vessel supply. The prominent production of reticulin is in relation to the vessels (Fig.9.19b). Dilated and neoformed blood vessels are common, and endothelial proliferations involve capillaries, arteries, and veins, sometimes also the meninges. Glomeruloid formations arise, formed by endothelial hyperplastic cells with an embryonal appearance (Fig.9.20). Sometimes the formations can be arranged like a "wall" towards normal tissue, necroses, etc. (Fig.9.21a). The significance of endothelial proliferations has long been discussed [758, 2961, 3014]. In personal experience, the cortical vascular tree for-

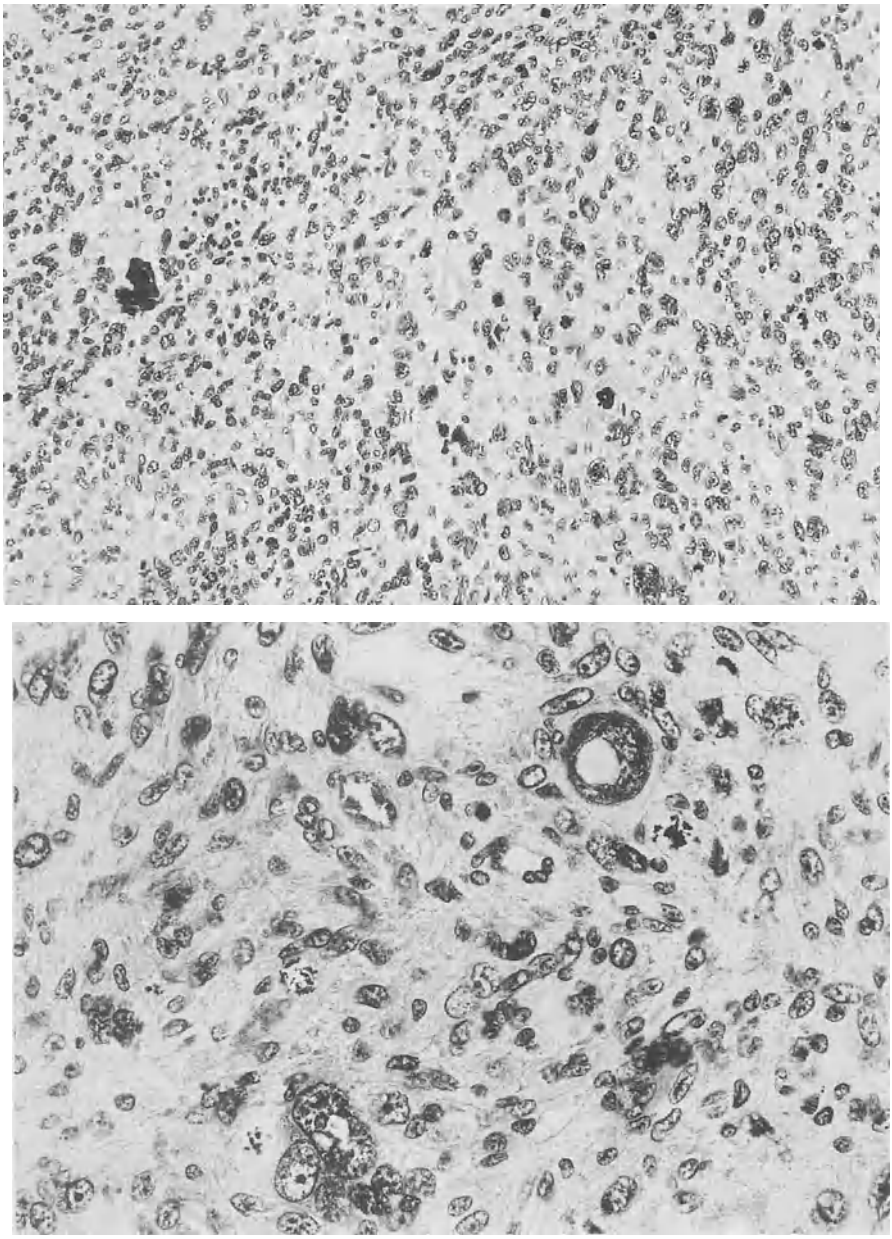


Fig.9.16a,b. Glioblastoma: **a** nuclear polymorphism with many mitoses, also atypical ones, H&E, ×200; **b** nuclear inclusions, H&E, ×400

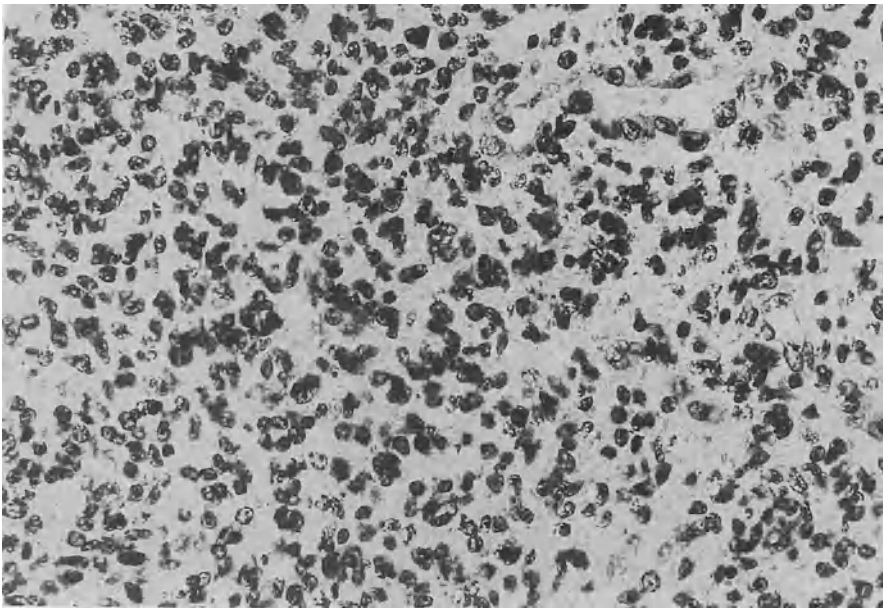


Fig.9.17. Glioblastoma: invasive area with high cell density and also isomorphic nuclei, H&E, ×300

med by the arteries penetrating from the meninges and by their collateral branches responds to tumor infiltration with endothelial hyperplasia which leads to its distortion and impairment of its functions. Circumscribed areas of necrosis arise due to local ischemia. Vascular glomeruli can also form in the healthy cortex around the tumor, but in personal experience, this happens when the overlying meninges are infiltrated. It has to be remarked that endothelial hyperplasia in glioblastoma is a phenomenon which does not precede but follows cortical tumor infiltration, and it is not synonymous with neovascularization [2521].

The blood vessels increase in caliber towards the center of the tumor. In this position there is usually a large area of central necrosis, and between this and the peripheral proliferative zone there are large and deformed blood vessels with thickened walls, sometimes featuring degenerative changes and often thrombosis.

The blood vessel network can be highlighted with techniques which stain the basement membrane, such as the immunohistochemical demonstration of laminin (Fig.9.21b) [927, 1838] and of type IV collagen [2065]. Generally, the membrane between the glial cells and adventitia remains relatively preserved.

The stromal component of a glioblastoma may be very active and show neoplastic features of the sarcomatous type. Apart from this transformation, which will be expanded upon later, some stromal peculiarities may be found. A rhabdomyoblastic component characterized by elongated cells with elongated nuclei and transverse cytoplasmic cross-striations and originating from the vascular component has, for example, been described. The term "gliomyosarcoma" has been proposed [963, 133]. Glioblasto-

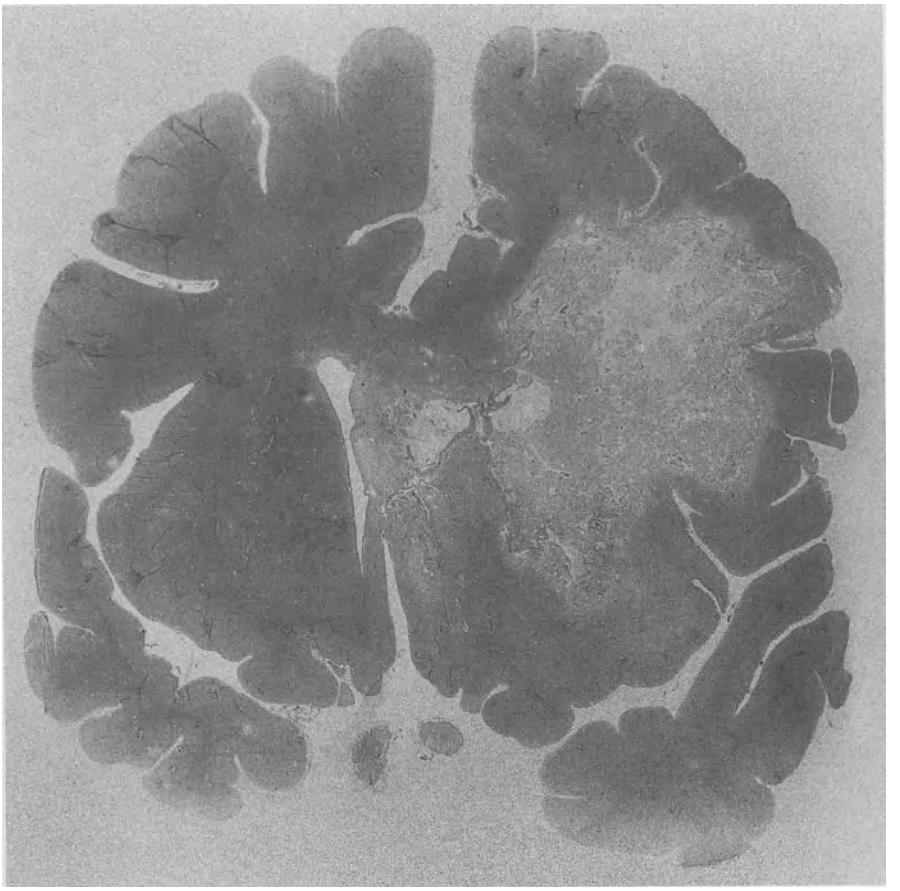


Fig.9.18. Glioblastoma: extensive central necrosis, H&E

mas associated with chondrosarcomatous [2317] or osteochondrosarcomatous [2451] components have also been described. All of these features were encompassed in the "ectomesenchymal" hypothesis, which states that neural crest cells may show both neuroglial and mesenchymal characteristics in both the CNS and PNS [670].

The infiltrative growth of glioblastoma leads to invasion of both cortex and white matter. The cells often reach the molecular layer, where they crowd. The subarachnoid spaces may become filled, and the tumor may reinvade the cortex from the subpial region. Unlike astrocytoma, glioblastoma elicits a strong glial reaction both in the cortex and in the white matter, as revelaed by the immunohistochemical demonstration of GFAP which highlights the stubby and long processes of reactive glial cells (Fig.9.22a). Reactive astrocytes, especially in the cortex, may be included in the advancing tumor and remain visible for a long time amongst the tumor cells (Fig.9.22b). As has been said, highly proliferating tumor cells are on the whole GFAP-negative, so that in many areas there is a mixed cell population which is GFAP-positive and GFAP-negative. GFAP-

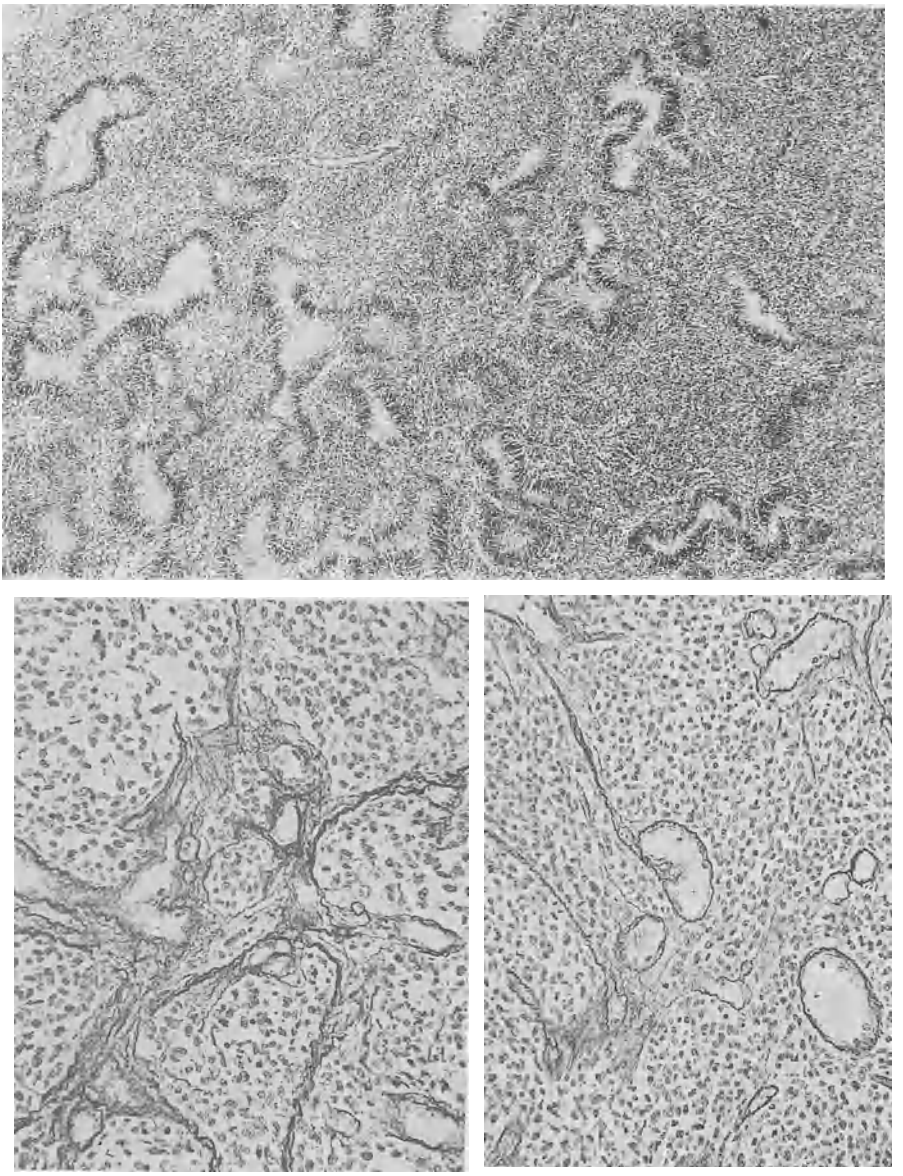


Fig.9.19. Glioblastoma: **a** many circumscribed necroses with pseudo-palisades in a proliferative area, H&E, ×100; **b** abundant reticulin network in relation to blood vessels, Gomori, ×200 [2486]

positive reactive astrocytes in these areas undergo modifications, even if only due to mechanical factors, and become indistinguishable from tumor cells in as much as they may undergo mitosis [2518]. This fact may lead to the wrong interpretation of the degree of malignancy when the diagnosis is made on small fragments.

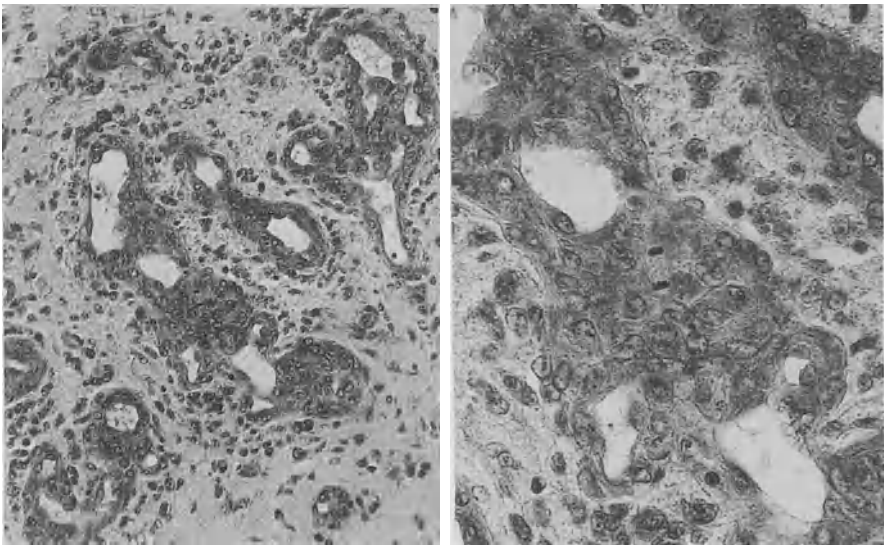


Fig.9.20a,b. Glioblastoma: **a** endothelial hyperplasia with mitoses, formation of buds, H&E, ×250; **b** the same at higher magnification, H&E, ×400 [2486]

Very often, lymphocytic or lymphoplasmacellular perivascular infiltrates are present. They are generally interpreted as indicating an immunologic reaction, because they are associated with a better survival [1818, 304, 2121]. In a series of 199 cases, such infiltrates were observed in 134 patients (67.5%) who survived longer. Infiltrates were more frequently seen in cases which had not previously been treated with steroids [246]. Other studies have, however, not found longer survival in cases with such infiltrates [2320, 2499, 2502, 2373], and doubt has been cast on the specificity of the reaction [3037].

EGFR has been demonstrated immunohistochemically in 79% of malignant and in only 9% of well-differentiated gliomas, but also in other oncotypes. However, a correlation with tumor proliferation, as judged with the antibody Ki-67, has not been observed [2292].

By means of in situ hybridization it has been demonstrated that endothelial cells also bear the β-receptor for PDGF and express the mRNA for the PDGF B-chain, which implicates them in an autocrine mechanism of stimulation [1113, 1827]. PDGF may, therefore, become a member of the family of angiogenic peptides.

Some data on TGF, another factor which is important for neoplastic transformation, are beginning to appear. Two types are known, α and β. The former shares a remarkable percentage of homology with EGF, and together they compete for the same membrane receptors [215]. TGF-β has been observed immunocytochemically both in benign and malignant gliomas [455, 2442], but not in normal nervous tissue, whilst TGF-α has been seen to prevail in malignant gliomas [2442], where it could be related to the progression of the tumor. For further information, see Chap. 2.

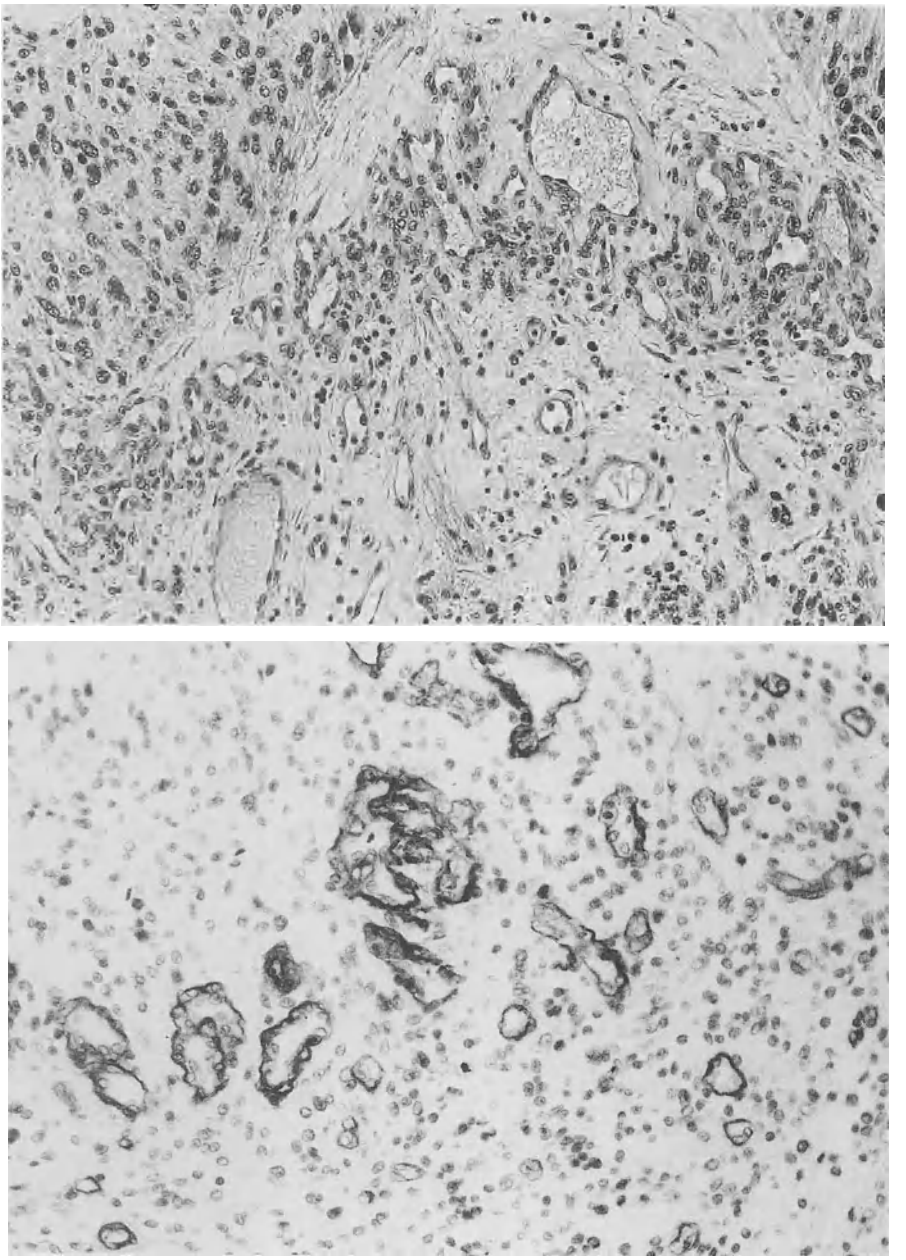


Fig.9.21a,b. Glioblastoma: **a** wall of vascular glomeruli, H&E, ×200; **b** thickened basement membranes evident with laminin, PAP-DAB, ×200

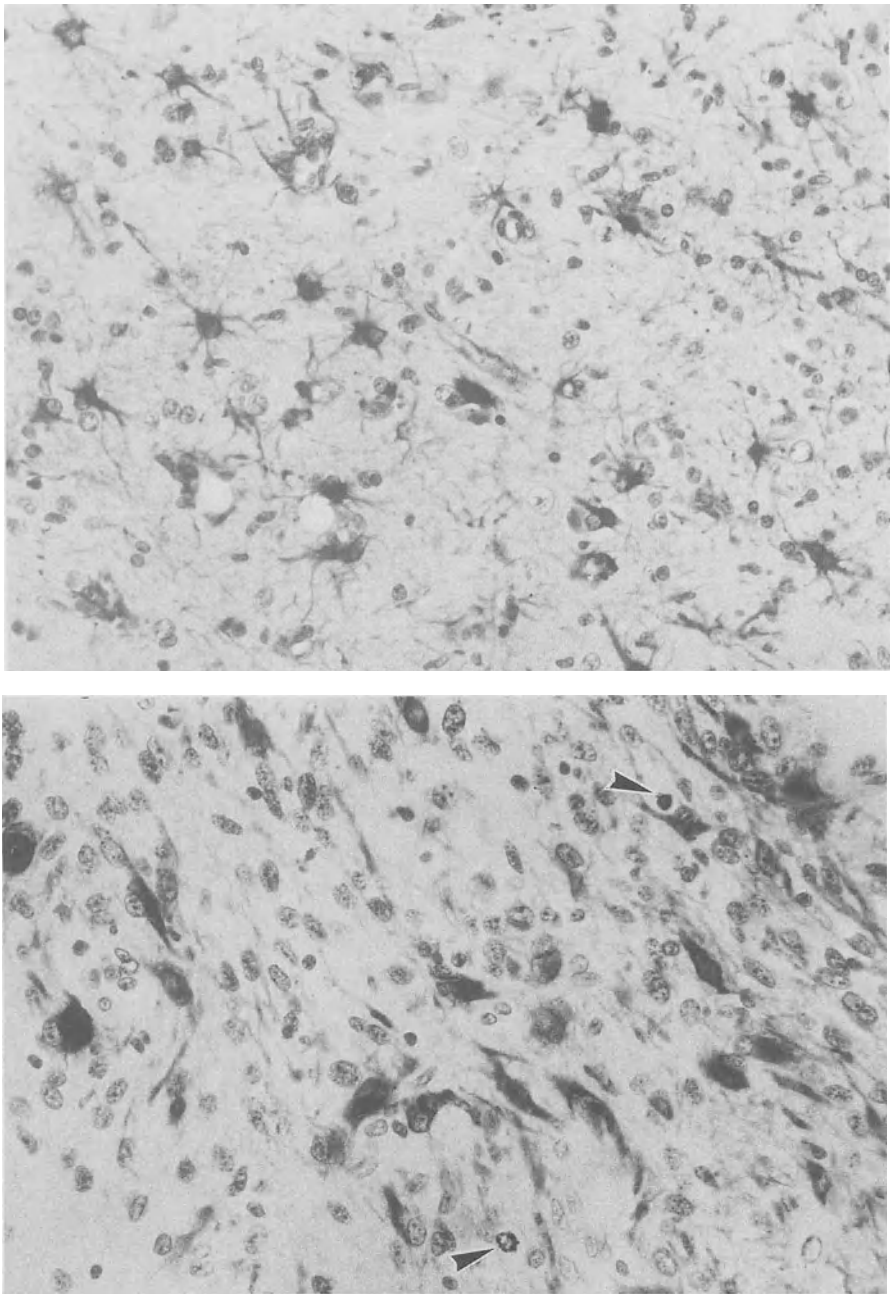


Fig.9.22a,b. Glioblastoma: **a** reactive astrocytes in the invaded cortex, GFAP, PAP-DAB, ×300; **b** reactive astrocytes intermingled with tumor cells; *arrowheads* indicate mitoses, GFAP, PAP-DAB, ×400

9.2.2.5 Tumor Spreading

Classically, the tumor grows from the white matter into the cortex, features satellitosis, and reaches the meninges. It may grow in the subpial region and spread to adjacent cortices (Fig.9.23a). A growth may occur in the subarachnoidal space, and the cortex can be reinvaded (Fig.7.6a), or meningeal gliomatosis may occur. Infiltration of the ependyma and of the subependymal layers is also characteristic, with the possibility of further diffusion into the subarachnoid spaces. The subependymal layers may, however, also form a barrier to the tumor. As already stated, tumor spread may take place and be detected only histologically, through fibrous structures such as the septum pellucidum (Fig.9.23b), hence simulating multicentricity [2483, 2484]. Glioblastoma may diffuse into the ventricular system, colonizing the walls of ventricles (Fig.9.24a) or even in the region of the cauda equina: blastomatous ependymitis [1073] and meningeal gliomatosis [2218], respectively. These events are, however, not precisely known from the quantitative point of view, because systematic studies are few [3110, 96]. In an autopsy series of 51 glioblastomas, CSF dissemination was found in 14. In 7 of these, there was pronounced dissemination and scarce local reaction with a poor expression of GFAP by the tumor cells, and in the other 7 there was scanty dissemination and extensive local infiltration with marked GFAP expression. The less differentiated cells could be more easily released into the CSF but are less invasive [2087]. The first proposition has been accepted, because it is in agreement with what is observed in other poorly differentiated tumors, such as medulloblastoma, whilst the second has not been considered as supported by valid correlations [2397]. The most important feature of the spreading of glioblastoma is that invading cells travel along the fiber tracts in the hemispheric white matter (Fig.9.24b). They can be found outside the hypercellular edge of the tumor, not only in the area usually noted as hypodense on CT scans, but even further. The cells are not easily identifiable on the usual histological preparations, but perhaps it is easier with special stainings on fresh tissue [568]. The invasion assumes a digitating aspect in the long axis of many gyri. The frequency of dissemination is obviously influenced by the "duration" of the tumor. The location on the walls of the ventricles may also depend on local ependymal defects, which are frequent and extensive, due to the hydrocephalus which often accompanies the tumor [2033]. Diffusion via the CSF can also reach the cerebellum, where secondary growth may occur. It seems that spread via the CSF is more frequent in children [1349], and this could have some importance in the establishment of radiotherapeutic treatment modalities.

9.2.2.6 Differential Diagnosis

A differential diagnosis has to include, apart from anaplastic astrocytoma, metastatic carcinoma, cerebral lymphoma, ependymoma, sarcoma and pleomorphic xanthoastrocytoma. In respect to carcinoma, distinction is based on the mode of infiltration of glioblastoma, which contrasts with the sharp edge between normal tissue and the carcinoma; on the appearance of necroses with pseudo-palisades which are different from the intervasal necroses of carcinoma; and on the peculiar and exuberant endothelial proliferation. In particular cases, the differential diagnosis is not easy, especially if only small areas of tumor are examined. The possibility of the formation of papillae represented by columnar cells resting on a delicate vascular-connective stroma [1945] and

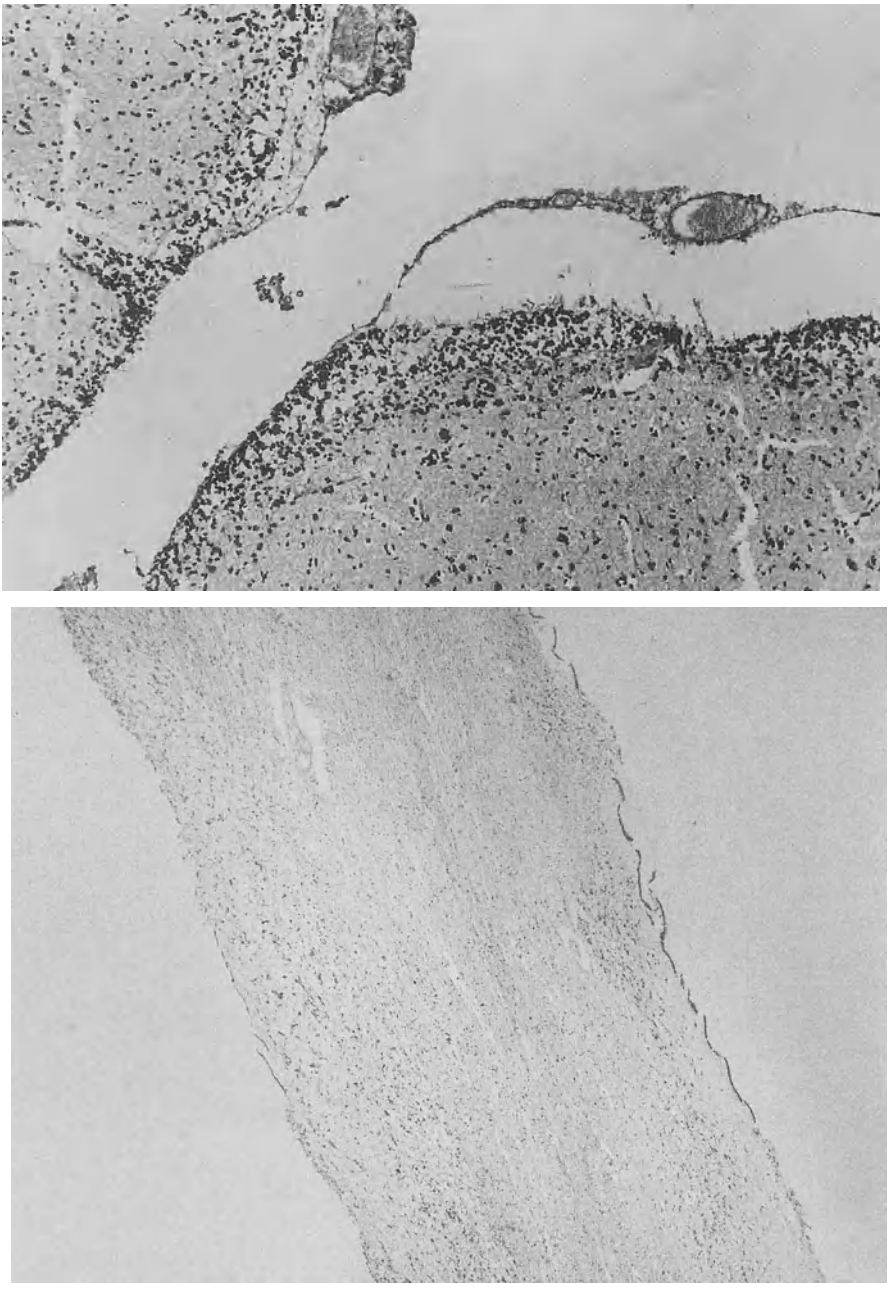


Fig.9.23a,b. Glioblastoma: **a** subpial growth, H&E, ×200; **b** diffusion along the septum pellucidum, H&E, ×100

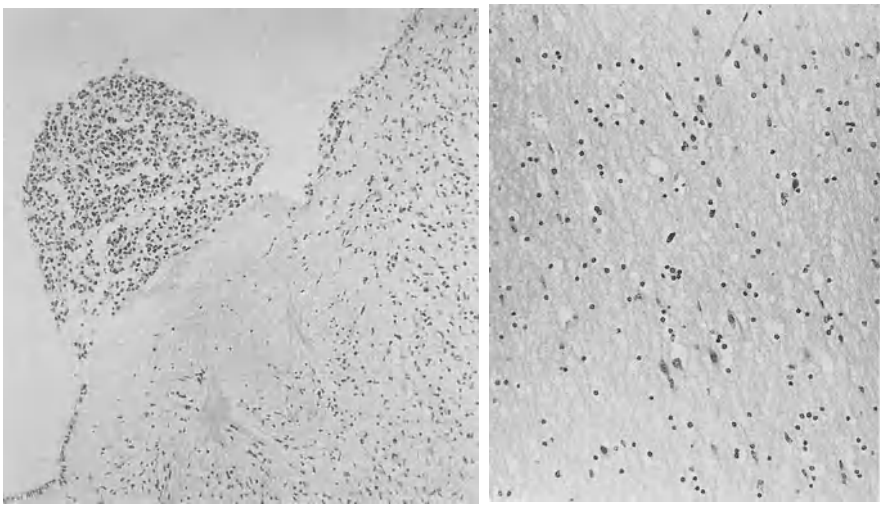


Fig.9.24a,b. Glioblastoma: **a** colonization on the ventricular wall, H&E, ×200; **b** infiltrating cells in fiber tracts of the hemispheric white matter, H&E, ×200

simulating medulloepithelioma or adenocarcinoma has to be taken into account. These papillary formations may represent an epithelial-sinusoidal differentiation or resemble an ontogenetic feature. It is also possible to observe foci with squamous differentiation, with the development of epithelial whorls, keratin pearls, and cytokeratin positivity, which represent extreme degrees of epithelial differentiation [1946].

Lymphoma is essentially distinguished by its intra-advential growth, especially at its periphery, as highlighted in reticulin preparations. Sarcomas generally show abundant reticulin and totally lack GFAP. Ependymoma is recognizable if its characteristic tissue elements, such as perivascular radial crowns, rosettes, and canals, are present. The pleomorphic xanthoastrocytoma does not usually show mitoses or circumscribed necroses [3130].

Cases have been described, considered as variants of glioblastoma, which are characterized by the presence of strongly lipidized, GFAP-positive cells, besides necroses and mitoses [1392]. These tumors are usually deeply situated [911], but they have also been described in superficial locations. Because of the above mentioned features, they are different from pleomorphic xanthoastrocytoma.

9.2.2.7 Giant Cell Variant

The giant cell variant is characterized by numerous large, giant cells with polymorphous nuclei and is otherwise not different from classic glioblastomas (Fig.9.25). Despite the importance of polymorphism, they show a reduced proliferative potential [1200] and a longer survival [155, 333, 914, 1836]. The existence of this variant [2391, 2419] has long been contested because tumors with monstrous cells have for a long time been diagnosed as "monstrocellular sarcomas " [3134]. For the differential diagnosis from gliosarcoma, see Sect. 9.2.2.8. There is no doubt today that this variant exists. In addition

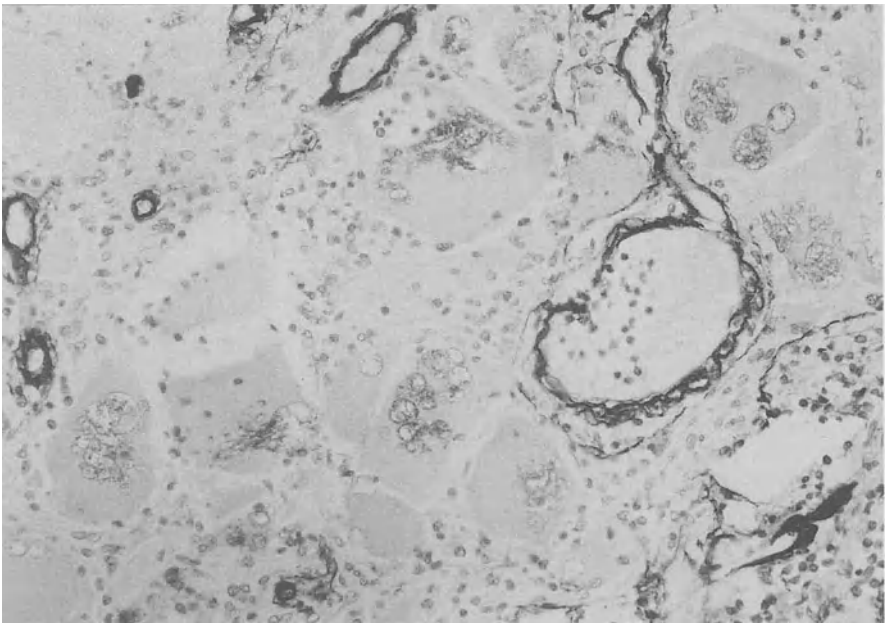


Fig.9.25. Giant-celled glioblastoma, H&E, ×200

to the features indicated above, it is characterized by a lack of endothelial proliferations and by the presence of circumscribed necroses without pseudo-palisades [343]. The tumor is usually circumscribed on CT scan and occurs preferentially in the temporal lobe [1764].

9.2.2.8 Gliosarcoma

9.2.2.8.1 General Considerations

It is not rare to find mixed neuroepithelial and mesodermic tumors. They may develop because of a gliomatous reaction to a preexisting sarcoma or because of a sarcomatous reaction of the meninges to infiltration by glioblastoma [2386, 2419], but more often they are true mixed tumors in which the sarcomatous component arises from the blood vessels of a glioblastoma or anaplastic astrocytoma. The term gliosarcoma was first used by Stroebe [2751], but it only really began to be applied with the fundamental work of Feigin and Gross [756] and was subsequently widely accepted [758, 1924]. Cases with sarcomatous growth prevailing over the glial one have been described, a feature commonly found in cultures [1020]. A large body of opinion holds that the sarcomatous component originates from the proliferating endothelium of blood vessels. However, contrary observations indicating a derivation from adventitial fibroblasts or histiocytes, or even that the glioma is secondary to a fibrosarcoma, namely "sarcoglioma" [1556], have been made.

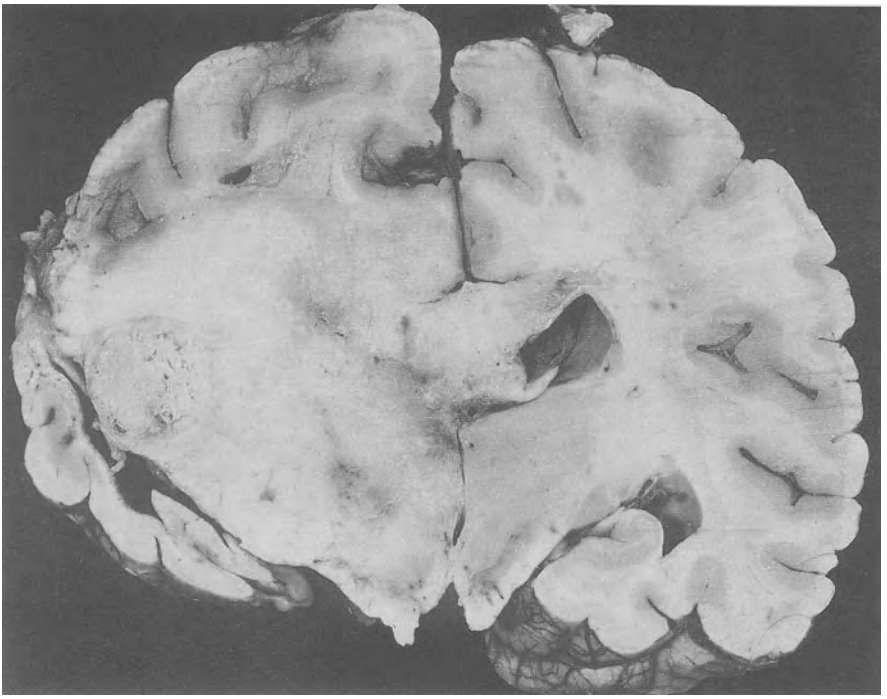


Fig.9.26. Gliosarcoma [2504]

9.2.2.8.2 Frequency, Age, Site

The incidence of gliosarcoma in respect to malignant gliomas is difficult to calculate because of the multiplicity of the diagnostic criteria. It varies from 1.2% [758, 1469] to 8% [1924]. In our series they represent 6.6%. Gliosarcomas arising from blood vessels in oligodendrogliomas [760, 2137] or in ependymomas [1693] have also been described. The mean age is close to that for glioblastoma, being in 33% [1924] and 50% of cases [1860] over 60 years. The tumor is frequently located in the temporal lobe; however, in one series it was more frequently located in the frontal lobe [1860].

9.2.2.8.3 Macro- and Microscopic Appearance

The tumor is reddish-gray, has a hard consistency, and is usually well delimited from the surrounding tissues (Fig.9.26). Two intimately admixed components, a fibrosarcomatous and a glial one, are observed histologically (Fig.9.27a). The richness in reticulin and the fibronectin-positivity (Fig.9.27b) of the fibrosarcomatous component and the GFAP-positivity of the glial component are fundamental diagnostic elements. In a large series, the mesodermal component was recognized as either a malignant fibrous histiocytoma or a fibrosarcoma [1860]. There is a sharp demarcation between the two formed by a basement membrane (Fig.9.28a), easily visible under the electron microscope or by immunohistochemical demonstration of laminin [927]. The blood vessels

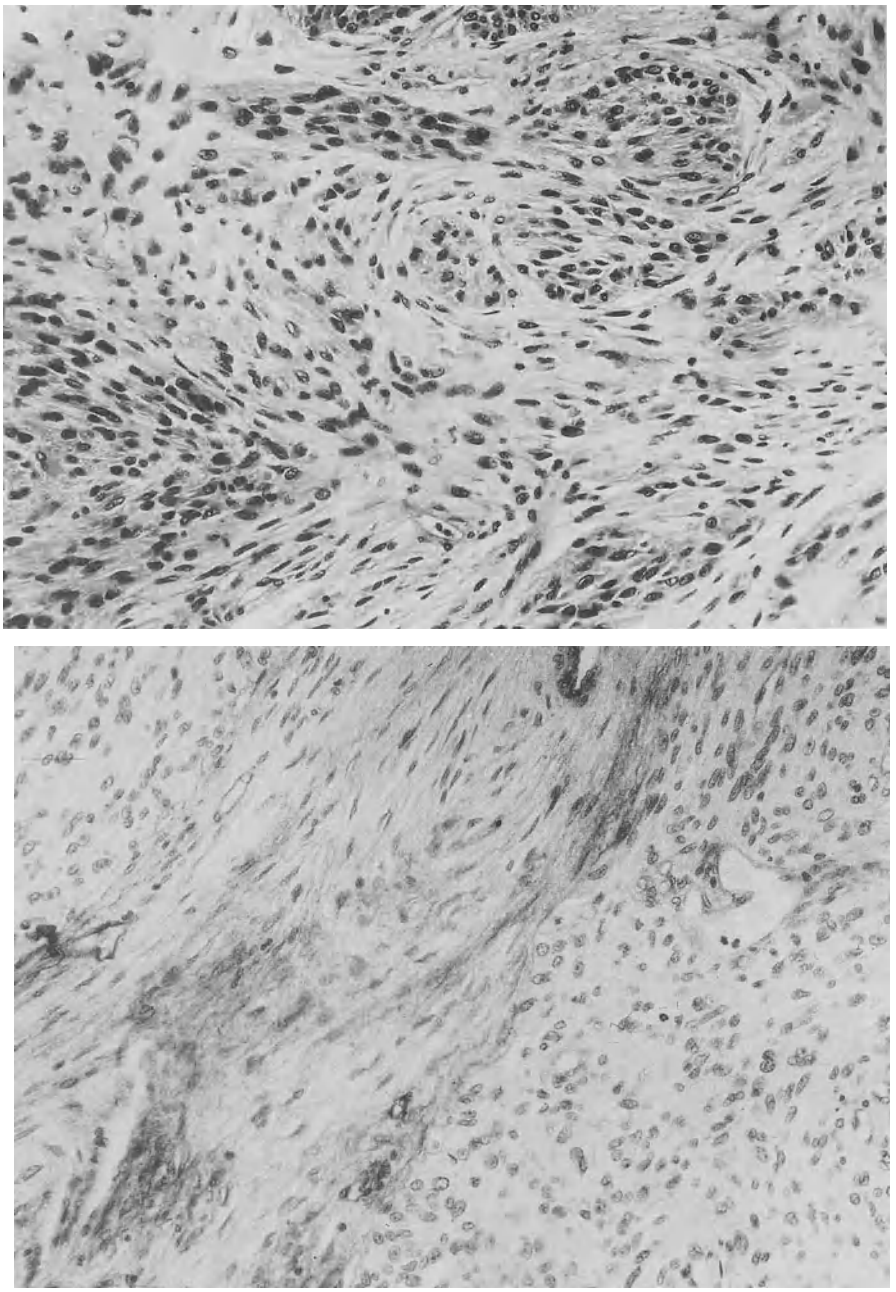


Fig.9.27a,b. Gliosarcoma: **a** glial and fibroblastic proliferations are almost indistinguishable, H&E, ×300; **b** the mesodermic component is fibronectin-positive, PAP-DAB, ×200

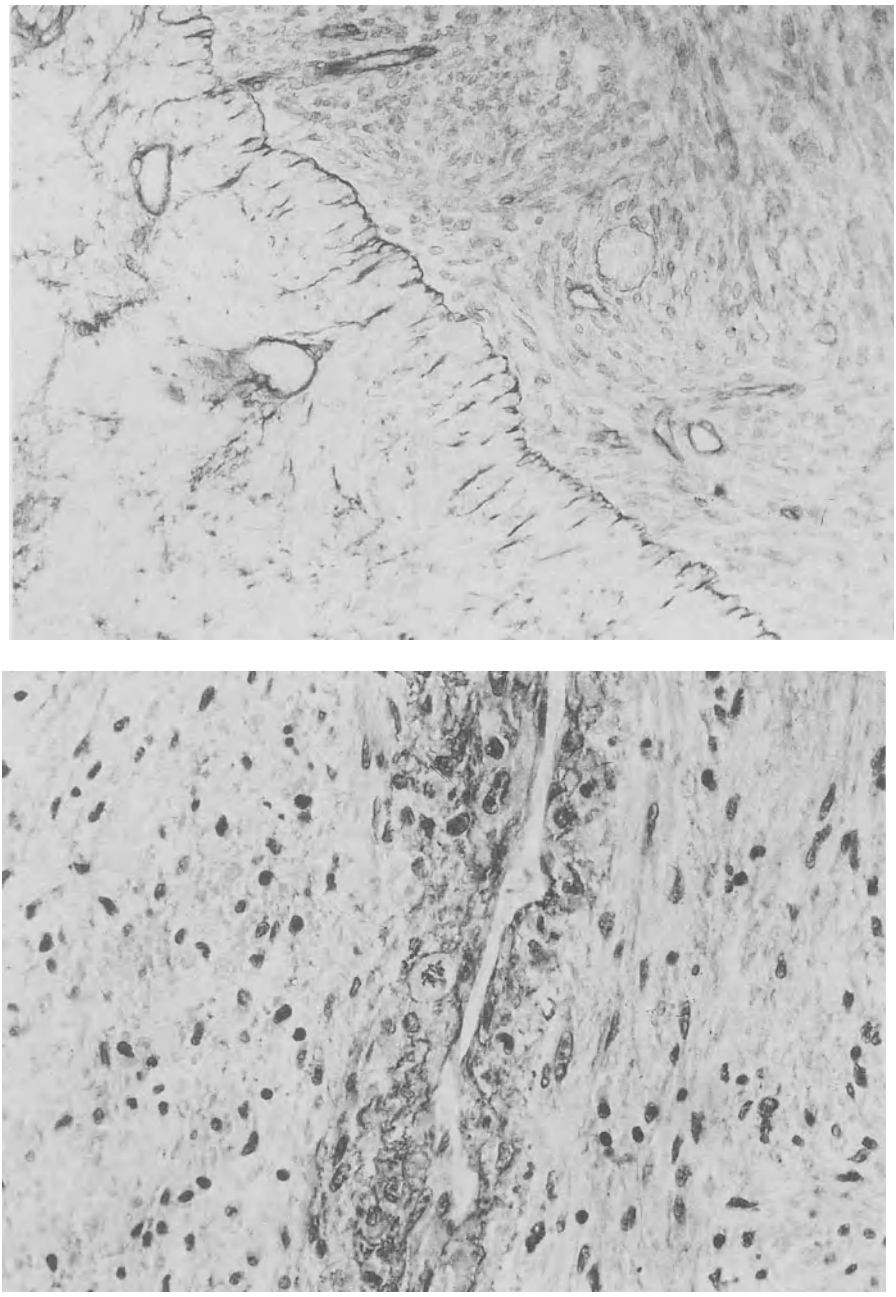


Fig.9.28a,b. Gliosarcoma: **a** basement membrane separates the two components, laminin, PAP-DAB, ×200 [2511]; **b** vessel with slit-like lumen in the mesodermic component, H&E, ×300

have different features in the two components. They are similar to those of glioblastoma in the glial component and are "slit-like" and practically without a wall in the sarcomatous part (Fig.9.28b). The two components sometimes may be so intimately admixed that the glial cells may be seen as isolated elements only by GFAP staining (Fig.9.29a) or as ribbons narrowed by mesenchymal trellises (Fig.9.29b) or take up adenoid features and simulate the cells of an adenocarcinoma [1397]. GFAP-positivity usually resolves the doubt. A diagnostic complication is the possibility that foci of marked epithelial differentiation will develop from the glial component and present as cytokeratin positive squamous cells and keratin pearls [1946].

Gliosarcoma raises some biological problems which have only been partially resolved. The first is related to the presence of giant and monstrous cells. Some authors interpret them as being of a glial nature and the tumor as a variety of glioblastoma called "gigantocellular" [155, 1724, 1037, 2419]. Others see these cells as sarcomatous and name the tumor "circumscribed monstrocellular sarcoma of blood vessels" [3134, 1147, 214, 309]. With the immunohistochemical demonstration of GFAP, it has been found that the great majority of giant cells are glial, but that there may also be giant cells in the sarcomatous component. Therefore, "monstrocellular" gliosarcoma is not an inappropriate term, because of the presence of giant cells, especially in the glial component, but also in the sarcomatous one [2504].

A second and more important problem is that of the precise origin of the sarcomatous component. Factor VIII/RAg is a typical marker for endothelial cells. It is positive in the glomeruli of glioblastoma, but only in the cells delimiting the lumina [1841], and negative in the fibrosarcomatous cell populations of gliosarcoma. These must therefore originate either from pericytes or fibroblasts or even from endothelial cells which have lost the capacity to express factor VIII/RAg. Sometimes it is possible to see a transition between factor VIII/RAg-positive endothelial cells of glomeruli and the factor VIII/RAg-negative fibrosarcomatous proliferations [2511, 2667]. It is possible that in the process of neoplastic transformation, the endothelial cells lose the capacity to express the marker, as has been observed in other conditions, for example, angioreticuloma [1014]. An alternative interpretation based on the demonstration of histiocytic markers such as α_1-antichymotrypsin, lysozyme, and α_1-antitrypsin, which are abundant in the sarcomatous component, is that the adventitial histiocytes are the major source of the fibrosarcomatous proliferation [1469]. Taking into account that the histiocytes are positive for fibronectin [549] and are more concentrated around blood vessels than in fibrosarcomatous areas, it is possible that they themselves are potential fibroblasts [841] which may promote the proliferation of mesenchymal cells such as fibroblasts or endothelial cells [1469]. However, the positivity for antiproteases and monocyte/macrophage series markers in the mesenchymal areas does not seem sufficient to establish the histiocytic nature of the tumor. The mesenchymal component may derive from fibroblasts or from undifferentiated mesenchymal elements of the blood vessel adventitia [993]. In the fibroblastic proliferations which originate from blood vessels in irradiated glioblastomas, collagen type III, typical of fibroblasts, is expressed with fibrils which under the electron microscope seem to be produced by endothelial cells [2522].

The study of the various types of collagen has brought useful information on this point. For example, collagen type IV, typical of basement membranes, is also found in glioblastomas. It can be found in vascular buds, but never in fibroblastic-type proliferations such as those found in glio-

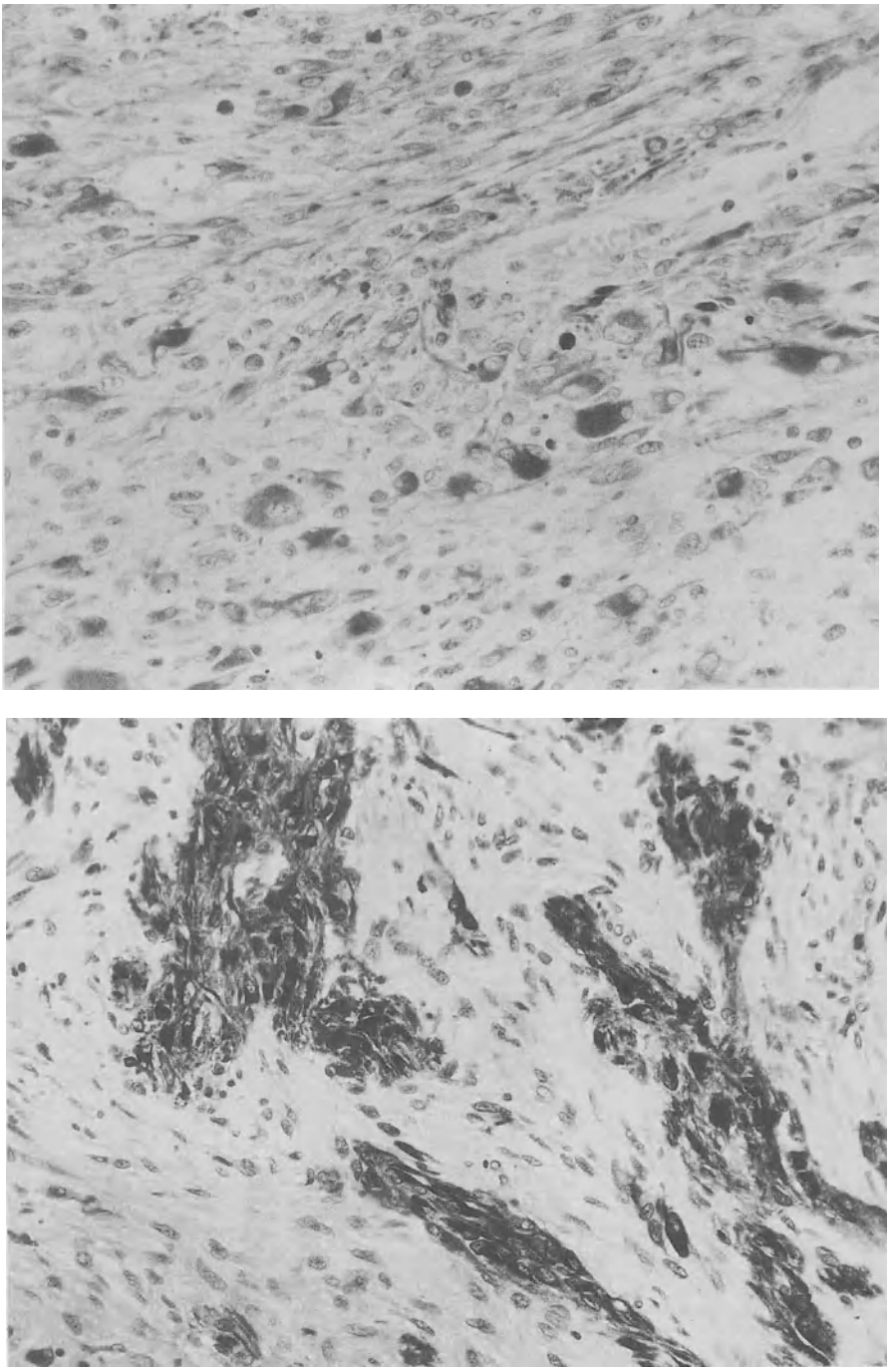


Fig.9.29a,b. Gliosarcoma: **a** GFAP-positive, isolated glial cells in the mesodermic component, PAP-DAB, ×400; **b** narrow ribbons of GFAP-positive cells in the mesodermic component, PAP-DAB, ×400

sarcoma. On the contrary, the latter proliferations express collagen type VI, which is typical of interstitial microfibrils but is never found in endothelial proliferations [2150]. These data do not confirm the endothelial origin of the fibroblastic proliferations. The finding of collagen type VI in the pial-glial basement membranes [1843] might simply be due to adjacent phenomena. In fibrosarcomas arising after the irradiation of glioblastomas, a diffuse histiocytic character is observed, as is also found in fibroblastic meningiomas with which the tumors have been likened [2072].

Two recent observations on the nature of gliosarcomas must be quoted. One refers to the immunohistochemical positive staining for α-sm-actin of spindle and polygonal cells, which are GFAP-negative, suggesting that gliosarcoma represents one end of the spectrum of glioma-induced vascular smooth muscle proliferation [1036]. The second observation refers to a contemporary positive staining for α-sm-actin and GFAP of spindle cells in reticulin-rich areas of the tumor, suggesting the total glial origin of tumor cells [1320].

Some peculiar observations have been made in this tumor. A myxoid component, for example, was found in one case and attributed to the transformation of glial cells [1433]. Rhabdomyoblastic [963, 133], osteochondrosarcomatous [2451], and chondrosarcomatous [2317] metaplasia have been described in other cases. GFAP-negative cartilage has been found, due not to the transition from astrocytes [1399] but to mesenchymal metaplasia [122].

A rare benign tumor composed of cells that exhibit both GFAP-positive glial and collagen producing mesenchymal cells has been called gliofibroma [829]. Some examples have been reported. The existence of the tumor as an entity is, however, controversial [2547A, 2677A].

9.2.2.8.4 Prognosis

The prognosis of gliosarcoma grossly overlaps with that of glioblastoma in many series, with possibly a greater number of cases with longer survival. There is some tendency to leptomeningeal spread.

9.2.2.9 Blood Vessel Architecture and Angiogenesis in Gliomas

In well-differentiated hemispheric astrocytomas there is no neoformation of blood vessels. The tumors utilize the preexisting blood vessels and modify them. In pilocytic astrocytomas of the midline, especially of the cerebellum, but principally in glioblastoma, there are very important changes due essentially to the endothelial hyperplasia leading to the formation of glomeruli. In glioblastoma, three zones may be distinguished for blood vessels: a peripheral zone, rich in neoformed vessels with endothelial proliferation; an intermediate one featuring larger dilated vessels; and a central necrotic one with degenerated large vessels.

The intensity of vascularization cannot always be used as an indication of malignancy. A positive correlation, for example, exists for hemispheric astrocytic gliomas but not for those of the midline or for cerebellar ones. Precise morphometric measurements have demonstrated that an oligodendroglioma can be more vascularized than an anaplastic astrocytoma. This means that the richness in blood vessels depends also on the type of tumor [2585].

Most studies of blood vessels have focused on the difference between normal and tumor blood vessels and capillaries. Normal capillaries are characterized by a continuous basement membrane and by endothelial cells with tight junctions, except in some areas, such as the area postrema and choroid plexus, where the junctions are of the fenestrated type. Endothelial cells have scarce pinocytic vesicles, and the pericapillary space is small and free from collagen and fibroblasts, because the basement membrane is in direct contact with that of the astrocytes [1135, 2961]. Pericytes may occasionally

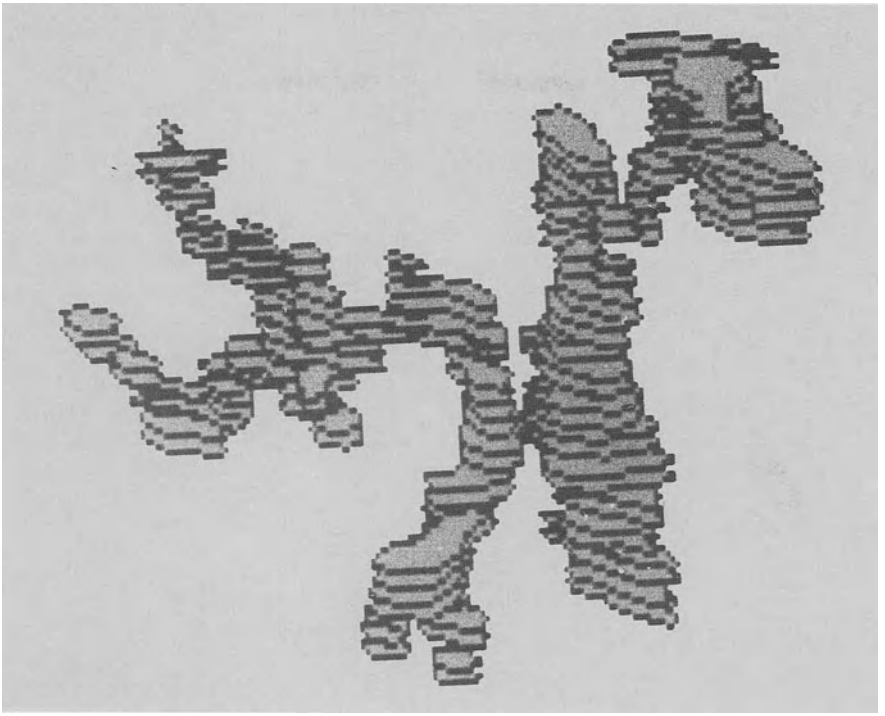


Fig.9.30. Glioblastoma: computer-assisted three-dimensional reconstruction of vessels with endothelial hyperplasia [2521]

be present [1689]. Tumor capillaries are completely abnormal: The lumen is wider, there are more endothelial cells with a greater number of junctions and more pinocytotic vesicles, and the basement membrane is thickened by collagen in the pericapillary space [2961]. There are different degrees of endothelial attenuation with fenestrations and opening of the junctions. Typical features of malignant gliomas are blood vessel thrombosis and endothelial proliferation.

Endothelial cells increase in number, feature mitoses, and modify the blood vessels, which become tortuous and glomeruloid. The study of the transition between the normal tissue, infiltration zone, and tumor has demonstrated that endothelial cells progressively increase in number and acquire immature features such as a paucity of organelles and a high nucleocytoplasmic ratio [3014]. Clusters of immature capillaries similar to the normal ones which appear during development [364] and immature buds with a slit lumen and single basement membrane [3013] form in the transition zone.

The endothelial proliferation has been considered, on one hand, as a source of new capillaries and, on the other, as a consequence of vessel thromboses [2744, 368]. A particular relationship seems to occur between endothelial proliferations and circumscribed necroses. It has been hypothesized that endothelial proliferations may represent a response to necrosis. On the other hand, circumscribed necroses may be due to the imbalance between the proliferative potential of the tumor and endothelial cells [1202, 1008]. Morphometric and three-dimensional reconstruction studies have demonstrated that glomeruloid formations represent an extreme degree of deformation of the cortical vascular tree due to endothelial proliferation (Fig.9.30). The vascular tree becomes inade-

quate to nourish the increasing number of neoplastic cells, hence the necrosis (Fig.9.31b) [2521]. The neoplastic invasion of the cortex induces the hyperplastic response of the endothelial cells. New, small blood vessels are formed by sproutings (Fig.9.31a) [1974] and only occasionally enrich the infiltrated zone with capillaries. Endothelial proliferation is thus not synonymous with angiogenesis, which does not precede but follows tumor infiltration. The endothelial cells within the tumor are also rich in Weibel–Palade bodies [1527], which are usually rare in normal endothelium. There is also a distinct but participation of α-sm-actin-positive pericytes to the process of endothelial hyperplasia (Fig.9.32a) [2521]. Proliferated endothelial cells are immunohistochemically positive for factor VIII/RAg, but only those lining the vessel lumen (Fig.9.32b) [3013]; however, by immunoelectron microscopy study it can be demonstrated that cells far from the lumen also contain Weibel–Palade bodies rich in gold granules (Fig.9.33) [1886].

The origin of circumscribed necroses with pseudo-palisades in glioblastoma also have been differently interpreted. It has been proposed, for example, that necrosis of the glial cells releases FGF, a potent mitogenic and angiogenic factor, which stimulates tumor cells and endothelial cells to proliferate, hence the pseudo-palisades and the blood vessel hyperplasia [2154].

The hypothesis that circumscribed necroses follow the endothelial proliferation and that this follows tumor invasion may be confirmed in the invaded cortex by the observation that if the infiltration proceeds from the white matter towards the cortical surface, the glomeruli will be found in the deep cortical layers (Fig.9.34); if, on the contrary, the infiltration descends from the subpial region towards the white matter, the glomeruli will be found in the superficial cortical layers [2521]. This sequence derives from the fact that endothelial hyperplasia affects the cortical vascular network, which is formed by the penetrating meningeal branches and their lateral branches [1060, 124].

All the investigations on angiogenesis refer to the hypothesis that all solid tumors are angiogenesis-dependent and that every increase in the tumor cell population has to be preceded by an increase in capillaries which converge on the tumor [795]. Originally, the experimental demonstration that the tumor could induce the formation of new capillaries despite the tumor cells being separated from the vascular bed [1000] led to the supposition that the tumor released a diffusible factor, which was later isolated. Further progress was due to the use of the corneal microchamber in rabbits, the chorion-allantoid membrane in the chick embryo, and in vitro cultures of endothelial cells. The studies were then extended to the enzymatic degradation of the basement membrane, to the locomotion of endothelial cells, and to their proliferation. The enzymatic degradation of basement membranes is accomplished by means of various proteinases. Endothelial cells produce a collagenase which degrades type I collagen and also the type IV collagen of basement membranes [936]. Substances derived from the retina may stimulate the degradation of type IV collagen, laminin, and fibronectin by endothelial cells. At the same time they stimulate endothelial cells in culture to release plasminogen activator, which converts plasminogen into plasmin, which in turns degrades laminin and fibronectin.

Various angiogenic factors are recognized nowadays [796]. First of all, there are the heparin-binding growth factors for endothelial cells, among which is FGF (fibroblastic growth factor), derived from the brain, ECGF (endothelial cell growth factor), derived from the eye, and an acid factor derived from the retina. The corresponding receptors have been found in endothelial cells. These factors are found in all tissues. In particular, for FGF, another autocrine stimulation has been proposed [2575]: The endothelial cells express FGF, and as they bear the corresponding receptor, they stimulate themselves to proliferate in an autocrine fashion. FGF has been demonstrated immunohistochemically in endothelial cells in the majority of cerebral tumors [2154], as well as its receptor in human endothelial cells [2011]. Antibodies against FGF inhibit in vitro the growth of endothelial cells [2429]. This could represent a good therapeutic "hook," but there are no data on cerebral tumors. An autocrine stimulation had already been proposed for PDGF-β and for its receptor, both expressed by endothelial cells [1113] (see Chap. 2).

Another factor isolated from a human adenocarcinoma cell line is angiogenin, which has sequence homologies with pancreatic ribonuclease. It is a potent angiogenic factor in the embryonal chorion-allantoid membrane of chick embryo, but its mechanism of action is unknown [772]. There are then the TGF (transforming growth factors), α and β, and a series of factors among which those of low molecular weight are mitogenic for the endothelium [765]; others isolated from fluids and from macrophages may stimulate the locomotion, but not the proliferation, of endothelial

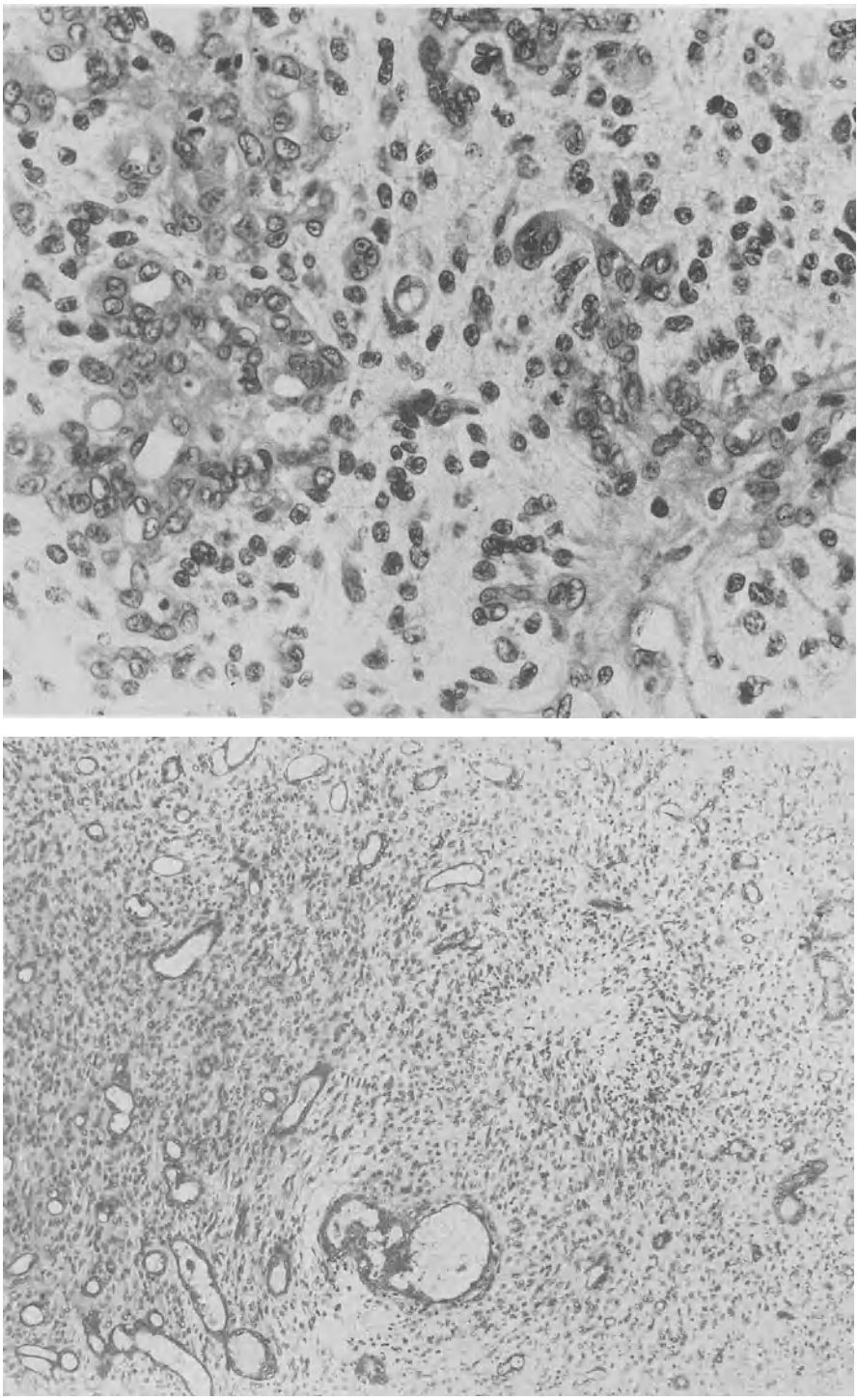


Fig.9.31a,b. Glioblastoma: **a** endothelial sprouts from small vessels in the invaded cerebral cortex, H&E, ×400; **b** circumscribed necroses are found among glomeruli, H&E, ×150

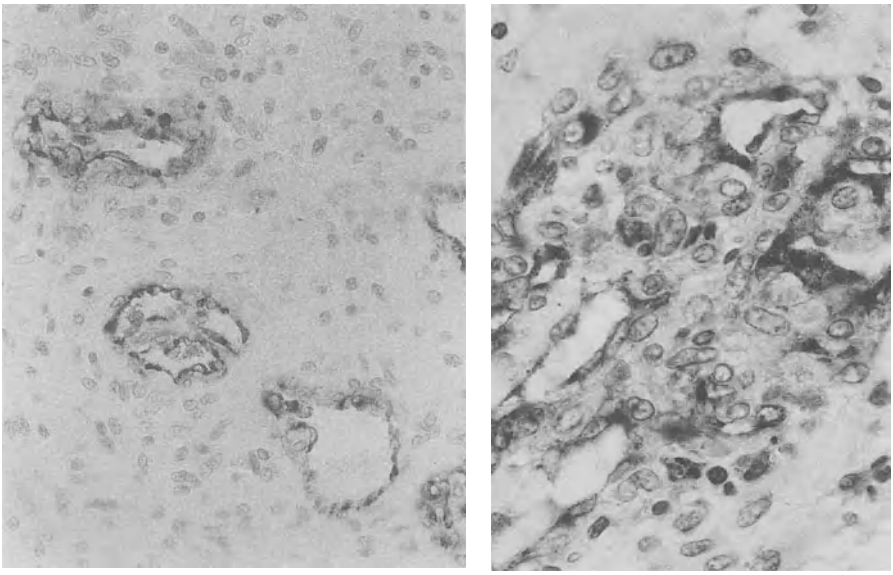


Fig.9.32a,b. Glioblastoma: **a** α-sm-actin-positive cells in hyperplastic endothelium, PAP-DAB, ×300; **b** factor VIII/RAg is positive only in cells lining the lumen, PAP-DAB, ×400

cells [3064]. Macrophages, prostaglandins PGE_1 and PGE_2, and a factor isolated from T lymphocytes may be angiogenic. The presence of a renin-angiotensin system in the CNS has been demonstrated and the components localized immunohistochemically [874], angiotensin II in rat embryonal neurons and renin both in neurons and glial cells [2479]. The small cerebral blood vessels contain receptors for angiotensin II [2709]. The renin-angiotensin system is able to induce angiogenesis [767] through a mechanism well-studied in the ischemic kidney [2157]. In glioblastoma, renin has been demonstrated immunohistochemically in tumor cells, especially around blood vessels, while it has not been found in astrocytoma cells and reactive astrocytes in gliosis [74].

Among the various factors recognized as modulating angiogenesis through a series of mechanisms and associations are heparin and copper [796].

Some angiogenic factors stimulate endothelial locomotion or proliferation or both (796). Indirect stimulation may occur through macrophages [121, 114] or through the release of endothelial mitogens contained in the extracellular matrix [2945]. The angiogenesis may, however, be regulated by physiological mechanisms which inhibit it. One of these is represented by the contact of the pericytes with endothelial cells [2091] or by the binding of cortisone derivatives with heparin fragments. Some observations in cerebral tumors have been made. If culture medium from human malignant gliomas is added to endothelial cells from human umbilical cord vein in culture, they cause endothelial proliferation [1377]. Similar results were obtained also with well differentiated gliomas [1144]. Using the chick chorion-allantoid membrane model, angiogenic activity has been caused by extracts of glioblastoma, meningioma, and neurinoma [1723]. From personal experience with this method, it is also possible to demonstrate angiogenic activity in carcinoma metastases.

9.2.2.10 Cellular Kinetics

As has been said in Chap. 7, there are various ways to study cell kinetics in gliomas which do not differ significantly in value and reliability. Generally, both the MI and the LI obtained with [^{3}H] thymidine, BrdU, or Ki-67 are lower and more uniform in anaplastic astrocytomas and higher and widely variable in glioblastomas. This means that

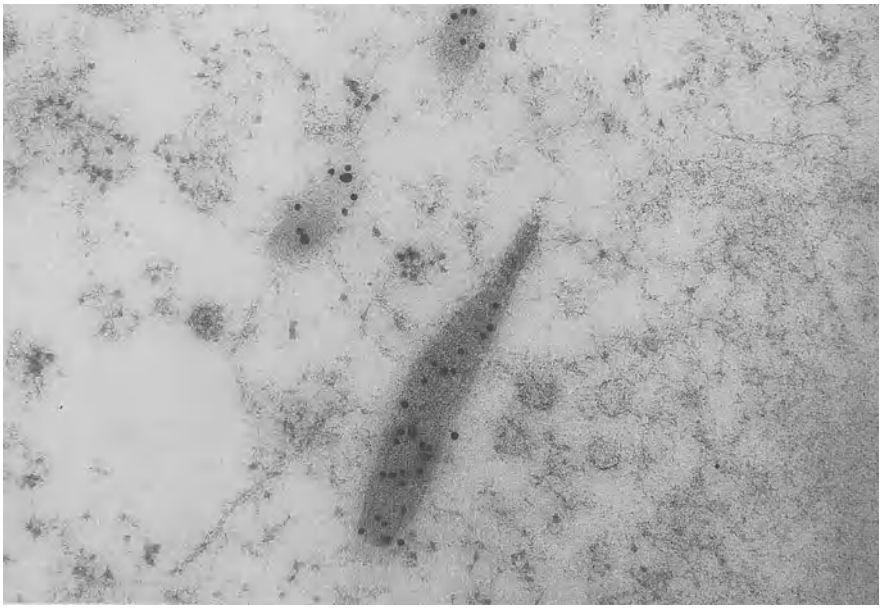


Fig.9.33. Glioblastoma: Weibel–Palade bodies in hyperplastic endothelial cells containing factor VIII/RAg, immunogold, ×40 000

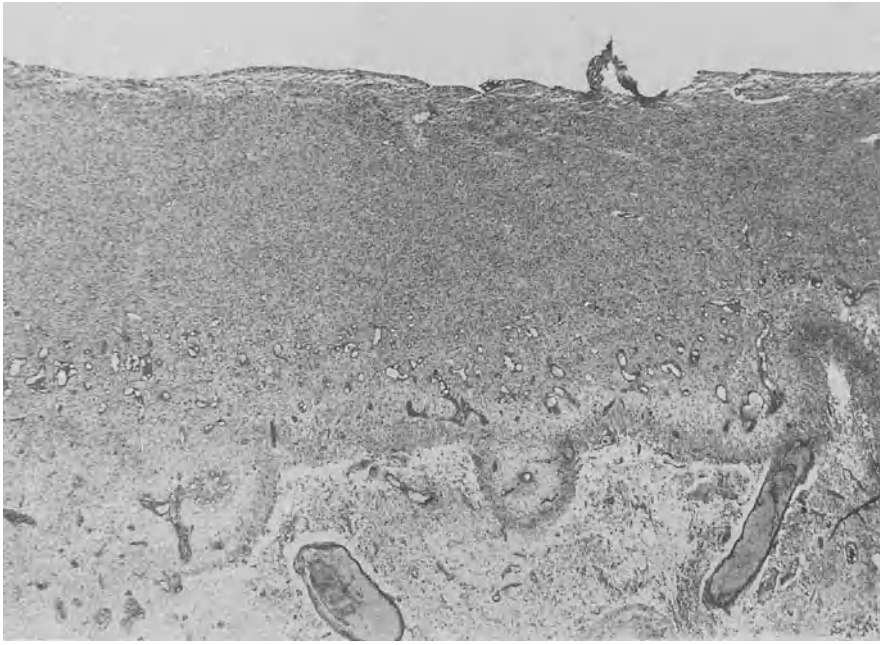


Fig.9.34. Glioblastoma: glomeruloid formations in the deep cortical layers, bordering central necrosis, H&E, ×50 [2484]

great morphological and proliferative heterogeneity in malignant gliomas exists and that the different areas of the tumor are not equivalent. For this reason, the principle of not using averages of several measurements but taking the highest labeling value as characteristic of the tumor is widely accepted [1937]. This is especially important in the examination of surgical or stereotactic biopsies, where the quantity of material available is very limited.

9.2.2.11 Metabolism

The level of ATP gives a measure of the metabolic efficacy of a tissue, and in malignant astrocytomas the mean ATP and total adenylate levels are higher than in normal tissue [1699, 1211]. Brain tumors utilize more glycolysis than respiration for the production of ATP [2984], continuing lactate production even when oxygen is present. ATP production through glycolysis is anaerobic, and allows growth independent of oxygen provided that a satisfactory supply of glucose is maintained: Tumors survive ischemia longer than normal tissue [1432, 2136]. As a consequence, the cerebral glucose uptake and consumption by a tumor may be up to three times normal [2690], as demonstrated by using deoxyglucose with PET [1260, 627, 2146, 2878]. Perhaps the reduction of the citric acid cycle and oxidative phosphorylation, due also to the lower number of mitochondria of tumor cells in comparison with normal [1647], accounts for this [2162].

In the glycolytic pathway, a decrease in hexokinase and phosphofructokinase activities in malignant gliomas has been demonstrated [1700, 1791], with normal pyruvate kinase activity and lactate production, due to the depressed citric acid cycle activity. Some enzymes of the glycolytic pathway occur in altered or in more primitive forms.

In the citric acid cycle, citrate synthetase and malate dehydrogenase activities are decreased in tumors with normal succinate dehydrogenase activity [2933, 1700]. Less acetyl-CoA is utilized, and pyruvate accumulates, increasing the level of lactate. Since NADH is not produced, oxidative phoshorylation is depressed. Its associated enzymes are in fact decreased [1647] and cytochrome oxidase activity appears to be inversely related to malignancy [35].

The pentose phosphate pathway, as an alternative pathway, is more active in gliomas, and the glucose-6-phosphate dehydrogenase activity is strongly increased [1700]. Through this pathway, not only is energy in the form of NADPH produced, but also pentose is provided for the synthesis of purines and pyrimidines [2156, 2933].

The synthesis of glycogen in brain tumors is practically absent. Very interesting are the changes in the enzymes of energy metabolism. For example, of the pyruvate kinase isoenzyme subunits, only the fetal type K is produced in glioblastoma [2850] and of the isoenzymes of hexokinase, only the type II [167]. Of the types H and M of lactate dehydrogenase (LDH), only the M subunit is produced in malignant gliomas. The level of isoenzyme LDH5, containing only the M subunit, is greatly increased [1040, 2848, 842].

ATPase and cAMP are inversely correlated with malignancy [1588, 2619]. Of the different cAMP dependent protein kinases, type III occurs in glioblastomas, similar to type II [817], which is activated by cAMP and cGMP. There is in tumors an increased response to cGMP and a decreased response to cAMP. Also, a relationship between malignancy and cAMP phosphodiesterase has been found [816].From the histoenzymologic point of view, different patterns have been described in gliomas, with various interpretations. Particularly interesting are the strong positive reactions for NADH and NADPH tetrazolium reductase in reactive-type cells and in endothelial cells of vascular proliferations [2488, 2006, 2485].

Acetyl-CoA is the key point in the cell metabolism, being involved in both catabolic and anabolic pathways. In normal nervous tissue, fatty acids are not utilized as a source of energy, and nothing is known about tumors in this regard. The synthesis of fatty acids begins with acetyl-CoA; the synthesis of sterols also begins with acetyl-CoA, and cholesterol is the major sterol in malignant gliomas [867]. The level of desmosterol, the immediate precursor of cholesterol, is elevated in malignant tumors [3007, 2129] and has been proposed as a marker of tumor activity [2129].

Among many other metabolic properties of gliomas, the increase of the arachidonic acid metabolite thromboxane B must be recalled [393], which is involved in BBB permeability. Other

compounds of interest include the polyamines such as putrescine, spermine, and spermidine, which seem to show higher levels in malignant gliomas [1059, 2948]. For further information, specialized review articles are available [1752].

9.2.2.12 Prognosis and Treatment

Glioblastomas have, in general, a worse prognosis than anaplastic astrocytoma [2970]. Even if the delimitation between the two oncotypes is sometimes uncertain, they have to be maintained as separate entities. It would not be correct, in the statistical evaluation of the effects of therapies, to put glioblastoma and anaplastic astrocytoma into one category of so called high grade gliomas. The median survival of adequately treated glioblastomas is 6–12 months with 8%–12% survivors at 2 years and 5% at 5 years [337, 2008, 1736, 3055].

In spite of this poor prognosis, individual histological parameters may have different predictive significance. Glioblastomas containing microcysts, necroses with pseudo-palisades instead of large necrotic areas, well-differentiated astrocytic cells, or large astrocytomatous areas are associated with longer survival times than those uniformely composed of small cells or cells with small average nuclear size [331]. A better prognosis has also been found to be associated with the presence of calcifications [2797], although an association has been subsequently denied [331]. The presence of giant cells is positively correlated with survival [333]. In general, the gigantocellular variant has, in fact, a better prognosis when compared with the classic tumor [1764]. The lymphoplasmacellular perivascular infiltrates do not seem to be important in glioblastomas in relation to prognosis [2502, 333, 331], while opposite results have been noted by gathering grades III and IV tumors into a single group [1818, 304, 2425]. The prognostic value of kinetic parameters, such as the LI with [^{3}H]thymidine, is controversial [1199, 258], and it also remains to be defined whether or not there are significant correlations with survival and the DNA "pattern" [819, 1938, 1142].

Age and neurological status are the most important prognostic factors: The percentage of survivors at 18 months is 64% for those under 40 years of age, 20% between 40 and 60, and 8% over 60 [414, 2685]. Above a certain age, doses of 30 Gy in 10 fractions lead to the same length of survival as standard doses [2023].

Studies carried out in the CT era demonstrate that in malignant gliomas extensive removals of more than 90% of the tumor are followed, under the same conditions of mortality, by a lower morbidity than incomplete resections [451, 744, 2922], especially when the preoperative neurological conditions were very good. Macroscopically, total removal is associated with longer survival [351, 52, 3055] than simple biopsy. As a consequence, a removal as total as possible should be performed in patients with good neurological conditions and with a reasonable life expectancy; in the opposite case, a simple biopsy should be done for diagnostic confirmation [2128]. However, the prognostic importance of total removal remains to be confirmed in randomized studies [2246A]. In recurrences of malignant gliomas after radiochemotherapy with a disease-free interval longer than the median of expected survival, an operation further prolongs an acceptable survival [52, 1068]. As a general rule, a reoperation must be taken into consideration whenever the recurrence is localized and accessible, independently of oncotype, provided that it is not too early.

External radiotherapy is presently the best postoperative treatment. The usual dose to the tumor is 60 Gy: Lower doses (50 Gy) are less effective [2970], but higher doses (70 Gy) are not more effective [414]. Above a certain age, doses of 30 Gy in 10 fractions lead to the same length of survival as standard doses [2023]. There is no general agreement on the amount of brain to be included in the target: tumor volume plus 2 cm [1162] or more [1052] outside the external border of enhancement seen on CT. With MRI, it has been demonstrated that tumor cells are present in T2-weighted images in which hyperintense areas are larger than the peritumoral hypointense areas seen with CT [1376]. However, irradiation of the whole brain did not prove to give better results than that of a more limited area [2613]. The likely explanation is that glioblastoma recurs locally before spreading to a distance. Usually, the irradiation is performed with 60 Gy to the volume of enhancement corresponding to the tumor plus 2–3 cm [1607], or a double volume irradiation is performed: 60 Gy to the volume of enhancement and 43–45 Gy to the remainder of the brain. The total dose is given in single daily fractions of 1.8–2.0 Gy. Minimal residual tumor on CT scan after surgery and radiotherapy is a positive prognostic factor [1972, 3074].

The major risk of radiotherapy is delayed radionecrosis. Its clinical incidence with little residual tumor after conventional radiotherapy is 3–5% [1887, 1772], but it increases in long-term survivors, going from 3% to 12.5% when survival is prolonged from 18 to 24 months [2686]. Factors of individual hypersensitivity, such as vascular diseases, systemic hypertension, diabetes, etc., play a predisposing role; however, the risk of delayed brain damage depends mainly on the number of radiation fractions and, therefore, on the fraction dose [1773]. Concentrated treatments with a few fractions of high dose expose the patient to a greater risk [2426] and must be avoided in those with a prognosis longer than 6 months.

Until now, attempts to modify the conventional treatment by increasing the number of daily treatments (hyperfractionation) have not given better results [273, 1573]. Re-irradiation at recurrence does not seem to be useful and increases the risk of brain damage (662). Preoperative radiotherapy, with some exceptions, does not prolong survival and increases morbidity because of vessel fragility at surgery.

New therapeutic modalities involving hypoxic cell radiosensitizers [624] and neutrons [1581] did not prove to be effective. Regarding hyperthermia, thiol-depleting agents, and a halogenate thymidine analogue, studies are still in progress [2801, 1095, 2435].

The tendency of malignant gliomas to recur locally [1162], with the development of multiple lesions in only 5%–9% of cases [441], and the high radioresistance both in vivo [273] and in vitro [2247] allow one to consider interstitial irradiation (brachytherapy) as a possible therapeutic measure. The best results have been obtained with doses of 50–120 Gy upon the recurrence of malignant gliomas after conventional treatment [1608]. Studies are in progress concerning the possibility of associating brachytherapy as a boost to external radiotherapy in the postoperative treatment of malignant gliomas [1374 , 180]. Little is known to-day about radiosurgery in malignant gliomas, but studies are in progress [1032].

Also, intraoperative photodynamic therapy has been tried in malignant gliomas, using hematoporphyrin or dihematoporphyrin ether as photosensitizers [2184, 2185, 1371, 3023], with no clear advantage in comparison with traditional therapies.

Among the many chemotherapeutic drugs tried [1487] the only ones which have been demonstrated to be useful in the postoperative treatment of malignant gliomas, and very modestly at that, are BCNU and procarbazine. In controlled studies carried out between 1970 and 1980 in the USA, the median survival after surgery, radiotherapy, and BCNU treatment varied between 45 and 54 weeks, with 18%–28% of patients alive at 18 months. BCNU administered intraarterially does not offer advantages in the postoperative treatment of glioblastomas [2607].

BCNU remains the most effective drug in the treatment of recurrences. Other drugs show some efficacy, such as CCNU, 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)1-nitrosurea (PCNU), 1-(4-amino-2-methyl-5-pyrimidimyl) methyl-3-(2-chloroethyl)3-nitrosurea (ACNU), procarbazine, dianhydrogalactichol, cisplatin, and azyridinylbenzoquinone (AZQ), lonidamine, but never equal to that of BCNU. Semustine (MeCCNU), hydroxyurea, teniposide (VM 26), bleomycin, dacarbazine (DTIC), 5-fluoruracil, and methotrexate are ineffective or toxic. No polychemotherapy has been superior to BCNU alone. Studies on intraarterial chemotherapy are in progress. The rationale is that a high drug concentration is achieved in the well-vascularized tumor, avoiding toxicity elsewhere [2739]. In order to facilitate the passage of hydrosoluble drugs through the BBB, the intracarotid injection of mannitol has been suggested [2014], but also criticized [786]. Also ineffective has been bone marrow transplantation coupled with high doses of BCNU, both for the initial treatment and recurrences [776].

Immunotherapy did not prove to give better results than conventional therapies [593].

Glioblastoma metastasizes extracranially to the lungs, lymph nodes, pleura, liver, etc., almost exclusively in patients who have undergone brain surgery. The occurrence of extracranial metastases in the absence of surgery is very rare; just over 10 cases have been reported [1610].

9.2.3 Gliomatosis Cerebri

The term "gliomatosis cerebri" was used to indicate a diffuse increase in glial cells found in large areas of the brain with a poor tendency to grow as a discrete tumor [2021]. These cases were assimilated to others previously described as "gliomatosis" [1128], diffuse glioma [1564], the blastomatous type of diffuse sclerosis [390], diffuse systematic blastomatous growth of the glial apparatus [2571], diffuse cerebral schwannosis [791], diffuse central lemmoblastosis [2952], "glioblastosis diffusa" [3002], etc. Recently, 10 new cases with a review of 48 others from the literature have been reported [83].

The diagnosis of the disease is not usually made clinically. There is a progressive cerebral syndrome with intracranial hypertension, even if cases with acute onset are not lacking. The duration of the illness is very variable and may be up to 20 years. Even from the radiological point of view, it is very difficult to recognize. By CT scanning, the lesion appears as iso- or hypodense, even after contrast enhancement. Sometimes the only finding on CT may be the swelling of parts of the brain. If necroses or hemorrhages appear, these can be seen but not attributed to the disease [83]. MRI is now the imaging modality of choice [2369A].

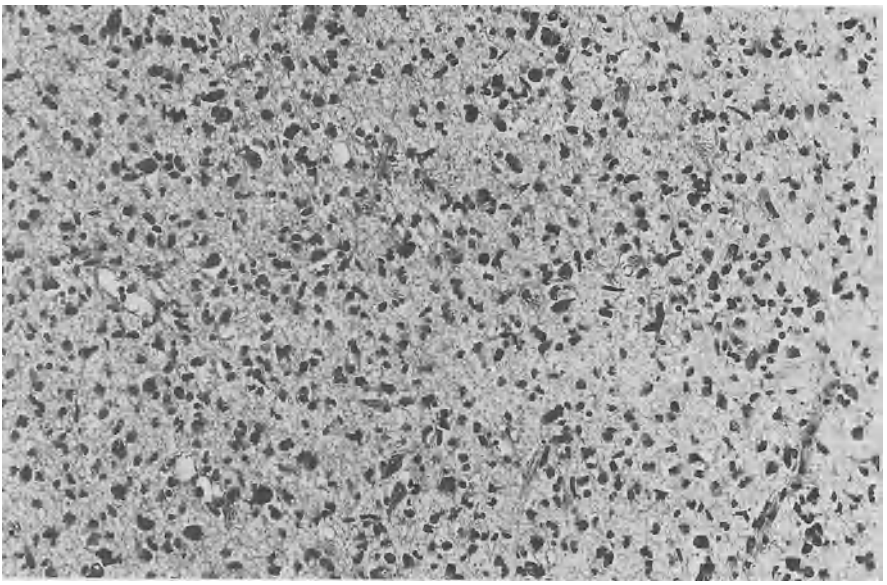


Fig.9.35. Gliomatosis cerebri: diffuse astrocytic proliferation, H&E, ×200

Macroscopically, the brain is slightly deformed but maintains its normal shape.

Histologically, there is a diffuse proliferation of glial cells in the white matter, with a prevalent "spongioblastic" elongated character and a possibly polymorphous aspect (Fig.9.35). Mixed areas and also foci of undifferentiation up to a glioblastomatous appearance may be present. The cells are variably GFAP-positive.

Apart from the hemispheres, the brain stem, cerebellum, and spinal cord may also be involved. A case in which the main localization was spinal has been reported; besides astrocytes, there was a diffuse microglial component [2025] which is difficult to interpret unless a neuroectodermal origin for microglia is accepted. This remains, however, a widely discussed topic.

The differential diagnosis includes multicentric and mixed gliomas.

9.2.4 Xanthoastrocytoma

This is a neoplasm affecting almost exclusively infants and adolescents with a peak incidence in patients between 10 and 20 years old [1394, 1395, 1521, 2430, 1743, 2753, 3012, 969, 1739, 2123, 2138, 991].

The tumor is located supratentorially, mostly in the temporal lobe. Infratentorial and extraparenchymal extensions are exceptional [2138], as is infiltration of the brain stem [2753].

9.2.4.1 Macroscopic Appearance

The tumor is superficially located with involvement of the leptomeninges and sparing of the dura, even if there is erosion of the skull bone [1395, 1743]. A cystic component

containing xanthochromic fluid may be present, and the tumor can be confined to a yellowish mural nodule. Rarely, necrosis is present [1395, 1743].

9.2.4.2 Microscopic Appearance

The neoplasm extends into the leptomeninges and invades the cortex both directly and along the Virchow–Robin spaces. It features a polymorphous proliferation with a moderate cellular density and a mostly fascicular pattern of growth (Fig.9.36). The stroma is formed by an abundant reticulin network which surrounds single elements or small groups of cells. There is no particular reticulin thickening around the blood vessels, which are not significantly increased in number and do not show endothelial proliferation.

The cell composition is polymorphous. Beside fusiform cells with oval nuclei, there are large, often giant, roundish or polygonal ones with microvacuolar (xanthomatous) cytoplasm with a thin peripheral eosinophilic rim which may be GFAP-positive (Fig.9.37). Some cells contain PAS-positive cytoplasmic globules while others are large with giant, sometimes multiple and bizarre nuclei. There are no necrotic areas, and mitoses are rare or absent.

Perivascular lymphoplasmacellular infiltrates are constantly present, with the exceptional formation of lymphoid follicles [1395]. Rarely, mast cells are also seen [2138].

GFAP is variably present [581, 969, 1395, 1521, 1743, 2123, 2138, 2430, 2753, 3012]. It is often absent in fusiform cells including those that apparently aid the infiltration of the neoplasm along the Virchow–Robin spaces. The majority of cells are strongly vimentin positive. The abundance of reticulin is due to the involvement of the leptomeninges and to the presence of basement membranes around subpial astrocytes, seen under the electron microscope, produced by the astrocytes themselves and not by the pial cells [2269, 2187]. It is known that the capacity of nervous tissue to synthesize collagen begins during embryogenesis and that it is at times maintained by glial cells in adult life [472].

α_1-Antichymotrypsin may be present in the cytoplasm of some reactive histiocytic cells, likely of subarachnoid origin [1743, 1739]. It may be coexpressed with GFAP or vimentin in the same cell, possibly indicating that glial cells acquired phagocytic activity. Ultrastructural investigations [1395, 1521, 1743, 2138, 3012] have demonstrated that besides masses of 8–10 nm filaments, lipopigment granules and microtubules occur in the cytoplasm of tumor cells.

The nosographic problem of this tumor is essentially that of its relationship with leptomeningeal fibroxanthoma [1393]. GFAP expression may, in fact, be limited to a few cells and may be absent in the meningeal neoplasm [2148]. It could also be the result of a process of phagocytosis or endocytosis. According to some authors, the tumor is considered a fibroxanthoma of the meninges [2148], in agreement with the original interpretation [1393]. Two cases have been reported with prominent vascularity and desmoplastic changes, and the existence of an angiomatous variant has been suggested [2762].

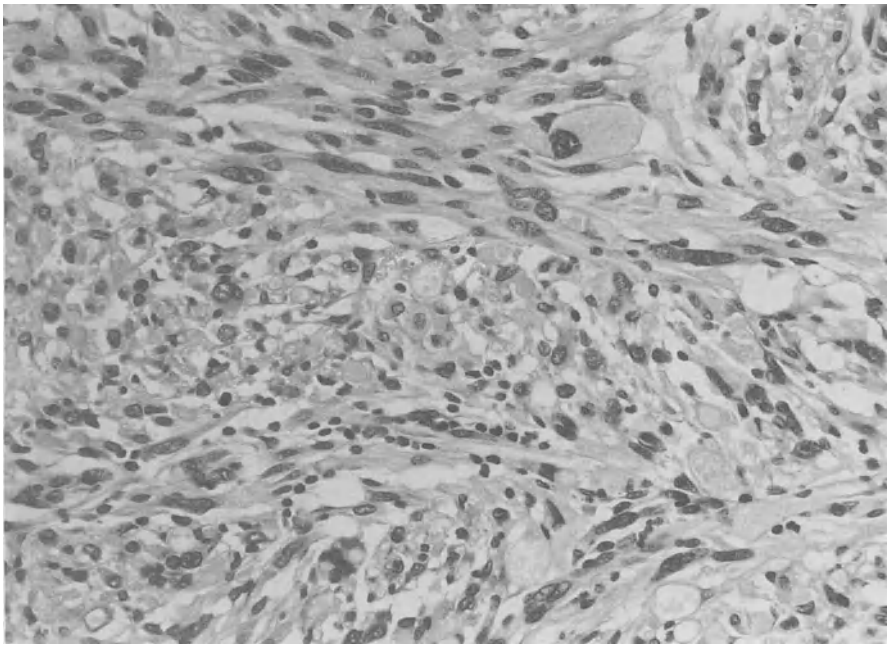


Fig.9.36. Xanthoastrocytoma: spindle cells admixed with xanthomatous cells, H&E, ×400 (Courtesy of Dr. F. Zorzi, University of Brescia)

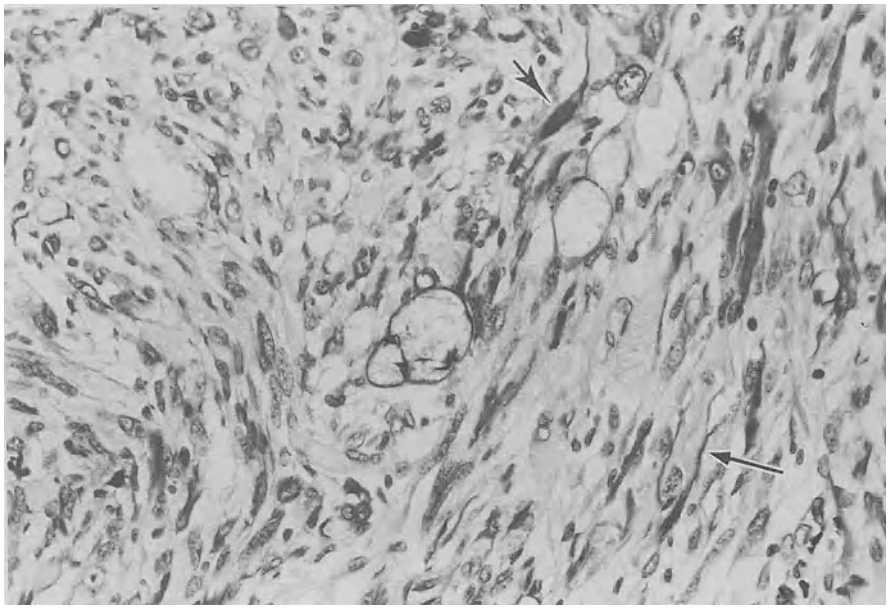


Fig.9.37. Xanthoastrocytoma: processes and peripheral cytoplasmic rims are GFAP-positive, PAP-DAB, ×400 (Courtesy of Dr. F. Zorzi, University of Brescia)

9.2.4.3 Prognosis

The tumor has a relatively good prognosis [1395, 1521, 2753, 969, 2123, 2138], with long survival periods (up to 25 years), although cases of rapidly fatal evolution have been reported [3012, 2138].

The superficial location allows an easy surgical approach. Recurrences have been described in some cases [1395, 1521, 2753, 3012, 969] with morphological modifications towards malignancy, such as the appearance of necroses, thus justifying the name of malignant glioma or glioblastoma.

The differential diagnosis must include fibrohistiocytomas (xanthomas) of the meninges or brain [1393, 1557, 32, 1343, 2648] and atypical meningiomas or meningeal sarcomas [1521, 1743, 2753]. GFAP-positivity may be helpful in the distinction.

9.2.5 Subependymal Giant Cell Astrocytoma (Tuberous Sclerosis)

The subependymal region is one of the sites at which the hamartomatous lesions of tuberous sclerosis may become manifest. The others include the kidney, lung, heart, etc. Apart from the cerebral cortex tubers, nodular, smooth, pinkish, "candle guttering" masses arise from the surface of the lateral ventricles (Fig.9.38), especially in the frontal horns. They can grow to a large size and obstruct the foramina of Monro, are sometimes calcified, and can also appear in subjects in whom tuberous sclerosis is not suspected. It must be stressed, however, that in the Mayo Clinic series of the 345 patients with tuberous sclerosis complex, 20 were identified as having subependymal giant cell astrocytoma. No example of this tumor without features of tuberous sclerosis was found [2618A]. Maybe this is due to the investigations being carried out in pre-MRI era. Usually, individuals under the age of 20 years are affected. About 20 newborns affected by tuberous sclerosis have been described [2098], and in three of these, subependymal tumors were present.

The tumor is composed of giant astrocytes with eosinophilic cytoplasm, sometimes elongated in shape, gathered in bundles with clearly evident processes (Fig.9.39). Nuclear polymorphism is marked, but mitoses are rather rare. The differential diagnosis includes gemistocytic astrocytoma, which is usually situated in the white matter and affects older subjects. The absence of features of malignancy, such as circumscribed necroses and marked mitotic activity, distinguishes this tumor from glioblastoma.

In the older literature, mention is made of the possibility that at least part of these cells with ganglionic appearance are neuronal in origin [940]. In two cases, in fact, it has been observed that the large cells were GFAP-negative but neuronal-specific enolase (NSE)-positive [2722]. In other reports, the GFAP-positivity was limited to the peripheral part of the cytoplasm and absent in the processes [682], present only in a certain percentage of cells [2923], or even completely absent [1999]. In a series of 22 cases, it was found that GFAP is constantly present in a variable number of cells in tumors not associated with the tuberous sclerosis complex. In tuberous sclerosis-associated tumors, on the contrary, GFAP-positive cells are scarce or absent. Positivity for the 68-kDa NF subunit has been observed in 6 and for NSE in 13 out of 18 cases [255]. Because there do not seem to be any doubts about the glial nature of the tumor, it can be concluded

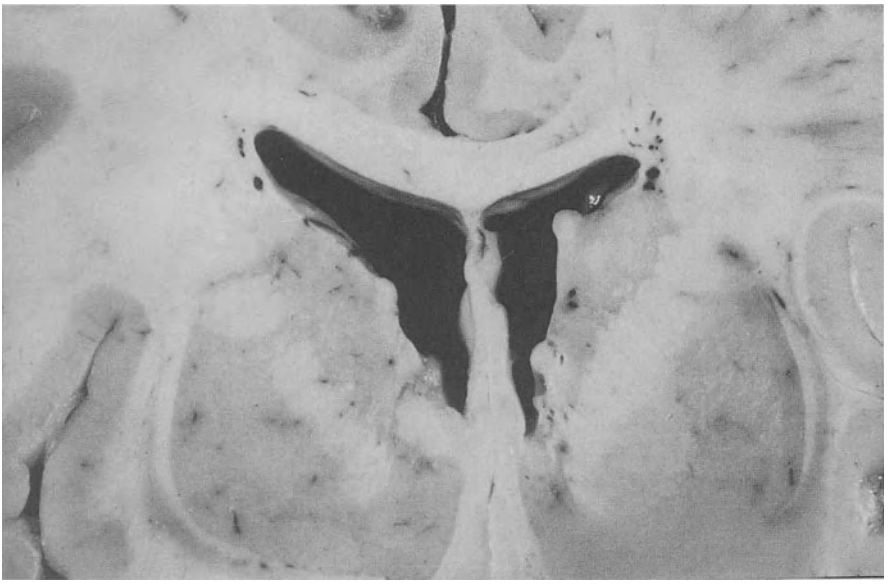


Fig.9.38. Tuberous sclerosis: "candle guttering" masses on the ventricular wall

that the GFAP-negative cells are incapable of producing such proteins. They could be dysgenetic cells whose dysplastic nature is responsible for the positivity for neurofilaments. There is, therefore, a bidirectional differentiation which never completely reaches full neuronal expression. Even in a case of a subependymal tumor in a premature infant, tumor cells were either positive or negative for GFAP and positive for neurofilaments, in line with a dysplastic origin [440].

The significance of the positivity for NSE is very doubtful. This marker may be positive in frankly glial cells [2939].

Dense core vesicles, similar to those found in ganglioneuroma and ganglioglioma [2339, 2399], even in the glial component [2399], have been found by electron microscopy [2640]. In only one case were eosinophilic neurosecretory granules seen [1999].

Rosenthal's fibers are present [2529, 2640, 2420].

The necessity of surgical removal is debated [851]; however, it leads to long-term survival without recurrence.

9.2.6 Astroblastoma

This is an extremely controversial tumor, accepted by some as an entity and denied by others. It has been described in the cerebral hemispheres and in the paraventricular region in the first decades of life. The tumor "ought" to be characterized by a perivascular astrocytic arrangement with convergence of broad cellular processes on the blood vessels on which they terminate (Fig.9.40). In reality, this feature is found both in astrocytomas and glioblastomas. In fact, in the first description of this oncotype two forms, one

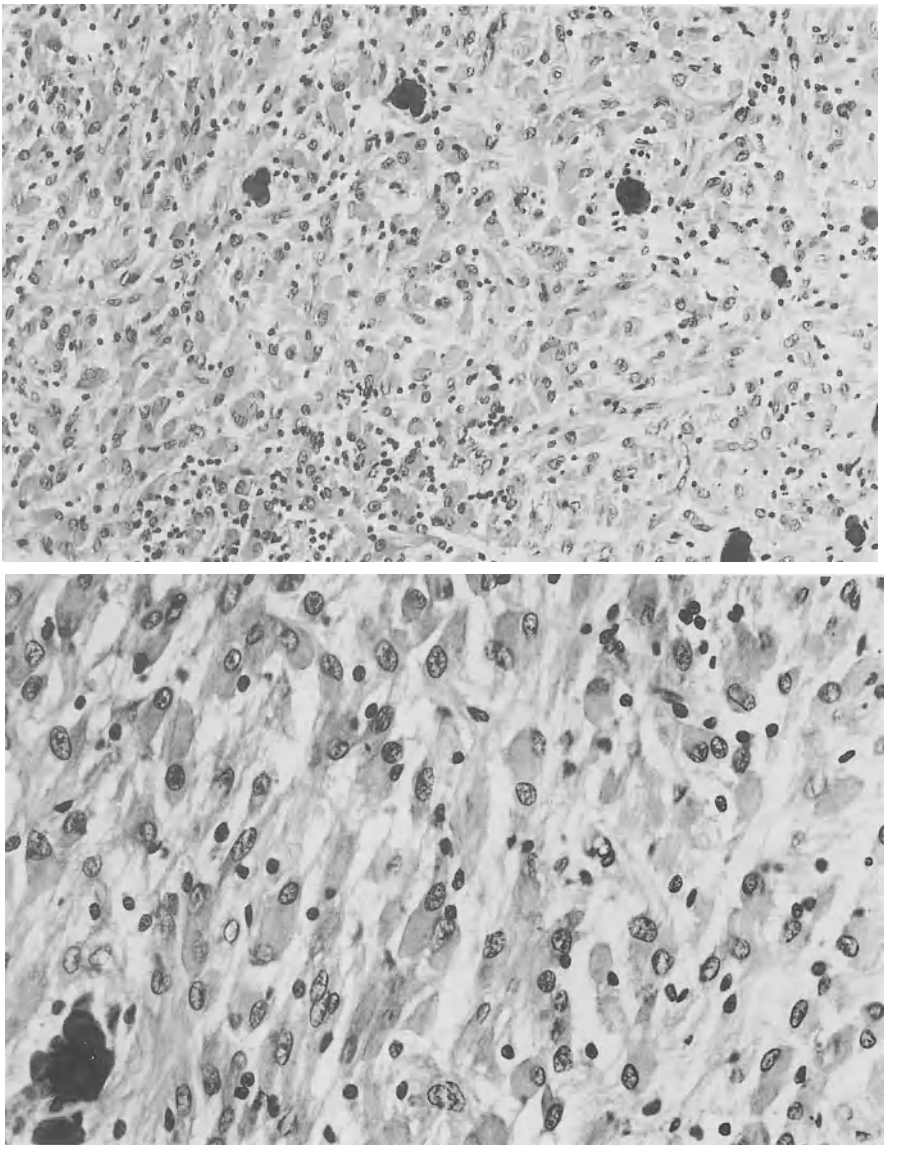


Fig.9.39a,b. Subependymal giant cell astrocytoma: spindle cells and calcifications, H&E, **a** ×200, **b** ×400

well differentiated and one clearly malignant, were described [109]. Recognized as an oncotype per se [106], midway between protoplasmatic astrocytoma and glioblastoma, it has subsequently been considered as a stage in the process of dedifferentiation [1405], as a subgroup of astrocytomas characterized by large cells producing glial fibers [3134], and lastly as an oncotype per se again, even if rare [2420]. There are not many recent descriptions [712, 2923, 1517, 1228, 1156, 2420].

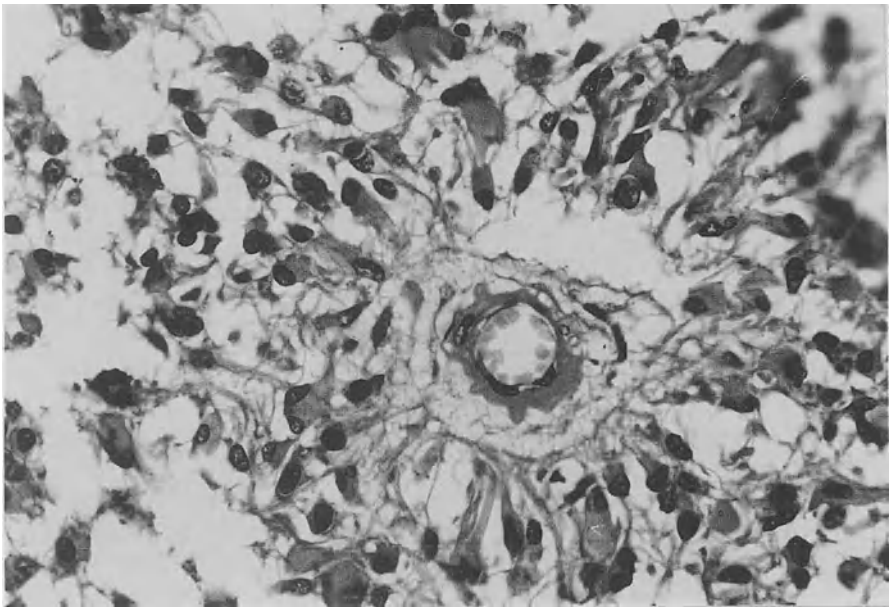


Fig.9.40. Astroblastoma: tumor cells with processes converging on a vessel, H&E, ×300.

Macroscopically, the tumor is well circumscribed, gray-pink, and sometimes cystic or with central necrosis.

Microscopically, its main feature are perivascular pseudorosettes with cells giving off processes which terminate with their end feet on blood vessels. The processes on the vessels are not the only ones, because others, more or less developed, may be seen. The intervascular cells show the same features. Nuclei may be polymorphous and mitoses present. Sometimes the blood vessels, with thickened and hyalinized walls, contribute to the architecture of the tumor and show only modest and inconstant endothelial hyperplasia. There is often a diffuse papillary appearance.

GFAP staining may be positive but with great variability, especially in the processes reaching the blood vessels.

A benign subtype with few mitoses and no endothelial proliferations and a malignant type with many mitoses and endothelial proliferations have been distinguished. Areas of necrosis and intermediate forms could be present in both types [252]. The differential diagnosis includes especially ependymoma. It is not the expression of GFAP which helps in this respect, because this may be expressed in radial crowns of ependymoma, more so than in the pseudorosettes of astroblastoma, but rather the perivascular processes with end feet which are characteristic of astroblastoma.

Only a few electron microscopy reports are available [1517, 1228, 1156]. The cells may resemble astrocytes, with various degrees of differentiation and numerous filaments. Rosenthal's fibers may be found. In two cases, characteristics intermediate between those of astrocytes (such as the production of glial fibers) and of ependymocytes (such as the development of microvilli on the free surface of the cells), the presence of

intercellular junctions, occasional cilia, and interdigitations on the lateral border of the tumor cells, have been described [2400]. These characteristics bring the cells of astroblastoma close to the tanycytes and support the hypothesis that astroblastoma derives from the proliferation of tanycytes [2420] or ependymal astrocytes.

These data indicate, on the one hand, the origin of the tumor, consistent with its occasional paraventricular location, but on the other, they render its nosological limits less distinct. It must be said that electron microscopy has contributed more than immunohistochemistry to the nosographic definition of the tumor.

The biological behavior of astroblastoma seems to be correlated with its histological aspect. Cases with histological features of a well-differentiated glioma have a more favorable prognosis than anaplastic tumors, although the latter may have long survival periods [252].

9.3 Astrocytic Tumors of the Midline

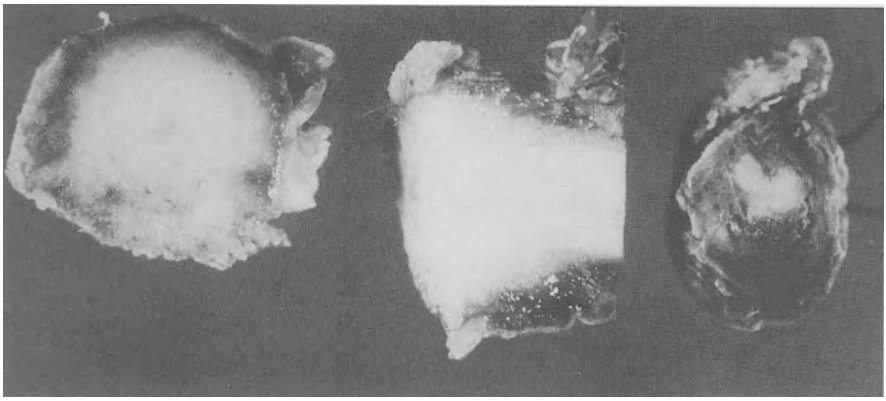
This is a controversial chapter, both from the point of view of the histological classification and of the general nosology. If site (midline) and cellular features (elongated cells resembling the spongioblasts of cytogenesis) have allowed some authors [3134] to gather these tumors in the spongioblastoma group, it is also true that the majority, but not all, of these tumors are pilocytic astrocytomas [709].

When Bailey and Cushing (1926) [112] replaced the term spongioblastoma by glioblastoma, the former remained to indicate a group of benign tumors characterized by a typical histological appearance and by a location in the optic nerve, chiasm, and hypothalamus [2380, 1189], which were then included in the group of piloid astrocytomas [709]. The studies supporting the definition of spongioblastomas as typical tumors of the dorsolateral prechordal leaflet have already been recounted. They are located in the dorsal and basal part of the neural tube: the spinal cord, medulla, pons, quadrigeminal plate, cerebellum, thalamus, hypothalamus, chiasm, and optic nerve.

9.3.1 Astrocytoma of the Optic Nerve

Astrocytoma of the optic nerve is typically a tumor of infancy, with an average age at diagnosis of 8 years [641] or even less, 3 and 1.5 years [263], sometimes occurring in cases of von Recklinghausen's disease. The tumor grows within the optic nerve sheath, thereby causing a fusiform dilatation of the nerve (Fig.9.41a). This is easily visible on transverse section where the nerve seems hypertrophic with evident septa (Fig.9.41b).

The histological appearance is characterized by bundles of elongated cells producing fibers and oriented along the major axis of the nerve. The bundles are separated by the septa of the nerve (Fig.9.41b), in which small and medium caliber blood vessels are found. The nuclei are also elongated and moderately polymorphous. There may be abundant Rosenthal's fibers. There is another histological aspect, characterized by a low cell density, loss of the bipolar appearance of the cells, the formation of microcysts, and the widespread presence of mucoid material.



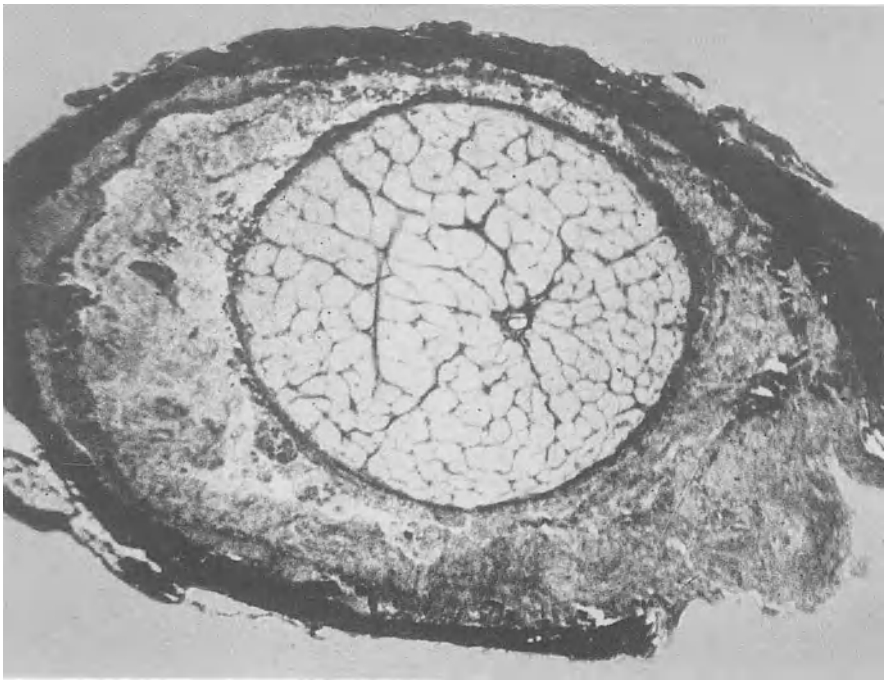


Fig.9.41a,b. Optic glioma: **a** the nerve seems hypertrophied; **b** fiber bundles are separated by the nerve septa, H&E

Outside the tumor, there is usually a strong fibroblastic meningeal response which mingles with pilocytic tumor cells (Fig.9.42). A strong fibroblastic response may also be found in the septa. The tumor is benign and is associated with long survival [263, 2823] if it does not involve the optic chiasm.

After apparently total removal, local recurrence is infrequent [47], and 85% of patients have a mean survival of 17 years [2410]. The merit of postoperative radiotherapy is therefore hot debated, but it is usually carried out in cases of incomplete resection

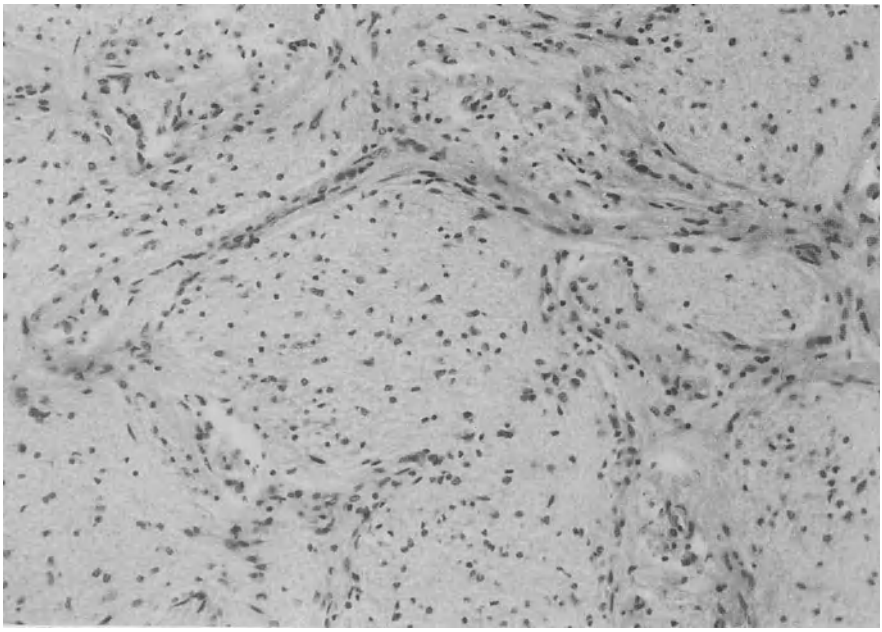


Fig.9.42. Optic glioma, pilocytic aspect, H&E, ×200

[3009, 47, 789, 1497]. It has also to be taken into account that in the adult there is a rare, anaplastic variety with a clearly worse prognosis [1215, 1061] which can come to resemble the picture of glioblastoma [1816]. Up to now, about 30 cases have been described [2808]. Cases with a malignant course have recently been reported also in infancy [3053, 1334]. When the tumor occurs with von Recklinghausen's disease, it is commonly bilateral and has a worse prognosis.

9.3.2 Astrocytoma of the Chiasm

As compared with the optic nerve form, astrocytoma of the chiasm affects older children, aged 6–14 years [641, 263]. The tumor may extend to the optic nerve or the optic tract, and it may shift or invade the third ventricle and infiltrate the hypothalamus. It may be cystic or hemorrhagic.

Histologically, it is similar to the optic nerve form but for the presence of septa. Rosenthal's fibers may be abundant. There may be endothelial hyperplasia in the small blood vessels.

Even if the anaplastic variety is rare [3053], according to some the prognosis is clearly worse than in the optic nerve counterpart, and only 50% of patients are alive 15 years after operation [263]. It seems that the risk of dying is higher in the first decade after diagnosis [2410, 1247]. The risk of spinal metastasis is practically only theoretical [1472A].

The standard therapy is irradiation, even though a full radiobiological rationale is lacking except for those tumors showing anaplastic features. A stabilization of the disease can be obtained [2823, 3072, 1497], but not without deleterious long-term sequelae. Surgery is of limited help, but recently a radical subtotal resection of exophytic growths has been proposed [3063].

9.3.3 Brain Stem Astrocytomas

Brain stem astrocytomas occur preferentially in children: 59% of patients are below 20 years of age [1758]. The average age for the infantile form is around 7 years [2854, 26]. The most frequent location is in the pons, followed by the medulla oblongata and mesencephalon. Sometimes the tumor does not form a mass but grows diffusely, giving the anatomical structure a "hypertrophic" appearance (Fig.9.43); however, it does not usually remain confined to the anatomical structures, extending into the cisterns and through the cerebellar peduncles into the cerebellum (Fig.9.44) and the fourth ventricle, or it forms small masses on the surface. It shifts surrounding structures and may even encase the basilar artery. The tumor has a hard consistency and is whitish, but hemorrhage and necroses may be present.

Histologically, most tumors are of the fibrillary type, but the general aspect is often modified by the influence of compact, preexistent structures. In particular, the growth along the long fiber tracts gives the cells an elongated shape. The frankly pilocytic variant accounts for 10%–15% of brain stem tumors [343].

The tumor very often undergoes malignant transformation, with the appearance of necroses, endothelial proliferation, and invasiveness, and takes the aspect of an anaplastic astrocytoma or even of a glioblastoma.

The rapid invasiveness of the tumor is due to its malignant transformation, but the tumor remains localized and never reaches the cerebral hemispheres [1758]. Contradictory observations have instead been made on its diffusion into the subarachnoid spaces [2035], which could be very important from the therapeutic standpoint.

An investigation by means of multivariate analysis of the correlation between histological features and survival [26] has demonstrated that the presence of mitoses is a clearly unfavorable prognostic sign, while that of calcifications or of Rosenthal's fibers is favorable.

The tumors which are an expression of neurofibromatosis usually carry a more favorable prognosis [1900].

It is clear that these tumors cannot be surgically removed. Operation is generally limited to the removal of the exophytic parts of the neoplasia or to biopsy. It is very important to take into account the marked discrepancy which may exist between biopsy and autopsy diagnosis, the latter revealing a higher proportion of malignant tumors [2854]. This may be due to the poor sampling of the tissue in biopsies and possibly also to the malignant transformation which occurs in the interval between biopsy and death.

The elective therapy is irradiation. Without it, the 1-year survival is only 25%, while with irradiation it is 45% [2936]. In general, the reported survival is poor [26, 1308];

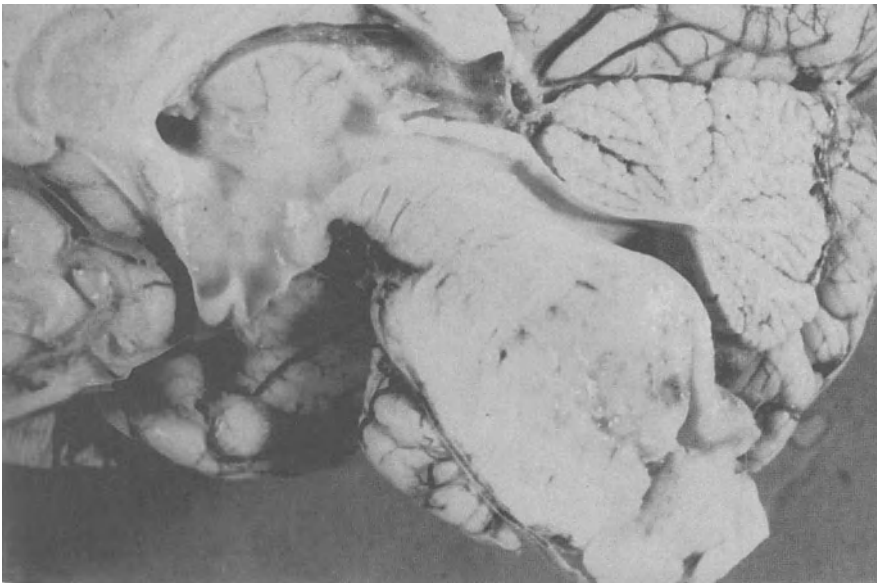


Fig.9.43. Glioma of the pons

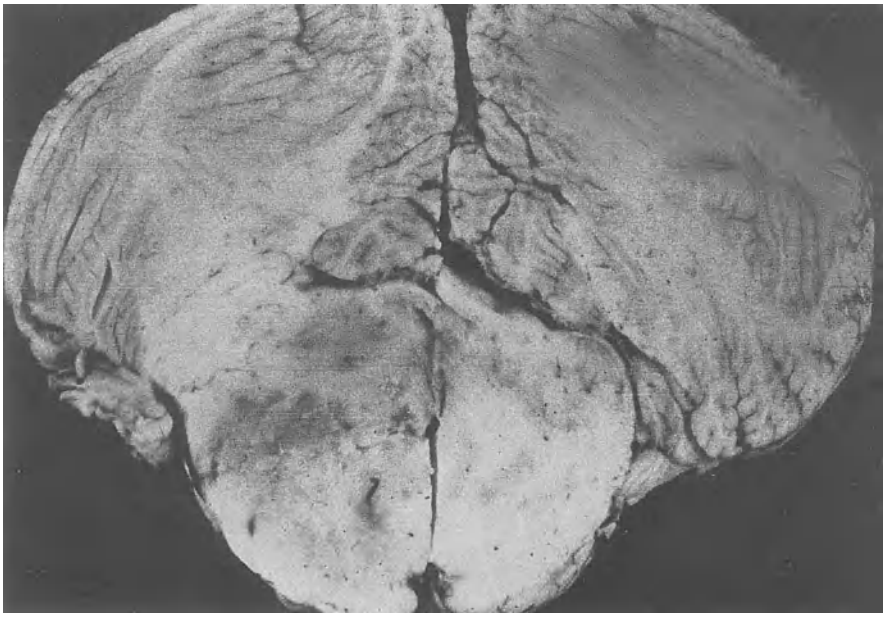


Fig.9.44. Glioma of the pons extending into the cerebellar peduncle

however, recently a 5-year survival rate of 59% was observed after hyperfractionated radiotherapy [1660].

The problem of establishing a prognosis is in relation to the debated question of the usefulness of a biopsy. In this regard, it has to be noted that, in general, patients with a biopsy-proven malignant tumor survive no more than 16 months, whereas those with a benign tumor have an actuarial survival time of 5 years [1671].

Like most gliomas, these tumors are usually markedly heterogeneous, so that the biopsy has maximum reliability only when glioblastoma is detected [720]. For this reason, some authors have questioned the usefulness of a biopsy, especially considering that statistical correlative studies have demonstrated that some clinical signs and CT findings, for example, heterogeneous density, allow one to establish malignancy and predict survival in relation to surgical and radiation therapy [2752, 1567]. A small group of tumors (16 out of 144) characterized by a dorsal exophytic growth into the fourth ventricle, with a benign histological appearance and a good prognosis and a median survival of 7 years, has been identified [1165].

9.3.4 Other Midline Astrocytomas

Other midline astrocytomas are, on the whole, tumors arising from the walls of the third ventricle, hypothalamus, etc. The histological features are similar to those already described. They are usually benign and most common in infants. Rarely, they may undergo malignant transformation [2035]. A case of hypothalamic astrocytoma with subarachnoid diffusion has been described [2055A]. For therapy, see Sect. 9.3.2.

Astrocytomas may arise in the neurohypophysis. They are very rare and of pilocytic aspect. Once they have reached a certain size, their starting point is no longer recognizable. They are very easily confused with astrocytomas of the third ventricle.

9.3.5 Cerebellar Astrocytoma

9.3.5.1 Nosographic Considerations

The definition of this oncotype has been debated for a long time. That the cerebellum is a frequent location of astrocytoma was known to Bailey and Cushing [112], but only later did Cushing [540] recognize the cerebellar astrocytoma as a benign tumor of the midline with a high frequency in the juvenile age group. Bergstrand [172] at first considered it an astrocytoma and, given the resemblance of its cell elements to embryonal glia, proposed the term "embryonal gliocytoma." Later, thought to originate from a congenital malformation, it was denominated "glioneuroblastoma" [173]. In the nomenclature of Elvidge [709] the tumor was placed in the piloid variant of astrocytoma, and in that of Bucy and Gustafson [316] it was considered as an astrocytoma, with its fibrillary and protoplasmic variants.

Zülch [3131] regarded the tumor as belonging to the spongioblastoma group on the basis of the above considerations, and so did Henschen [1109]. Ringertz and Norden-

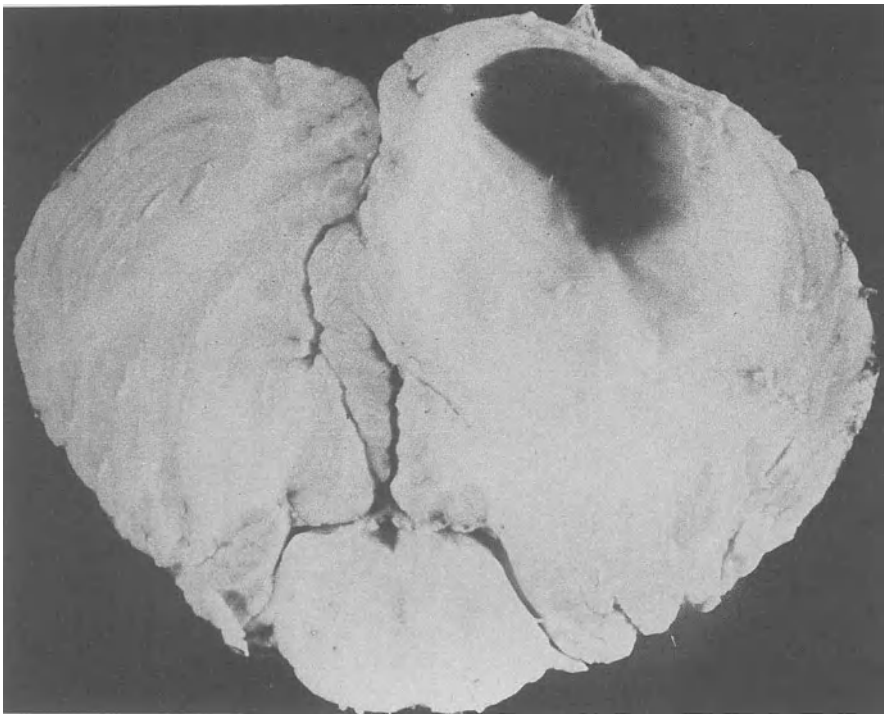


Fig.9.45. Cerebellar astrocytoma

stam [2327] also regarded the cerebellar astrocytoma as a polar spongioblastoma; however, 6 cases from their collection showed structures indistinguishable from those of cerebral astrocytoma. On the other hand, according to Ringertz [2326], this tumor type could occur in 11% of hemispheric cerebral astrocytomas. Russell and Rubinstein [2415–2419] considered this tumor to be partly a pilocytic astrocytoma of the "juvenile" type and partly a diffuse astrocytoma.

9.3.5.2 Frequency, Age

It is a frequent tumor, representing 4.7% [574], 6.4% [2486], or 10.1% [2327] of all gliomas. In the present series, it represents 3.2% of all intracranial tumors. In the posterior fossa, it is almost as frequent as medulloblastoma [509, 2486].

It affects adolescents: about 60% are found in subjects less than 16 years old [2486]. The peak of the distribution curve for age is between 5 and 10 years according to Zülch [3134], and between 11 and 20 years according to personal experience. However, cases are also known in the sixth, seventh, and eighth decades of life [952, 1241, 1242, 1402].

9.3.5.3 Macroscopic Appearance

The tumor has a grayish-yellow color, is soft in consistency, and is often cystic (Fig.9.45). Sometimes it forms a large cystic cavity with a mural nodule. It can be lo-

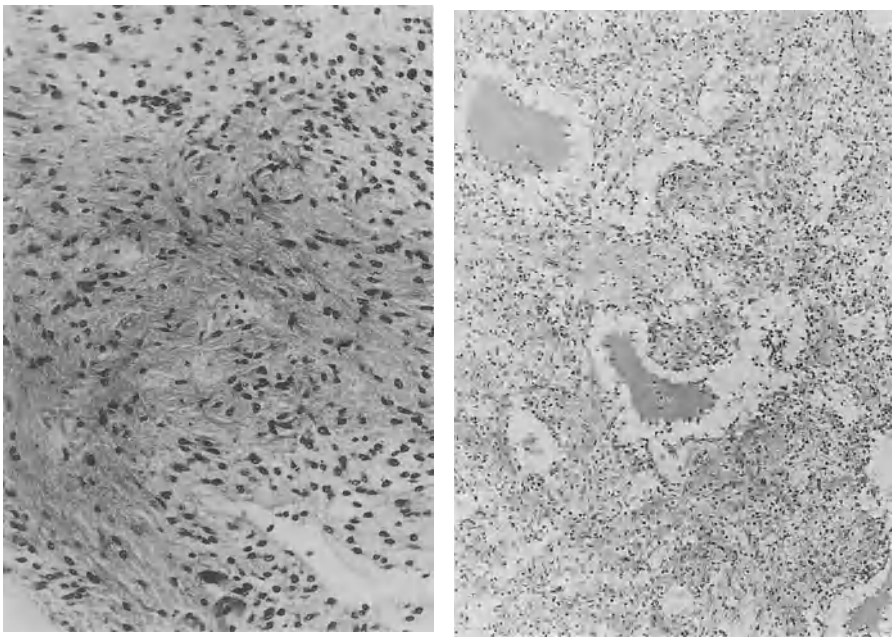


Fig.9.46a,b. Cerebellar astrocytoma: **a** pilocytic aspect of adult type, H&E, ×300; **b** pilocytic aspect of juvenile type and microcyst formation, H&E, ×150

cated both in the cerebellar vermis and, more often, in the hemispheres, where cyst formation is more frequent [952]. The tumor may invade the fourth ventricle and extend towards the quadrigeminal plate, the cervical spinal cord, or the cerebellopontine angle.

9.3.5.4 Microscopic Appearance

The cellular density is medium in nondegenerated areas. The cells are elongated, mono- or bipolar, with roundish or oval, clear nuclei, and send out long processes which group into compact bundles that are denser around the blood vessels (Fig.9.46). Mitoses are not usually encountered. The nuclei have a thin membrane, are clear, and contain isolated, easily distinguishable chromocenters and nucleoli.

Different aspects may be concurrently present. The appearance may be looser, with vacuolar or mucoid degenerative phenomena which lead to the formation of cysts of various size, often confluent and sometimes filled with an eosinophilic fluid (Fig.9.46b). In these areas, cells no longer exhibit a polar, pilocytic aspect; they form many processes and acquire a star shape (Fig.9.47a). The perivascular processes are usually spared by the degeneration and simulate perivascular condensations which are called "bushes." There is no unanimous agreement on the primitive or secondary nature of the stellate cell in the vacuolated areas. It is likely that both origins are possible.

The compact aspect goes under the definition of "pilocytic adult type" and the loose one under that of "pilocytic juvenile type" [2420]. From personal experience, a diffuse type of astrocytoma and even a protoplasmic one should be added.

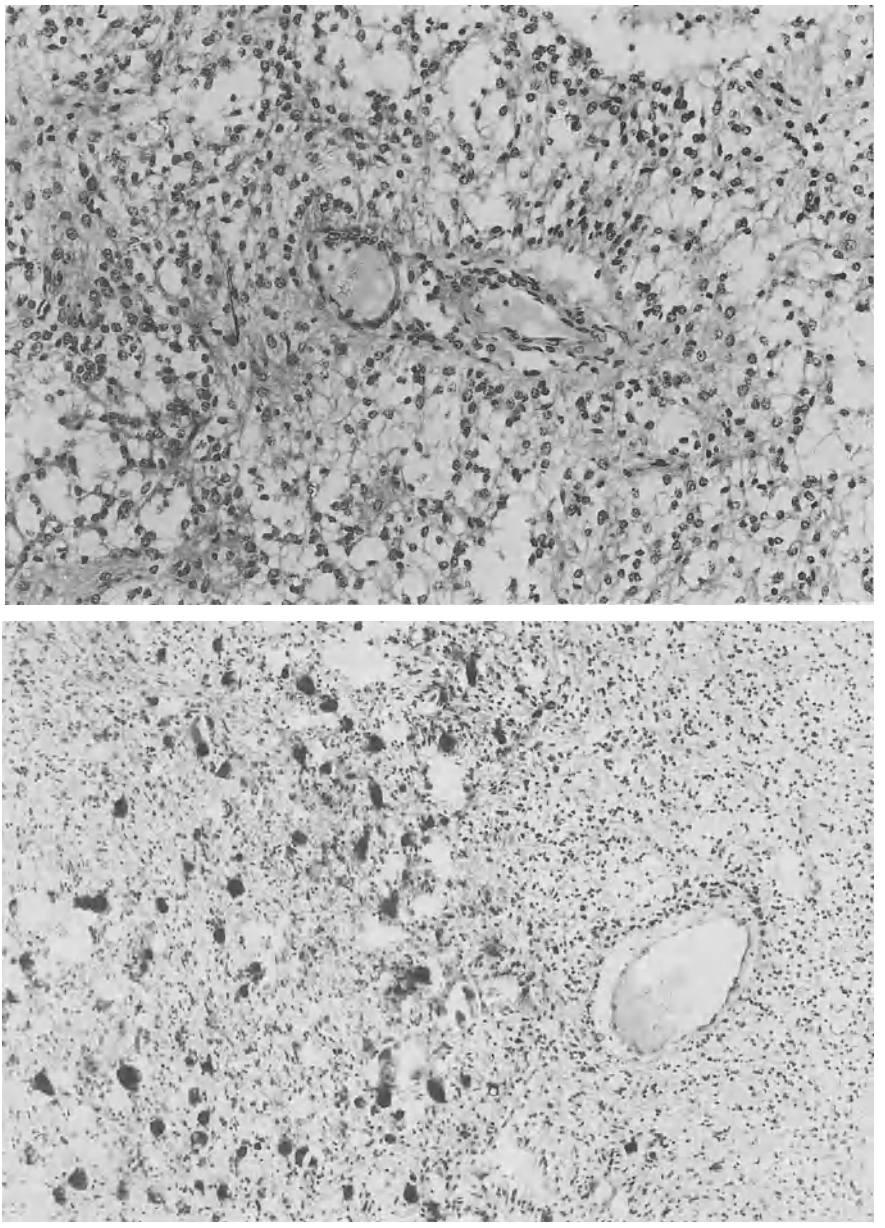


Fig.9.47a,b. Cerebellar astrocytoma: **a** loose architecture, H&E, ×300; **b** calcifications, H&E, ×200

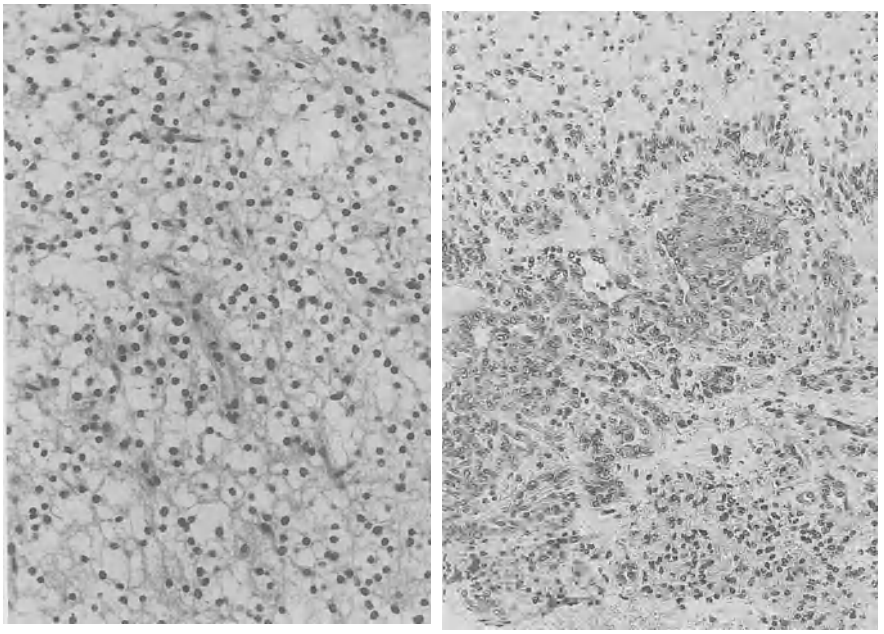


Fig.9.48a,b. Cerebellar astrocytoma: **a** oligodendroglia-like aspect, H&E, ×300; **b** vascular glomeruli, H&E, ×200 [2486]

Often, oligodendroglial features occur, recalling the "honeycomb" aspect of oligodendrogliomas (Fig.9.48a). In some tumors they appear as secondary degenerative phenomena related to the vacuolar-mucoid degeneration [3134]. According to many authors, on the contrary, foci with true oligodendroglial aspects do occur [319, 2419, 573, 1241], even if cerebellar oligodendrogliomas have only rarely been described [1328, 3083].

Both the bipolar cells in the solid areas and the stellate ones in the loose areas are GFAP-positive, thus allowing the processes to be clearly seen even in cross-section. The same structures are demonstrated with vimentin [2513] and are weakly highlighted by detecting glutamine synthetase [2672].

The histological appearance of cerebellar astrocytoma has been variously categorized. In parallel with the pair fibrillary–protoplasmic, the pair pilocytic of adult or juvenile type has been proposed, depending on the diffuse presence of microcysts or of a more compact arrangement of cells and their processes [2419]. Other pairs have been proposed [1241, 1242], such as that of pilocytic "juvenile type" and diffuse [343], but these distinctions do not contribute fundamentally to a better nosologic position of the neoplasia. Often, different features with various expressions coexist in the same tumor.

Calcifications are relatively frequent (Fig.9.47b). They have been found in varying percentages: 14% [2486], 22% [3059], and 26% [2415]. Blood vessels of small and medium caliber are quite regularly distributed and often tend to group, forming a sort of network with nodal points. Endothelial hyperplasia with the formation of true glomer-

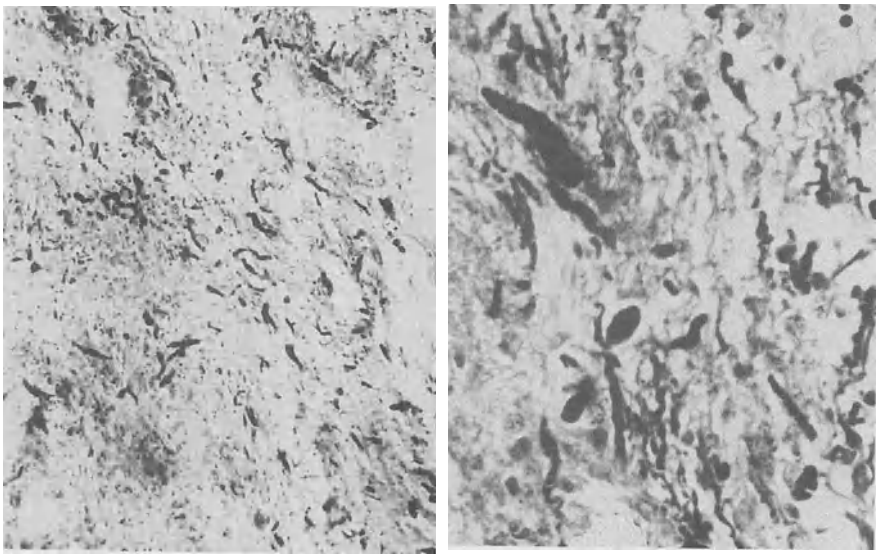


Fig.9.49a,b. Cerebellar astrocytoma: Rosenthal's fibers, ferric hematoxyilin, **a** ×200, **b** ×400

uli sometimes arranged in long tracts and showing mitoses is often present (Fig.9.48b). The endothelial hyperplasia never reaches the intensity typical of glioblastoma. Its frequency has been variously calculated: 52%–53% [3059], or 78.9% [1241, 1242] of cases. Sometimes the formation of blood vessels may be so marked as to suggest the picture of angioglioma, similarly to that which can be observed in other locations. The endothelial hyperplasia does not represent for most authors an unfavorable prognostic sign, as in hemispheric astrocytomas [1629]. This finding is of great importance in the prognostic evaluation made from the histological examination of small fragments.

At the periphery, the tumor has indistinct borders with the healthy tissue. In some areas, it is better delimited and acquires a more compact and clearly pilocytic appearance. In these zones, Rosenthal's fibers are frequent. The cerebellar folia may be involved by the tumor and show a scleroatrophic appearance. The tumor may grow exuberantly in the leptomeninges over the cerebellar folia in a desmoplastic pattern.

9.3.5.5 Rosenthal's Fibers

Rosenthal's fibers are elongated, carrot, comma-shaped, or roundish structures depending on the cutting section. Generally, they have a rounded pole and an extremity terminating in a thin process which gets lost in the glial network (Fig.9.49).

They have a characteristic staining pattern.

They are characteristically found in glial tumors of the midline, especially in the cerebellum, but they have also been described in various pathological conditions involving the subependymal glia: different tumor types including ependymomas, hemangioblastomas, craniopharyngiomas [3134, 997], ependymal granulations [2088, 637, 2486], syringomyelia [1643 , 522], etc. They have also been noted in locations not related to the subependymal glia, such as in the white matter

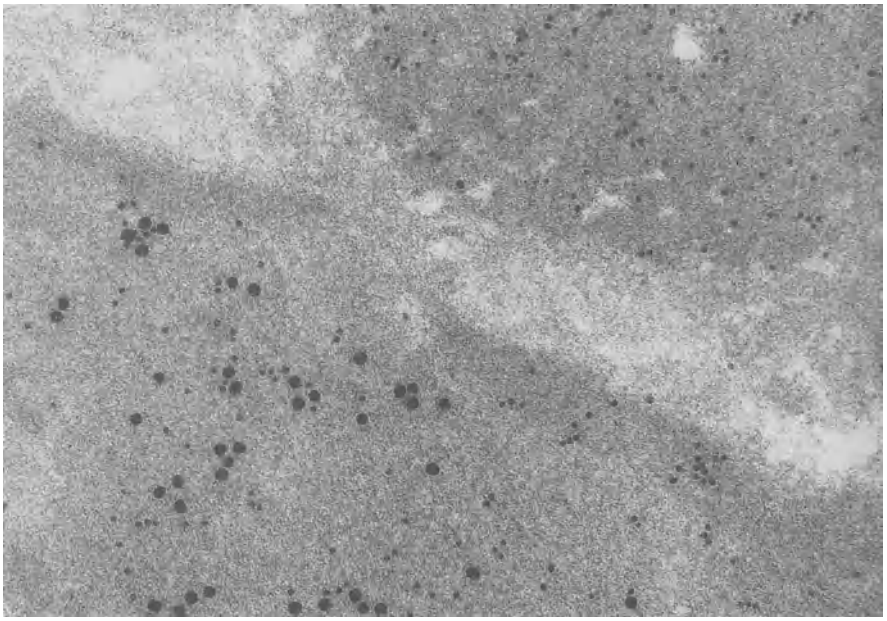


Fig.9.50. Cerebellar astrocytoma: Rosenthal's fibers. Double immunogold labeling for GFAP (small granules) and ubiquitin (large granules). Both are present in the periphery, and GFAP only is present in the amorphous core, ×80,000

of the cerebral hemispheres, in Alexander's disease [1114], in multiple sclerosis [2063], and, in our experience, even in the cerebral cortex around meningiomas. They have also been seen in cultures of astrocytomas of the optic nerve [1025], cerebellum, and spinal cord [1021, 1408].

They are not, therefore, characteristic of midline and cerebellar astrocytomas, but rather reflect the involvement of the subependymal glia independently of the type of process, tumoral, inflammatory, or otherwise. They are structures devoid of enzymatic activity [1025, 2006, 2493, 1055].

Under the electron microscope, they are composed of masses of degenerated glial filaments [1209, 733, 1023]. They form through an interfibrillary accumulation of osmiophilic material, followed by a granular fragmentation of the filaments [2529]. Small osmiophilic masses and filament overload seem to be the basic elements [1024].

The majority of large Rosenthal's fibers are GFAP-negative or only show a thin peripheral positive rim [2923, 2672]. This depends on the quantity of amorphous osmiophilic granular material contained. In fact, the small Rosenthal's fibers, with scarce material of this type, are GFAP-positive [1779, 2672]. This means that the central amorphous material derives from the aspecific degeneration of glial filaments.

Immuno-electron microscopy with colloidal gold demonstrated that the GFAP antibody is localized mostly on the glial fibrils (Fig.9.50), but it is also present on the amorphous material [638]. This demonstrates that the process begins with the accumulation of glial filaments and carries on with their gradual transformation into amorphous material. It has been shown that the peripheral parts of Rosenthal's fibers and also the GFAP-positive compact bundles of fibrils are ubiquitin-positive (Fig.9.50) [1698]. This could prove that the accumulation of GFAP is abnormal and destined to proteolysis but that the ubiquitin-dependent proteolytic system is overloaded, hence the formation of inclusion bodies; alternatively, the ubiquitin could be involved in a cytoprotective process tending to isolate the abnormal protein [643].

9.3.5.6 Malignant Transformation, Prognosis

The cerebellar astrocytoma is a tumor with a good prognosis, with survival periods up to 25–39 years after total removal or 10–25 years after subtotal removal [893]. Recurrences are much more frequent after subtotal than total removal [1240]. Some 94% of patients survive 10 years [3059] and 25% for 25 years [934].In other series, the percentage of survivors at 5 and 10 years are 94 % and 88%, respectively, for children and 83% and 71% for adults [1587]. In still another series of children, 88% survived to 10 years with no sign of recurrence [877]. The treatment of choice is without doubt surgical removal, but the strategy to follow is controversial in cases of subtotal removal, because permanent cure may follow a partial excision. According to some, radiotherapy is indicated [573], as it is advised for relapses [1577]. However, the radiobiological rationale for radiotherapy is lacking in this tumor. The empirical finding of longer survival after radiation is cast into doubt by the observation that long survival is known even without irradiation [952, 893] and that the survival of irradiated and not irradiated cases is in some series practically the same [877]; a trend toward a lower recurrence rate in irradiated patients with subtotally removed tumor has been reported [878].

There are a notable number of late recurrences. It has been found that the tumor violates Collins' law, which states that a patient may be considered cured from a tumor if he has survived the treatment without signs of recurrence for a period equal to his age plus 9 months. This violation occurs both because there are very late recurrences and because patients who underwent partial removal appear to be cured as well [92]. Recurrences obviously do not necessarily correspond to the malignant transformation of the tumor, which is a very rare event.

Cases have been reported in which the tumor has been found in old age with a very long preoperative duration [1402].

Besides the rare examples of malignant transformation of cerebellar astrocytoma [2327, 516, 177, 2577, 319, 1446, 89, 39] even after some decades [3062, 386], there are equally rare reports of primitive glioblastomas or anaplastic astrocytomas [645, 1702, 2127, 2843, 3128]. The distinction between anaplastic astrocytomas and glioblastomas is not at all easy, and according to some authors, they have to be considered as one unique tumor entity [1702, 2843]. In a review of the literature [1242], only 53 cases of glioblastoma and no more than 50 of anaplastic astrocytomas were found as reported. According to others, up to the end of 1985, not more than 65 glioblastomas have been reported [2729] and 77 to the end of 1989 [2365]. For others, malignant cases are not so unusual (5 out of 19 cases [2628]).

Two thirds of patients are adults [645], with a bimodal age distribution peaking in the 1st and 6th decades [3128]. The rarity of glioblastomas in the cerebellum has also been explained by the lower tendency of cerebellar astrocytes to undergo anaplasia in comparison with the cerebral ones [732]. Cases with anaplastic features (Fig.9.51), albeit focal, carrying a poor prognosis undoubtedly exist [1396]. In a personal series, there were 6 anaplastic astrocytomas from a total of 108 cases, but they did not show a different survival rate to nonanaplastic tumors.

In principle, the tumor grows slowly, and the application of "grading" according to Kernohan et al.[1405] has little value, since few grade 3 and 4 tumors have been recorded [1726, 952].

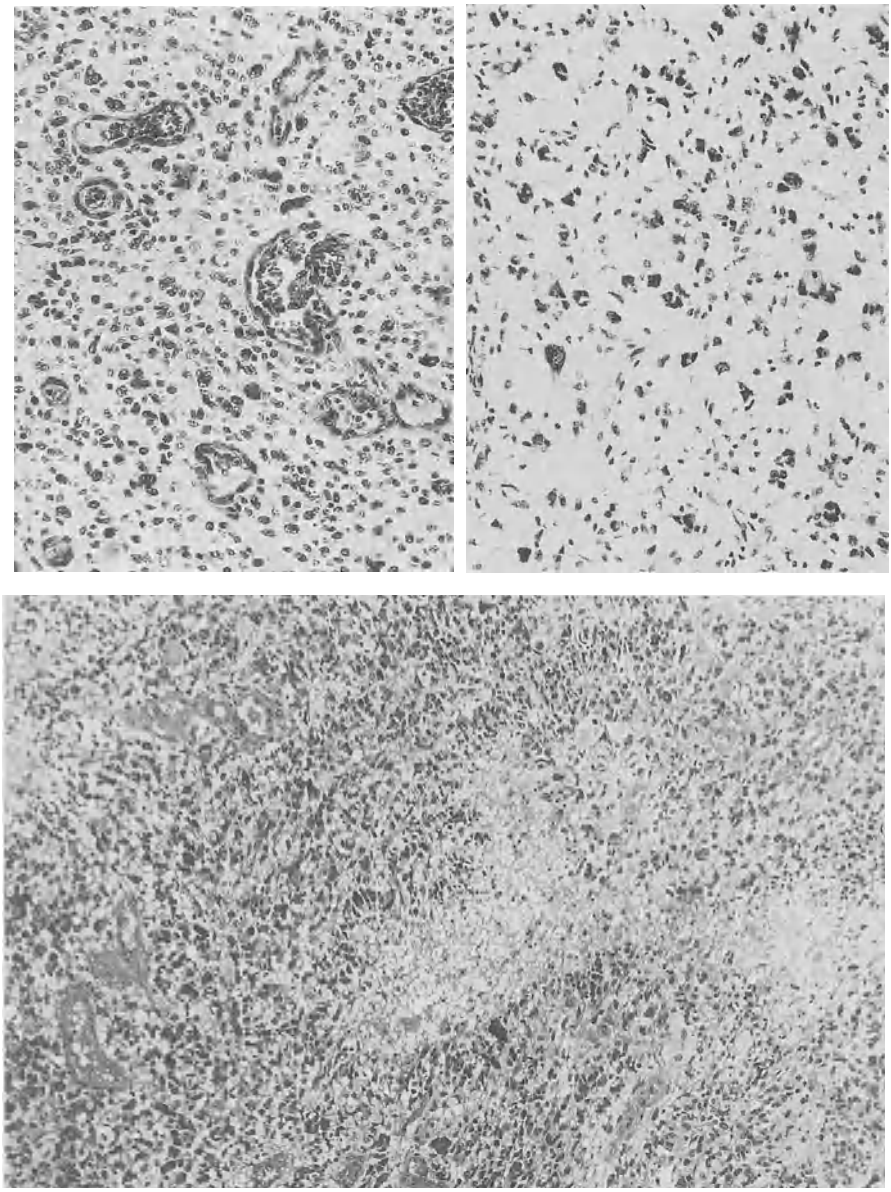


Fig.9.51a–c. Cerebellar astrocytoma: **a** and **b** nuclear polymorphism, H&E, ×200 [2486]; **c** circumscribed necrosis, H&E, ×200

The identification of prognostic signs by the statistical analysis of survival has also been tried for this tumor. While a typical histological appearance has a 94% survival rate at 25 years, infiltrative growth was associated with only 38% survival [934]. The association of microcysts, leptomeningeal growth, Rosenthal's fibers, and oligodendroglial foci in a series of all cerebellar gliomas had a clearly better prognosis than the

association of necroses with high cellular density, mitoses, and perivascular pseudorosettes [3059]. Nuclear polymorphism resulted to be an unfavorable prognostic sign only when marked [1242]. Also, the presence of mitoses in any numbers, marked cellular density, marked desmoplasia, and necrosis have the same significance. Hypotheses have been formulated on the possible role of radiotherapy in the development of malignant astrocytomas of the cerebellum. Cases have been reported after radiotherapy for medulloblastoma [2090, 1455], lymphatic leukemia [2253], and craniopharyngioma [1725]. A malignant transformation of irradiated astrocytomas 28 and 13 years later has also been reported [319, 732].

The possibility of identifying malignancy by neuro-imaging is very important; the occurrence of edema and mass effects have been exploited in this sense [3128, 2061], but they do not seem to be of great help.

In anaplastic astrocytoma and cerebellar glioblastoma, radiotherapy is indicated [1480].

9.4 Astrocytic Tumors of the Spinal Cord

9.4.1 Frequency, Age

Astrocytomas occur much less frequently in the spinal cord than in the brain, and this may be related to the difference in weight of the two organs. They are more commonly situated in the thoracic region, followed by the cervical, lumbar, and sacral areas. The most affected decades of life are the third, fourth and fifth. Children may also be affected, but the ratio with intracranial tumors decreases from 20:1 in adults to 10:1 in children [1481].

9.4.2 Macroscopic and Microscopic Appearance

The macroscopic appearance is usually that of swelling of the cord, often over several segments. The consistency is usually hard and fibrous-like, but it can also be soft if areas of degeneration are present. Cysts may be present.

The cellular density is medium to low, and the cells have a stellate astrocytic appearance, even though their cytoplasms are often not well demarcated. Given the low cellular density, it is sometimes difficult to understand from the appearance of the nuclei alone whether or not one is dealing with a true tumor, unless the nuclei are decidedly polymorphous. Therefore, the diagnostic distintion from reactive gliosis is sometimes difficult. Blood vessels are scarce and of small caliber. Rosenthal's fibers may be present. They are not pathognomonic of the neoplasia in that they may also be found in reactive processes, for example, the walls of a syringomyelic cavity.

The tumor may undergo anaplastic changes with an increase in cellular density, the appearance of circumscribed necroses, and endothelial proliferation which can suggest the picture of anaplastic astrocytoma or frank glioblastoma.

The prognosis can be established on the basis of histological appearance. Survival seems to be influenced by the type of treatment, i.e., total or subtotal removal or decompression with biopsy [2293]. The usefulness of radiotherapy is highly controversial because of the frequency of well differentiated tumors. However, in contrast to ependymomas, only 6% of intramedullary astrocytomas can be removed completely, even with microsurgery techniques [449]. Postoperative radiotherapy has resulted in improved long-term survival rates. Survival at 5 and 10 years was 58% and 23% [1481], and 60% and 40% [449], respectively, in two series. The recommended dose is 50 Gy [449].

In infancy, radiotherapy is only carried out in the event of recurrence after a second operation, so as to avoid severe damage to the developing nervous system [720].

10 Oligodendroglial Tumors

10.1 Oligodendroglioma

10.1.1 Frequency, Age, Site

Oligodendroglioma has not encountered great nosological difficulties, as it was recognized at the very beginning of modern studies [112, 108]; however, it has seen its boundaries widen or narrow depending on the interpretation of some histological aspects. As a consequence, its frequency varies greatly in the different series, ranging from 1.3% [542] to 9.6% [3138] of all intracranial tumors and from 5% [2417] to 18% [3138] of all gliomas. In the present series, they represent 4.2% and 9%, respectively. It is typically a tumor of adults, but the average age is difficult to ascertain, because there is a notable discrepancy between the time of onset of the first symptoms, diagnosis, and surgical intervention. From Cushing's various series, an average age of 28 years has been derived. Other series have reported averages of 36 [692], 37 [2280], and 44 years [2486]. In Zülch's series [3138], the age peak was between 35 and 40 years. It is rather rare in infancy. However, cases have been reported [887, 1894, 3132, 175, 2580, 2164, 2916, 2107] even in neonates or in breast-fed infants [2773, 1473].

The tumor develops in the white matter of the hemispheres with a predilection in decreasing order for the frontal, parietal, temporal, and occipital lobes [3134, 2118, 1757, 2564, 2486, 425]. Spinal cord [824] and cerebellar [2107] locations are rare.

10.1.2 Macroscopic Appearance

The tumor has a fairly characteristic appearance. By infiltrating the cortical gyri from the white matter, it takes on gives a "garland" appearance and frequently burrows itself mushroomlike passages. It may invade the meninges and reach the dura, or it may grow deep and penetrate into the ventricles, or even be predominantly intraventricular [1774] (Fig.10.1).

It has a variable soft or gelatinous consistency and is gray-pink in color, sometimes cystic, and often calcified. The tumor limits are often sharp on the surface and ill-defined deeper down.

10.1.3 Microscopic Appearance

The tumor has a medium to high cellular density. The cells are fairly round and regular and have scanty cytoplasm, sometimes with short processes (Fig.10.2a). The nucleus

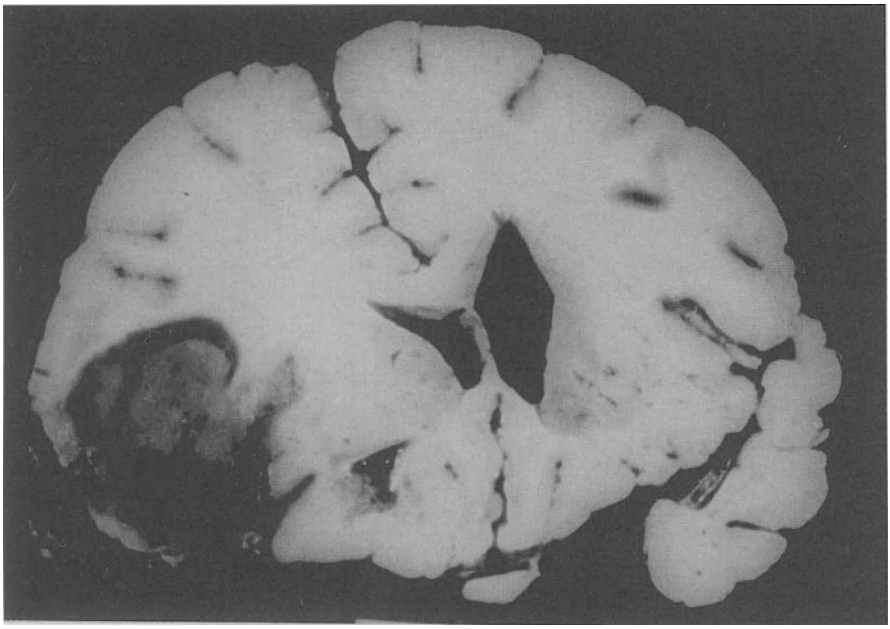


Fig.10.1. Frontotemporal oligodendroglioma

has a fairly characteristic chromatin pattern with a central nucleolus. These characteristics are typical of normal oligodendroglia, even in its variations, and are clearly evident in acetic carmine preparations (Fig.10.3a,b) [2480]. The nuclei may also be large or polymorphous, but this does not constitute an indicator of malignancy per se. Mitoses are found in moderate numbers. The cells are arranged without a particular pattern or are organized into more or less large lobules delimited by the septa of blood vessels. The cells may take on particular configurations when they cluster around blood vessels or around neurons in infiltrated cortical areas. Elegant images of perineuronal "satellitosis" may form (Fig.10.2b), very useful in the differential diagnosis, even though not pathognomonic of the tumor.

One of the characteristics of this tumor is the appearance of a perinuclear "halo" which imparts to the area a "honeycomb" appearance (Fig.10.4a). This is an artifact, due to fixation and to the presence of "mucoid" material (i.e., GAG) in the cytoplasm. In the earlier literature it was described as the degeneration corresponding to the "acute swelling" of the oligodendroglia of Penfield [2168] or the mucoid degeneration of Grynfelt [1013]. Histochemical reactions for GAG are strongly positive in these areas (Fig.10.4b) [2491, 2486, 925], and the "honeycomb" degeneration is the most typical of those associated with an accumulation of GAG [925], in analogy to what occurs in experimental ENU-induced oligodendrogliomas [1823], even if the pathogenetic connection is not known. Various types of GAG may be identified, in particular, chondroitin sulfate [186]. The honeycomb appearance is a nonpathognomonic, regressive process, but nonetheless it is of notable help in the differential diagnosis. Microcyst formation may be related to these events.

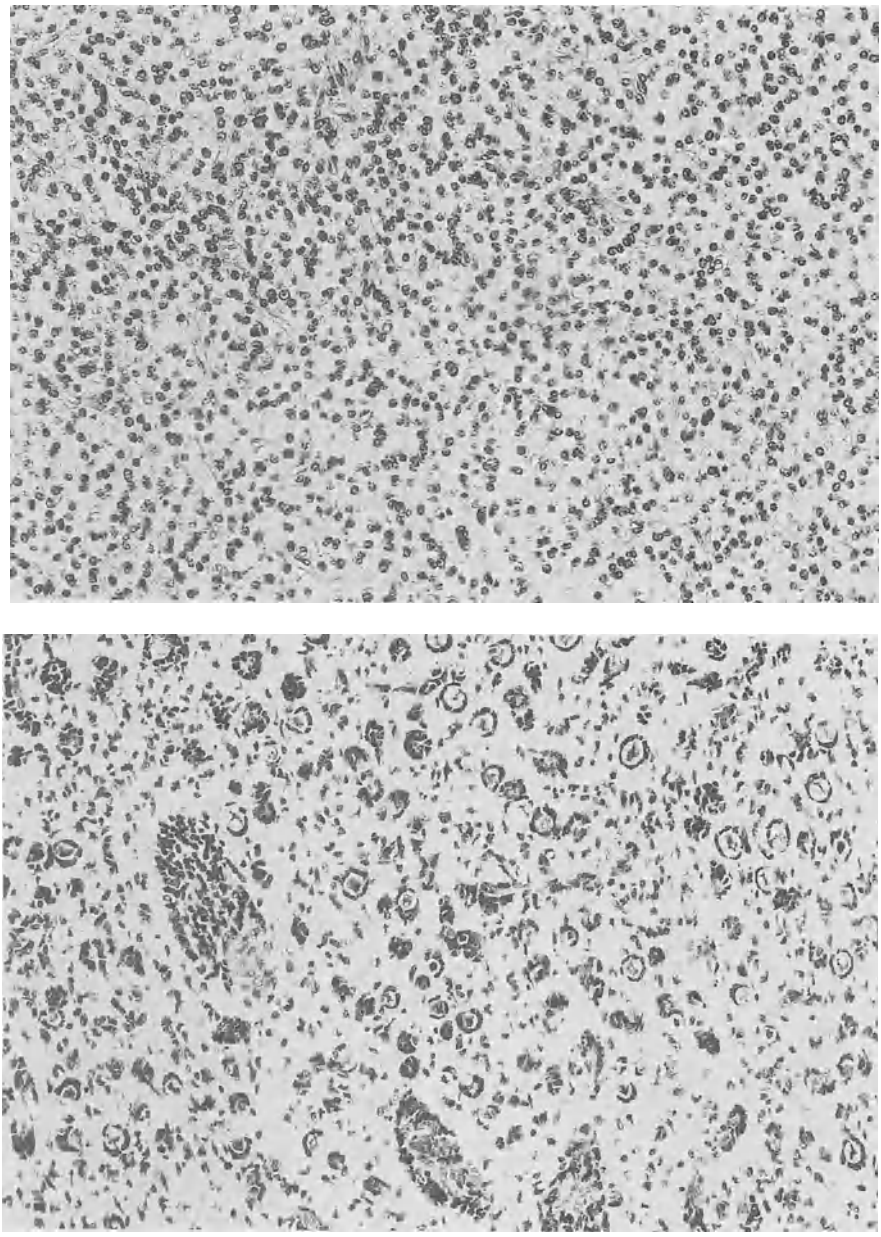


Fig.10.2a,b. Oligodendroglioma: **a** isomorphic aspect of tumor cells, H&E, ×200; **b** cortical perineuronal satellitosis and perivascular growth, H&E, ×200

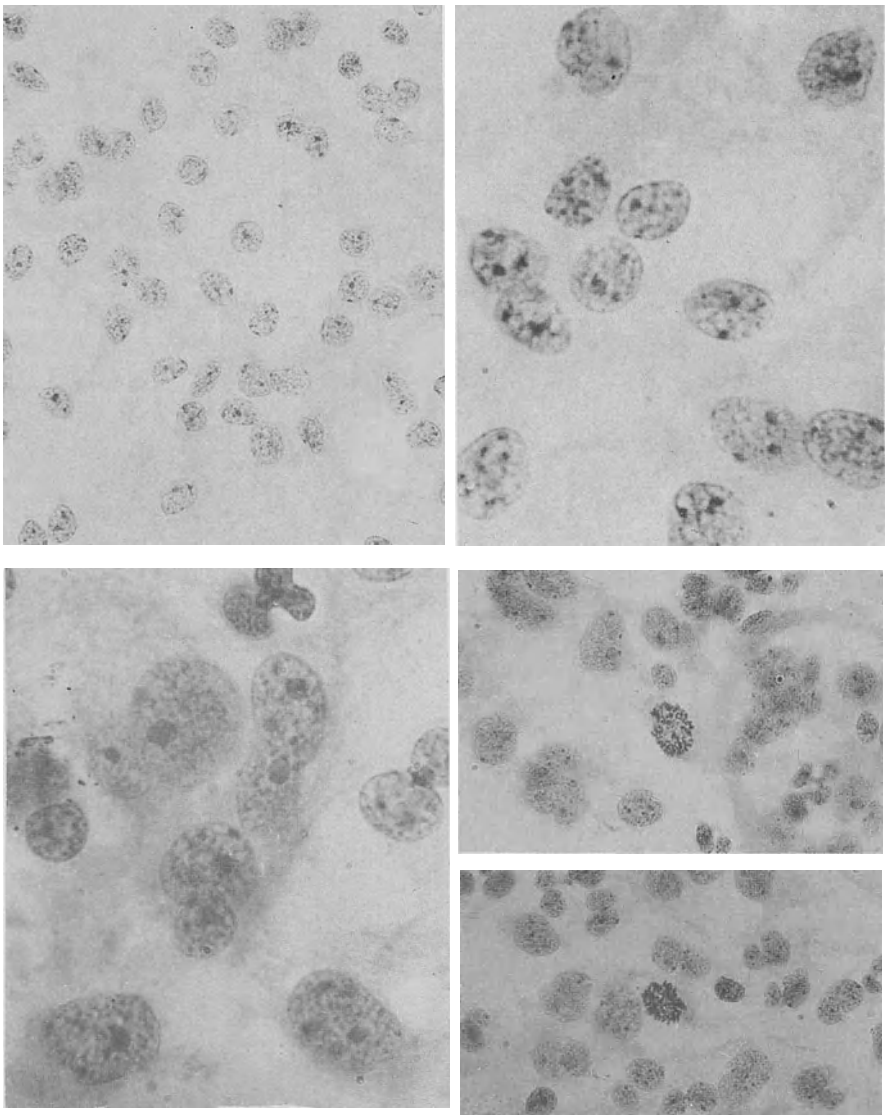


Fig.10.3a–e. Oligodendroglioma: **a,b** typical distribution of chromatin in the nuclei, even in **c** anaplastic variant; **d,e** mitoses, acetic carmin, ×400 and ×1000, respectively [2480]

The blood vessels have a typical distribution: They form short and angulated segments, like the branches of a tree, and tend to delimit lobules. They often have thickened, sometimes hyalinized walls and occasionally show endothelial hyperplasia (Fig.10.5a).

In circumscribed areas, there may be cells of uncertain origin with scanty but clearly visible eosinophilic cytoplasm and with a half moon peripheral nucleus about which

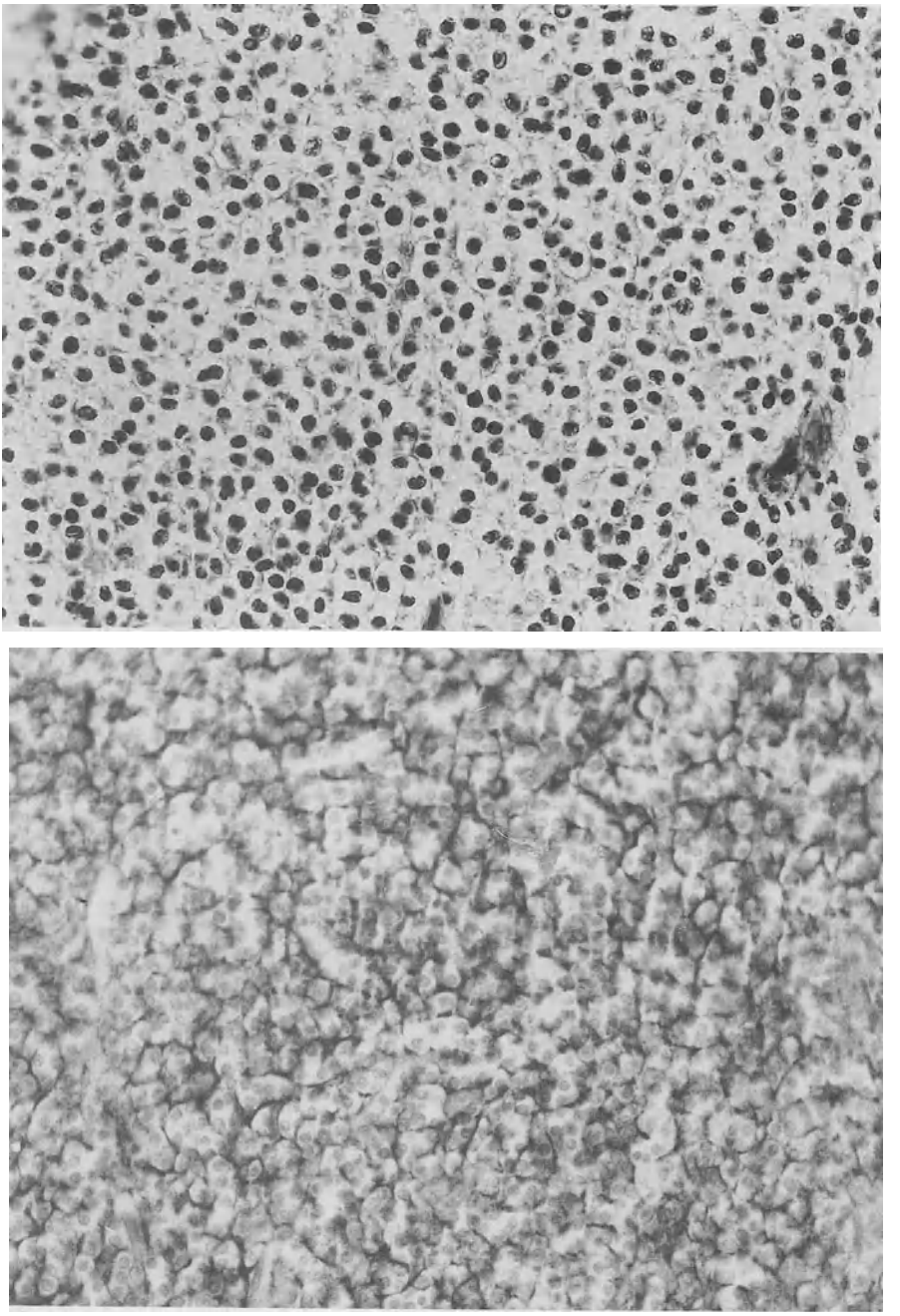


Fig.10.4a,b. Oligodendroglioma: **a** perinuclear halos, H&E, ×300; **b** alcian blue positive staining of the honeycomb aspect, ×400

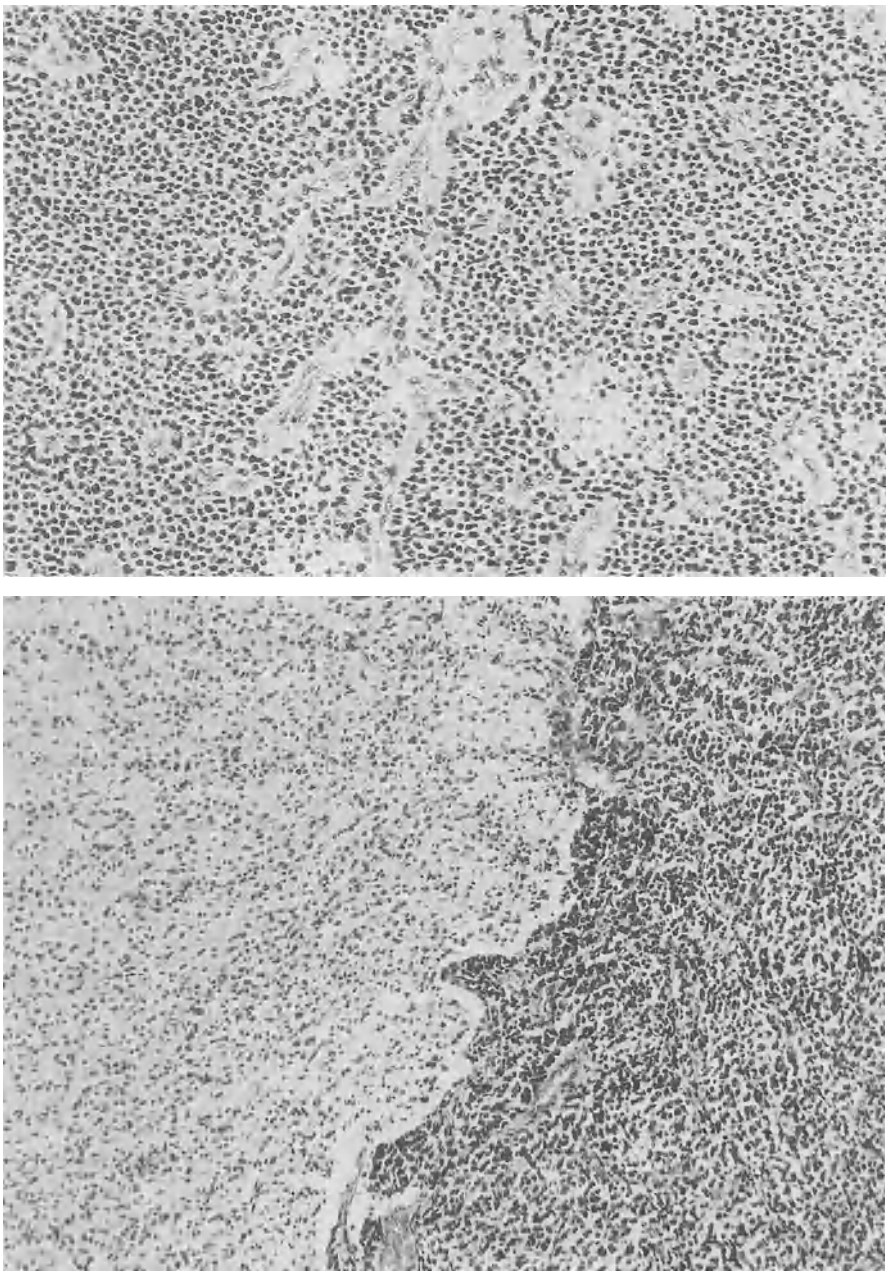


Fig.10.5a,b. Oligodendroglioma: **a** typical distribution of vessels, H&E, ×200; **b** subarachnoid growth, H&E, ×200 [2484]

more will be said later. Calcifications are characteristic of oligodendroglioma. Different types may be distinguished [1784, 3134, 2481]:(1) pseudocalcium-calcium (pCa-Ca) precipitations on capillaries or in the media and adventitia of larger vessels in the form of fine granules; these may become confluent and surround a blood vessel, like a sleeve, or be arranged in larger, roundish, lobulated deposits; (2) apparently homogeneous precipitations involving entire segments of blood vessels, the media, adventitia, or both in larger blood vessels; (3) roundish calcifications with polylobulated, rounded borders with annular stratification and variable dimensions; (4) roundish formations apparently not related to blood vessels.

The calcifications may lie deep in the tumor, but they are particularly concentrated at its periphery or in the adjacent infiltrated normal tissue. They often accumulate in foci, in which histochemical examination identifies an older center and a more recent periphery. Generally, the blood vessels are the most important substrate for calcification, but neuroectodermal structures such as neurons, which have become entrapped in the tumor, may also act as a substrate for the precipitation. The frequency of calcifications in oligodendroglioma is very high, occurring in 70% of the present series. Sometimes they are visible radiologically, with a convoluted appearance as in Sturge–Weber disease.

The tumor grows by infiltration and, in general, it ascends from the white matter into the cortex. It is, however, common to find infiltration of the cortex, especially along penetrating blood vessels from the meninges, originating from a subpial proliferation. In this event, the infiltration of the cortex decreases, going towards the white matter, or it merges with that coming from the white matter. The tumor grows in the meninges and may be adherent to the dura (Fig.10.5b).

Many blood vessels demonstrate adventitial infiltration by lymphocytes and plasma cells, especially at the periphery.

Oligodendroglioma may sometimes spread via the CSF and rarely metastasizes extracranially [1305].

10.2 On the Presence of Astrocytes and the Problem of Mixed Gliomas

In the WHO classification, the dignity of oncotype has been conferred to the oligoastrocytoma as mixed oligoastrocytic glioma. This tumor is characterized by the presence of numerous astrocytes, apart from oligodendrocytes. The pathogenesis of this mixed tumor, however, is unclear. The demonstration of GFAP has brought an important contribution showing that, apart from the clearly recognizable reactive astrocytes included in the tumor, there may be GFAP-positive neoplastic astrocytes (Fig.10.6a) [1994], belonging to the astrocytic component of the mixed tumor, and GFAP-positive cells of dubious oligodendroglial appearance (Fig.10.6b) [2903, 581, 1869, 2509]. These cells have been interpreted either as small gemistocytic astrocytes, without demonstrable gliofibrils [581], or as transitional cells between oligodendrocytes and astrocytes [2903], sometimes as bipotential precursors [2249], or as an expression of transition

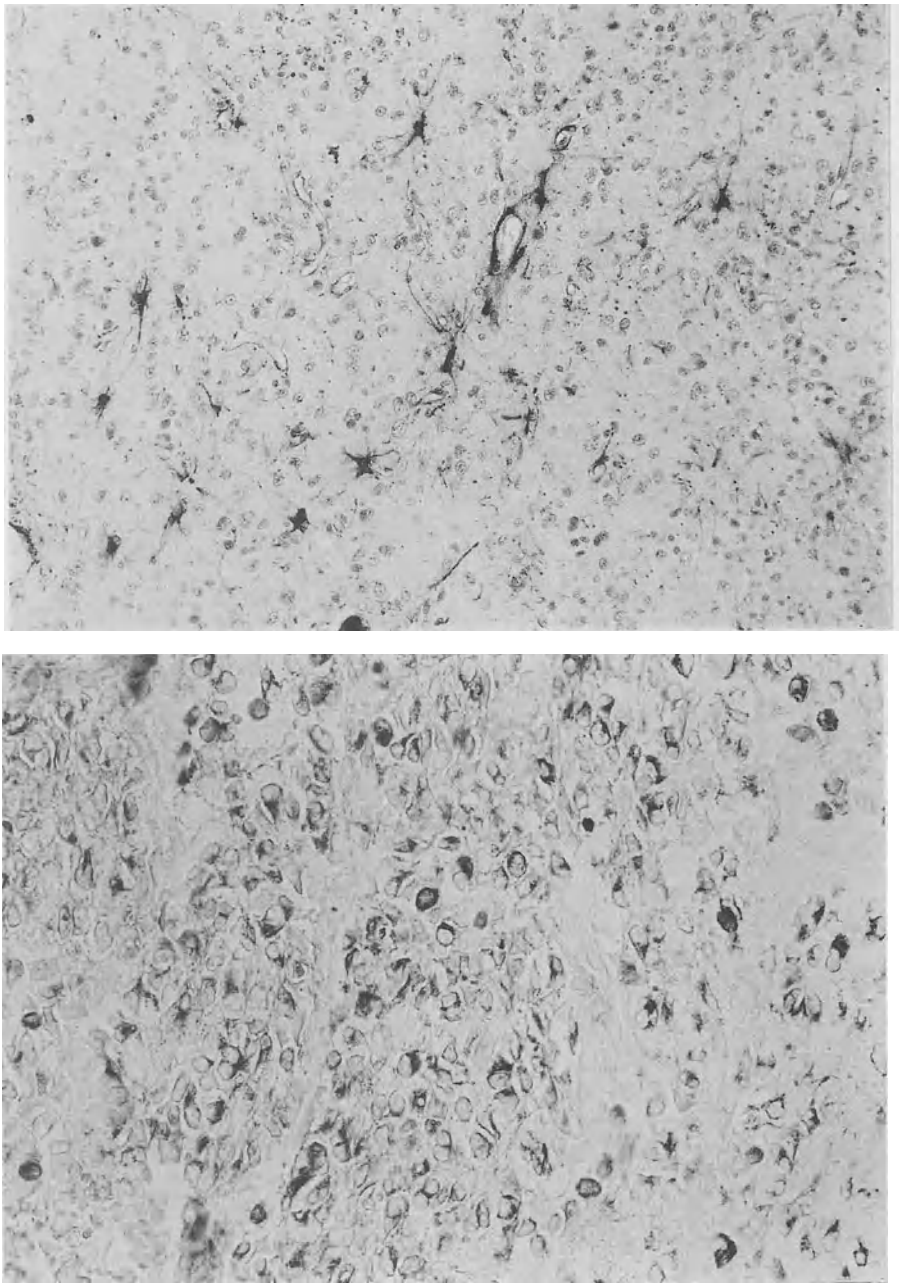


Fig.10.6a,b. Oligodendroglioma: **a** GFAP-positive stellate astrocytes, PAP-DAB, ×200; **b** GFAP-positive round microgemistocytes, PAP-DAB, ×400

forms between classic oligodendrocytes and oligodendrocytes expressing GFAP [1115]. The last is reminiscent of the myelin-forming glia which, during development, transiently expresses GFAP [434]. The transitional oligoastrocytoma is, therefore, a further subtype of oligodendroglioma. There are also alternative interpretations: One is that GFAP-positive astrocytes form halos with the assumption of oligodendroglial characteristics [1345]. Besides GFAP-positive minigemistocytes and gliofibrillary oligodendrocytes, there are also classic large GFAP-positive gemistocytes [1508].

Today there are numerous markers for oligodendrocytes, for example, the monoclonal antibody against Leu-7, anti-myelin associated glycoprotein (MAG), antibody against myelin basic protein (MBP), and antibody to carbonic anhydrase C. However, it is very difficult to use them for diagnostic purposes in paraffin sections, especially from embedded tissues. According to some authors, marking with the Leu-7-specific antibody is positive in a high percentage of cases, especially in the cytoplasmic membranes and processes [1994]. It is reliable in the diagnosis of oligodendroglioma [1952]. However, not all cases are positive, even though in tumors in which anti-Leu-7 reacts with the neoplastic cells, more than half the tumor cells are positive [2180]. It must be taken into account that this antibody also reacts with other CNS and PNS tumors [1662, 2180], although in a smaller proportion of cells.

The MBP-specific antibody does not react with tumor cells, but with myelin sheaths, whilst the MAG-specific antibody reacts only with occasional tumor cells. Carbonic anhydrase C antibody reacts only with a few tumor cells, while it is widely positive in normal oligodendrocytes both in man [1994] and rat [928]. Oligodendrogliomas react immunohistochemically with antibody to A2B5 and GC, thereby demonstrating a derivation of the cells from the A2B5-positive progenitor, in common with astrocytes. In mixed oligo astrocytic tumors, by contrast, there are cells which are positive for both GFAP and A2B5 [585].

10.3 Anaplastic Oligodendroglioma and Prognosis

Oligodendroglioma may become malignant in time, even though this transformation is not so frequent as for astrocytoma.

Anaplastic oligodendroglioma is characterized by an increase in cell density, nuclear polymorphism (Fig.10.7a), and the number of mitoses. Endothelial proliferation (Fig.10.7b) becomes more apparent, and circumscribed necroses appear (Fig.10.8). The picture may be so remarkable as to resemble that of glioblastoma. The recognition of the oligodendroglial origin is based on the persistence of differentiated tumor areas.

In the malignant transformation of oligodendroglioma, cells with astrocytic features may appear, represented mainly by the small GFAP-positive, microgemistocytic, round cells already described [343]. These cells contain intermediate filaments [2450].

Because endothelial hyperplasia and mitoses are commonly found in oligodendroglioma, the identification of the anaplastic variant in its initial stages is not easy. A difficult and long debated problem is, in fact, that of the predictability of survival on the basis of the histological appearance. The application of a "grading" which proved to be both useful [692] and not useful [1967] has not overcome the problem. The tumor shows

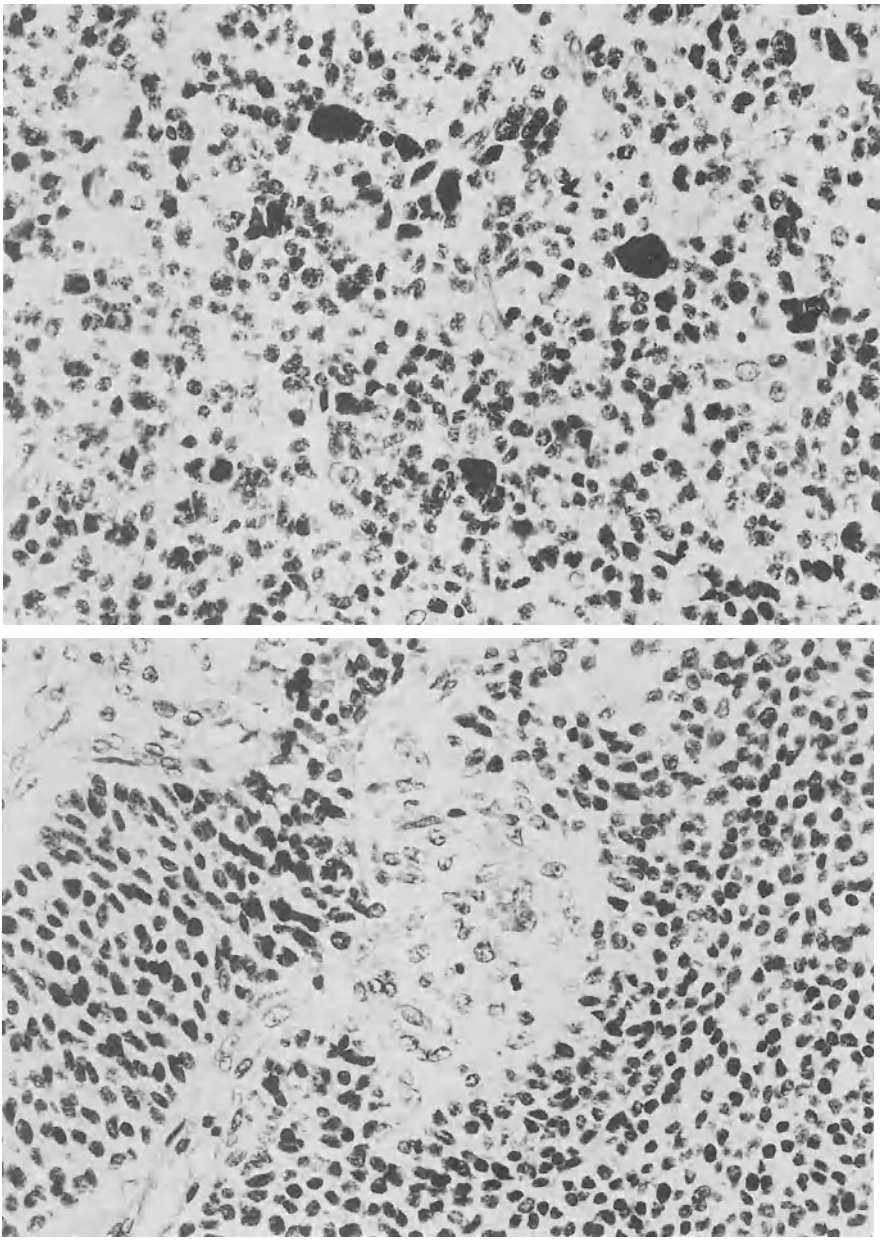


Fig.10.7a,b. Anaplastic oligodendroglioma: **a** nuclear polymorphism, H&E, ×200; **b** endothelial proliferation, H&E, ×200

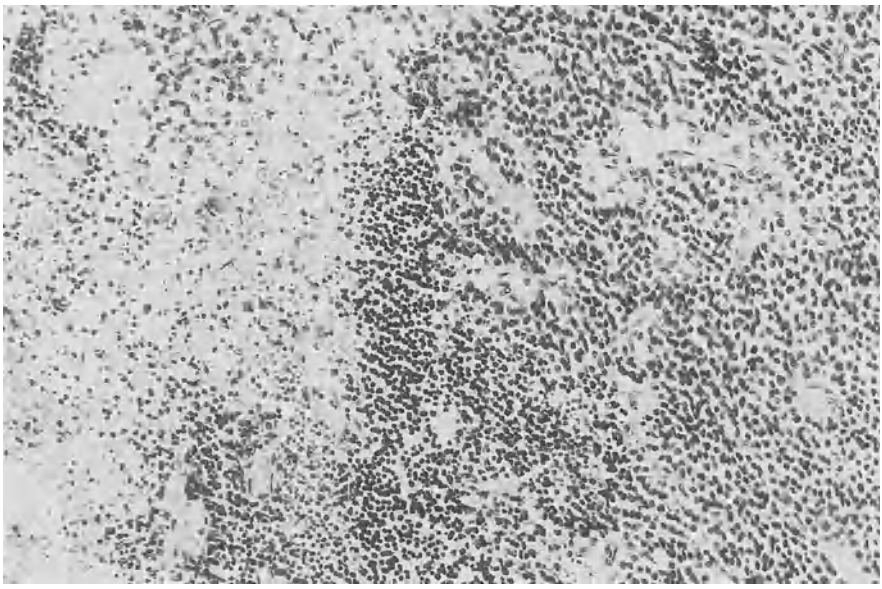


Fig.10.8. Anaplastic oligodendroglioma, circumscribed necrosis, H&E, ×200

an apparent morphological homogeneity, but in reality is characterized by multiple features, including the presence of mitoses, even in cases of certain and verified benignity.

The prognostic importance to be attributed to different histological factors has been the object of numerous studies with contrasting results. In some [2674], only the nuclear pleomorphism has been considered relevant, whilst in others microcysts, necroses and cellular density are important. Patients with tumors with low cell density, microcystic degeneration, and no necrosis survive on average 6 years longer than those who do not show these features [1943]. Less clear-cut is the negative prognostic significance of subpial growth. Also, in other experiences, necroses are a factor of certain prognostic significance, determinantly contributing to the definition of the anaplastic variant of oligodendroglioma.

Opinions diverge on the importance of the number of mitoses, according to whether these are considered [340] as a prognostic factor or not [1943]. This is very important, because, with respect to astrocytoma, they seem to play a much less predictive role. The presence of astrocytic areas does not seem to have any prognostic influence [2674, 340, 3044]; however, gemistocytes are an ominous sign [1508]. It is, therefore, improbable that, as proposed in the past [129, 1967], the malignant transformation of oligodendroglioma is a consequence of the possible transformation of its astrocytic component. In contrast to astrocytomas, there are no significant associations between age and histological factors (for example, the greater incidence of endothelial proliferation with increasing age [340]).

Recently, the importance of the application of "grading" for the establishment of the prognosis of oligodendrogliomas has been reevaluated [2674, 1704, 1507], utilizing

systems with four categories which are very similar, even if simplified, to the original ones of Kernohan et al. (1949) [1405]. The only significant differences are found between the extreme grades, i.e., between cases characterized by low cell density, little or no polymorphism, few mitoses, minimal endothelial proliferation, and absence of necroses, and cases defined as anaplastic, with high cell density, marked polymorphism, many mitoses, marked endothelial proliferation, and necroses. There is no significant difference among the intermediate grades.

The median survival of patients with oligodendrogliomas varies between 3 and 5 years in the larger, recent series [1943, 1704, 328]. Survival is, however, definitely shorter for cases variously defined as "malignant" or as having a "higher degree of malignancy" [2564, 2674, 2764], i.e., between 17 and 21 months. There are, on the other hand, numerous cases with a very long survival of between 25 and 40 years [1187, 2337]. Generally, oligodendroglioma recurs locally, but it may metastasize via the CSF with a frequency varying between 1.2% to 8.5% in clinical studies and around 14% in autopsy-based reports [1704]. Large intratumor hemorrhages may also occur, whilst extraneural metastases are exceptional.

Amongst the clinical factors which seem to influence the survival of patients with oligodendroglioma positively, are epileptic fits as the first and only symptom, good preoperative clinical status, blood groups O and B, radiological appearance of calcifications, and well-demarcated, nonnecrotic, or hemorrhagic macroscopic appearance, but not age (contrary to astrocytic gliomas) [1943].

Surgical removal, especially if macroscopically complete, seems to guarantee better survival [1187, 2916, 1943]. The usefulness of postoperative radiotherapy for subtotally resected cases has always been controversial [1607] and remains so even in the more recent series. According to some [328], it is not useful, while according to others it would improve, even if modestly, the median survival [1657] or increase the number of long-term survivors [2973]. For recurrent oligodendrogliomas, the efficacy of systemic polychemotherapy (procarbazine, CCNU, and vincristine) has been reported [356]. Responses have been reported also in newly diagnosed aggressive oligodendrogliomas treated with the same chemotherapy combination [1727]. New trials are now in progress on the therapy of oligodendrogliomas [357].

11 Ependymal Tumors

11.1 Ependymoma

Ependymoma is a tumor arising in close relationship to the ependymal covering of the ventricular system, as demonstrated by its location and by the morphology of its cells. However, despite its close relationship with the ependymal covering, this tumor may grow deeply into the white matter.

11.1.1 Classification Problems

This group of tumors was first outlined by Bailey [105] and by Bailey and Cushing [113] who distinguished ependymomas, composed of ependymocytes, from ependymoblastomas, composed of ependymoblasts. The latter name was subsequently used by various authors to designate the malignant variant of ependymoma. The plexus-papilloma was at first separated from the group [1189, 107], and then reintroduced [1403]. Various types were distinguished: a cellular one with a perivascular cellular arrangement, an epithelial one, characterized by ependymal canals, a papillary one, and the plexus-papilloma [1403].

Another variety, the ependymal spongioblastoma, characterized by the presence of spongioblasts typical of subependymal layers and mitoses, corresponding to the ependymoblastoma [943] was subsequently recognized. Lastly, the subependymoma was added to these varieties [2468, 2469].

Subsequent authors have, in general, accepted the subdivision into cellular, epithelial, myxopapillary, and subependymoma [2328, 3134, 2419, 1284, 2486, 985]. The significance to be given to each tumor type and their relationship with the formal origin of the tumor have not been definitively explained. The facts that the epithelial variety is more frequent in infratentorial and spinal locations, that mitoses are the rule in supratentorial tumors and rare in infratentorial ones, and that the myxopapillary variety is exclusively found in the cauda equina cannot alone facilitate the understanding of the formal genesis of the tumor. Instead, it is important to give significance to the individual structures which characterize the tumor. In the description of ependymoma, terms such as rosettes, pseudorosettes, radial crowns, and so forth, which require qualification and also definition from the cytogenetic viewpoint, often recur.

First of all, it has to be remembered that normal ependymal cells arranged around a lumen and hence forming "rosettes" may be found close to the ventricles, in the folds of the ventricular wall, or around the aqueduct. This finding is very important for the recognition of the significance of these structures inside the tumor, i.e., whether they represent a sign of differentiation or of undifferentiation, as a vestige of the capacity to cover the lumen of the neural tube.

Rosettes, characteristic of ependymomas and neuroepitheliomas, have been defined as structures formed by ependymal cells arranged around a true lumen, akin to the ependymal canal. They imitate the covering of the neural tube [1109]. Instead, structures characterized by a radial arrangement of ependymal cells so that the processes converge towards a virtual central point are called rosettes by some [2380, 496] and pseudorosettes by others [3134]. If a blood vessel is found in the center of these structures, they are considered to be perivascular pseudorosettes, gliovascular formations, or radial crowns. Formations similar to those described can be found in many other oncotypes, so that the problem is extended to involve various differential diagnoses. First of all, rosettes are found in retinoblastoma, where cells are arranged around a central lumen, delimited by a well defined membrane which stains with phosphotungstic hematoxylin. This type of rosette is exclusive to retinoblastoma [1022] and represents the tendency to imitate the neural tube [2287] and to replicate the layer of cones and rods [886]. Due to the fact that retinoblastoma derives from primitive rather than differentiated retinal cells, the rosettes appear only in the more mature tumors and point therefore, towards differentiation rather than immaturity.

From the ultrastructural point of view, rosettes are formed by cells featuring "terminal bars," cilia, and microvilli. However, rosettes in retinoblastoma have only one cilium per cell. The cilium features a concentric structure of nine pairs of peripheral tubules and none in the center. The model is called 9+0 [36, 2222] and is typical of cilia of neural derivation [555, 2871]. In ependymoma, on the other hand, the model is 9+2 [1717, 2458]. It has to be remembered that cilia have also been described in astrocytoma [2804] and in extraneural structures, for example, the meninges.

Rosettes are described in medulloblastoma, in which cells send processes towards a virtual central point, similar to the Homer–Wright rosettes of central and peripheral neuroblastomas, pinealoblastoma, and pinealocytoma. Strictly speaking, on the basis of what has been said above, these structures must be called pseudorosettes, which according to some are not at all specific for medulloblastoma, and neuroblastoma in that they can be found in various tumors outside the CNS [1022].

When the pseudorosettes are formed around blood vessels, they are called "radialed crowns." These have to be distinguished from astroblastic arrangements, characterized by perivascular endfeet and by processes extending into the perinuclear cytoplasm [2420].

On the basis of observations of the comparative anatomy of the common precursors of the ependyma and the adult glia, i.e., the tanycytes (also known as ependymoglia), a "tanycytic" variety of ependymoma has been recognized.

In the neural tube, tanycytes form processes directed towards the ependymal layer and also send long processes towards blood vessels and the pia mater. Similarly, in tanycytic ependymomas, there are bipolar cells with prolongations directed towards blood vessels [830]. These may resemble those of oligodendroglioma in cross section. This variety, which has to be differentiated from pilocytic astrocytoma, is particularly found in the spinal cord. The problem concerning the recognition of ependymoma cells as ependymocytes, astrocytes, or transitional cells involves the transition between ependymoma, subependymoma, and astrocytoma. One of the most important points of the whole question involves the transitional characteristics of cells of the subependymal layer which recall the transition from tanycytes to astrocytes [2734] (see Chap. 1).

As has been said in Chap. 1, in man two types of tanycytes are distinguished on the basis of GFAP expression and localization. The first type is found in the walls of the third ventricle and is GFAP–positive during development and negative in the adult form. The second type is more diffuse, has no secretory function, and is found in the ventricles, where it covers the white matter. It does not intervene in cellular migration or in the maturation of the ependyma but migrates in the subependymal layer where it remains as a "subependymal" or "transitional" glia. Tanycytes do not represent an immature form of ependymal cell, nor one of its stages of development; they develop in parallel to ependymal cells. This entails that finding tanycytes in tumors does not imply greater or lesser differentiation. A participation of tanycytes in the development of ependymoma had already been suspected [603]. Recently, however, they have been likened to the elements of pseudorosettes of other oncotypes such as astroblastoma, on the basis of their characteristics, which are intermediate between tanycytes and astrocytes, especially from the ultrastructural point of view [2400].

The last version of the WHO classification [1443] recognizes the ependymoma, an anaplastic variant, a myxopapillary variant, and the subependymoma.

11.1.2 Frequency, Age, Sex, Site

It is a relatively rare tumor and represents 3%–9% of all neuroepithelial tumors [541, 703, 2328, 2772, 1109, 134, 2486]. It is the most frequent neuroepithelial tumor in the spinal cord, representing 50% [1109] or 60% [1404] of such neoplasias.

Ependymoma occurs in all age groups: 7 months–81 years [3138], 1 month–64 years [794] and 4 months–64 years [1506]. In general, the average age of patients when supratentorial tumors appear is greater than for infratentorial ones [703, 2772, 1506, 794], whereas for spinal tumors it is usually higher than for other locations, varying between 30 and 40 years [703, 2328, 3070].

In infancy, this tumor occurs with a high frequency. Ependymomas represent one tenth of intracranial tumors at this age, and it can be said that half of all ependymomas occur in infancy [646]. In one series, they represented 12% of intracranial tumors [1672].

The average age of children with tumors has been calculated to be 5.4 years, with a range of 2 months–16.5 years [3099]. In a personal series [2523] children had 36% of all ependymomas. Ependymomas have been described in breast feeding infants [1444, 1722, 1506, 794, 134], and youngest cases are those described by Fokes and Earle (1969) [794] and Abbott and Namiki (1968) [2] in 4-and 6-week-old infants, respectively. Twenty-three cases diagnosed in the first year of life have been collected in Japan [1519].

The frequency of tumors in the two sexes is about equal.

Ependymomas can occur in any part of the ventricular system but are most common in the posterior fossa, followed by a supratentorial location, the spinal cord and the cauda equina. The ratio between infra- and supratentorial tumors varies according to the series: 70:52 [1506], 86:32 [794], 26:20 [1771], 34:14 [1939], and 30:13 [501]. In a personal series a ratio of 101:72 was found. However, while in adults the frequencies of infratentorial and spinal tumors are similar (30% and 32%, respectively), followed by supratentorial (25%) and by cauda equina/filum terminale (11%), in children the infratentorial location clearly prevailed (57%), followed by the supratentorial (33%), in the first year of life [1519]. Spinal cord and cauda equina/filum terminale tumors are less frequent (3.8% and 5.7%, respectively). In children older than 5–8 years, the relative frequency is the same as in adults.

A primitive location in the pontocerebellar angle is rare; usually, tumors involving the pontocerebellar angle occur in the fourth ventricle. Ependymomas of the foramen of Monro deserve particular mention because of the hydrocephalus they cause and their particular histological problems.

Spinal intramedullary ependymomas may be found at any level, situated between the posterior columns and usually involving more than one segment. Ependymomas of the conus/cauda equina/filum terminale region form a separate group clinicoradiologically and histologically speaking.

Ependymomas may be part of von Recklinghausen's disease or be associated with syringomyelia.

About 40 cases of ectopic, extraspinal ependymomas have been described, mainly located in the presacral region or posterior to the sacral bone [1926]. The most widely accepted theory is that they derive from ectopic remnants of ependymal cells [56].

11.1.3 Macroscopic Appearance

Even if they maintain a close relationship with the ependymal covering, tumors may grow deeply into the white matter of the hemisphere or exit from the ventricular system. Their macroscopic appearance and the extent of diffusion vary depending on the site. In the fourth ventricle (Fig.11.1), tumors usually grow from the floor as small, lobulated, grayish masses. They can fill the ventricle, exit from the foramina, and spread along the cerebral axis. One of the preferred sites for expansion is the pontocerebellar angle. The supratentorial tumors, if they grow into the ventricles, appear as grayish, intraventricular masses (Fig.11.2). If they expand in the white matter, they acquire a grayish-red color and appear well demarcated from the nervous tissue. Sometimes they are cystic and necrotic. Of particular interest are the ependymomas of the foramen of Monro. In the spinal cord, the tumor is more frequently located dorsally, lying between the posterior funiculi, being well circumscribed and extending for one or more segments.

The myxopapillary variant is typical of the cauda equina region. It arises from the conus medullaris and filum terminale. However, tumors with the classic histological aspect may also occur in this location. The tumor presents as a smooth and nodular mass which compresses and wraps around the spinal roots and other local anatomical structures. It may involve the bone and give it a "swollen" appearance. The roots may be infiltrated as well.

11.1.4 Microscopic Appearance

In the typical "cellular" ependymoma, the cells are usually isomorphous and regularly arranged without any particular pattern. Spaces devoid of nuclei, formed by cytoplasmic processes, are called "pseudorosettes" (Fig.11.3). When processes abut upon vessels in a quite regular fashion, the so-called radiated crowns or perivascular pseudorosettes are formed (Fig.11.4). The cells have round nuclei rich in chromatin. The rarer "epithelial" ependymoma is characterized by ependymal rosettes, composed of columnar cells arranged around a more or less large, real lumen. The ependymal canals show the same structure, being elongated instead of spherical (Fig.11.5). Among these formations are tumor cells without "epithelial" features. Blepharoplasts are usually thought to be characteristic of ependymoma. They are small, spherical, intracytoplasmic structures which represent the basal bodies of cilia. They are seen with phosphotungstic hematoxylin stain under oil immersion, especially if within rosettes. Their demonstration, not their absence, is important from the diagnostic point of view.

A rare papillary variant has been described, characterized by papillae which differentiate it from plexus-papilloma, because the epithelium covering their axis is multilayered, and typical structures, such as canals, are also present.

Mitoses are regularly found in variable numbers, especially in supratentorial locations. Blood vessels are numerous, often regularly distributed in groups forming multichannel, vascular structures (Fig.11.6). Sometimes their walls are widely rearranged by thickening and hyalinization. Endothelial hyperplasia may occur up to the formation of glomeruloid structures (Fig.11.7). In some tumors, the stromal component is particularly abundant and active, and in others the number of vessels may be extremely high.

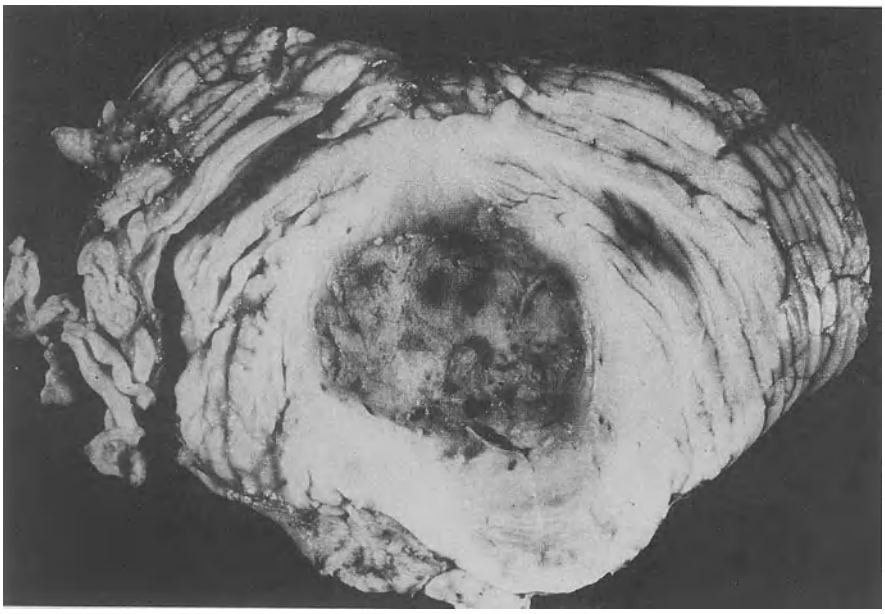


Fig.11.1. Ependymoma of the fourth ventricle

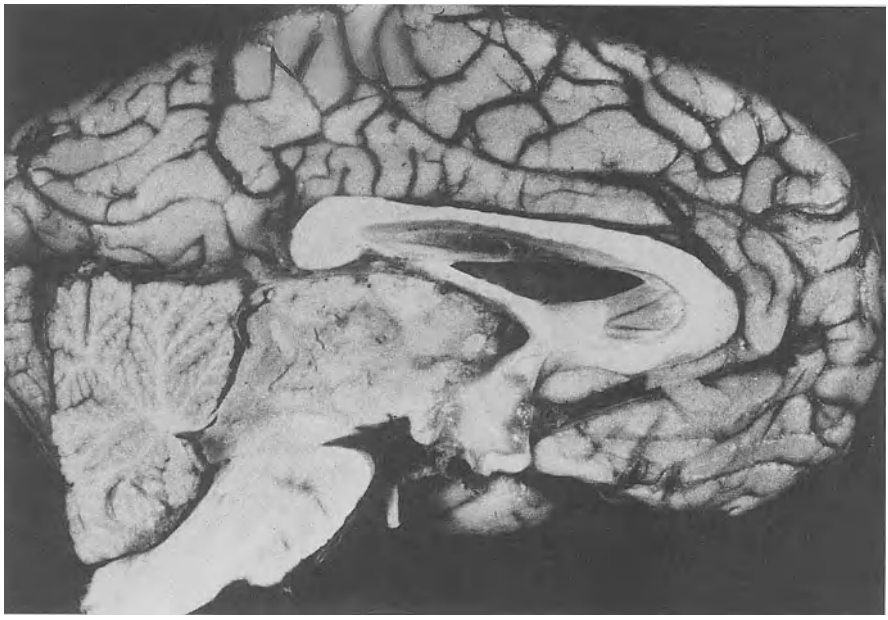


Fig.11.2. Ependymoma of the third ventricle

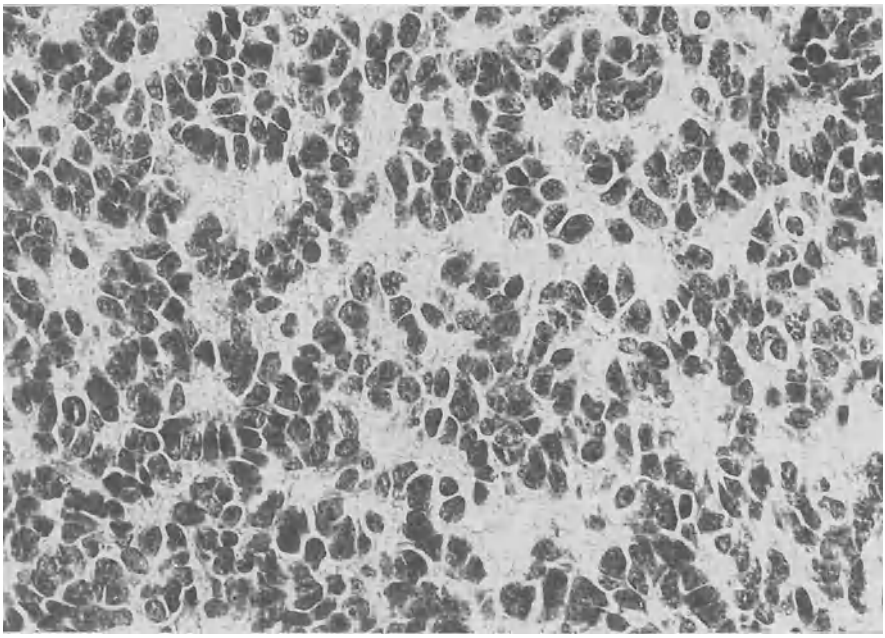


Fig.11.3. Ependymoma, pseudorosettes, H&E, ×400

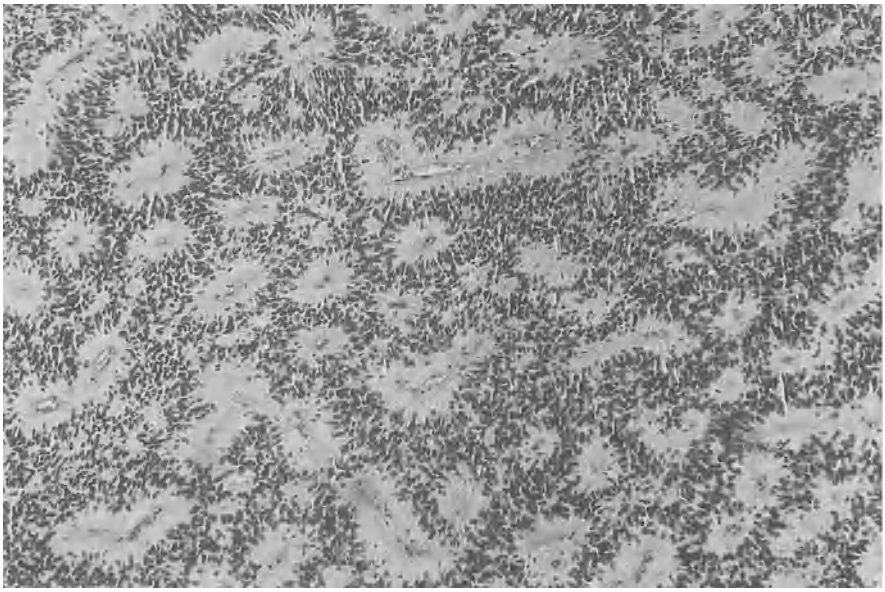


Fig.11.4. Ependymoma, perivascular pseudorosettes, H&E, ×200

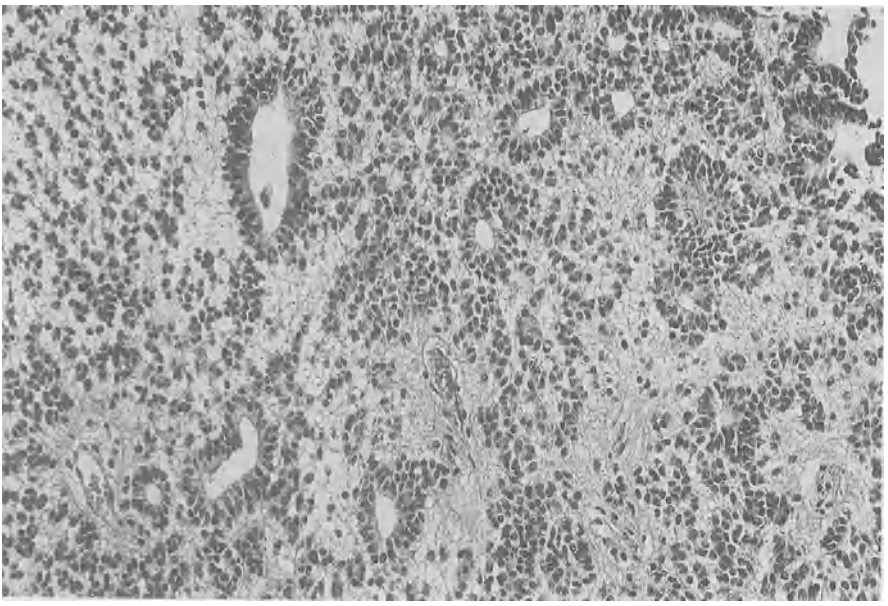


Fig.11.5. Ependymoma, epithelial variant with canals and rosettes, H&E, ×300

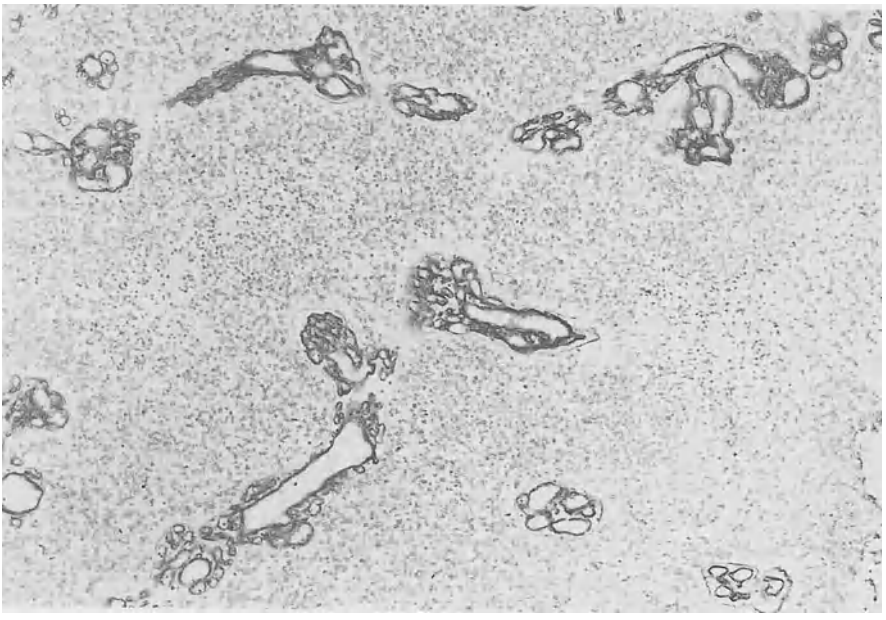


Fig.11.6. Ependymoma, multichannel vascular structures, laminin, PAP-DAB, ×200

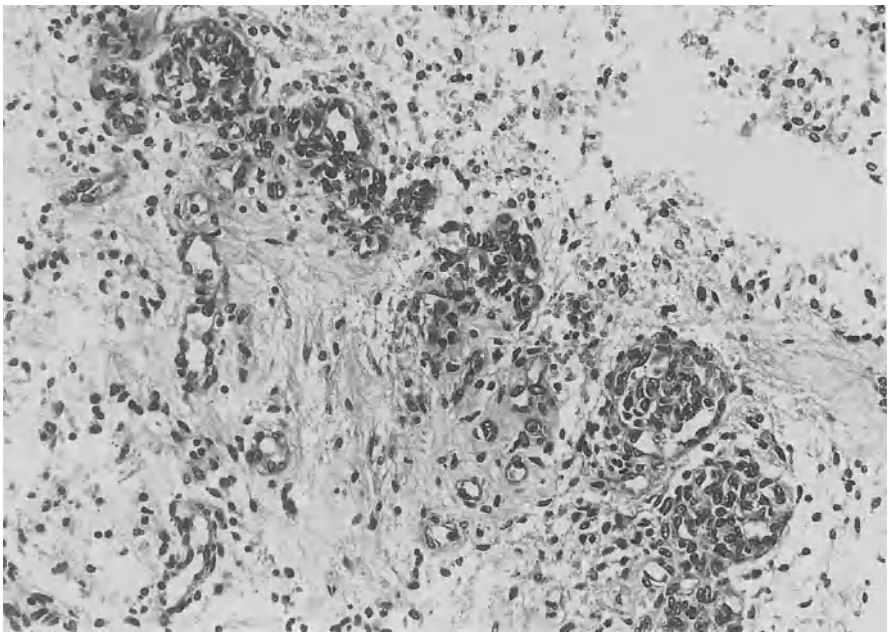


Fig.11.7. Ependymoma, endothelial hyperplasia of glomeruloid aspect, H&E, ×300

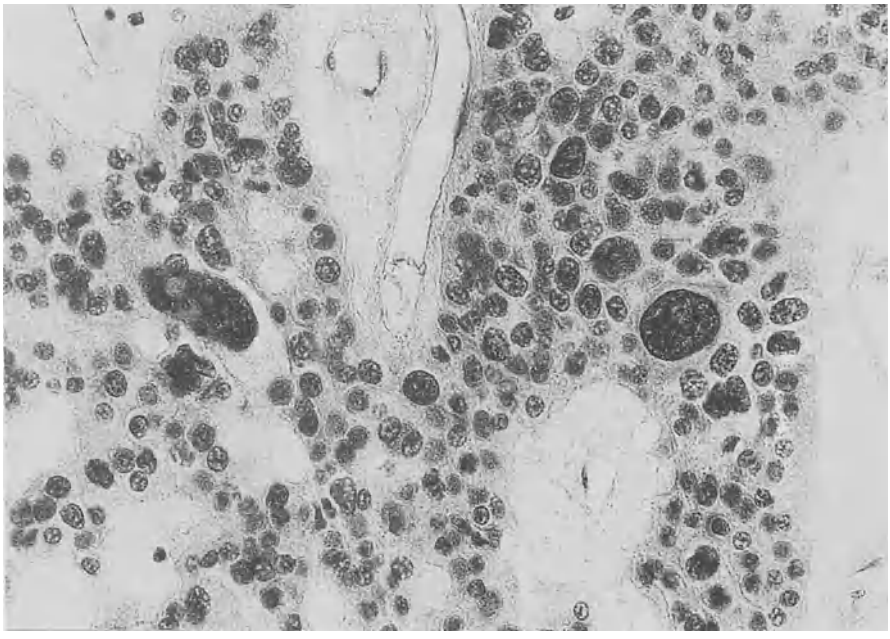


Fig.11.8. Ependymoma, nuclear polymorphism, H&E, ×1000

At the periphery of the tumors and in the peritumoral tissue, intensely GFAP-positive reactive astrocytes may be found.

Cell density, sometimes very high in circumscribed areas, nuclear polymorphism, number of mitoses, and endothelial proliferation vary greatly from one tumor area to another. Nuclear polymorphism may reach the aspect of monstrous nuclei, and round nuclear inclusions are quite frequent (Fig.11.8).

The various cellular features, epithelial and pseudopapillary, as will be said later, can coexist even if with site predilections. For example, the epithelial features are more frequent in the spinal cord. Subependymomatous areas may be present, especially when the tumor is located in the fourth ventricle. Tumors composed of ependymoma and subependymomatous areas are better classified as ependymomas [840]; they are associated with a shorter survival period than subependymomas and show a predilection for the first decade of life [2470, 1325].

11.1.5 Regressive Events

The main regressive events are represented by necrosis, cyst formation, calcifications, and vacuolar degeneration. The cysts, especially frequent in supratentorial locations, are formed following a process of tissue liquefaction. An identical process is at the basis of the oligodendroglial-like features, present especially in ependymomas of the foramen of Monro, for which they are almost characteristic. These tumors are known as "clear cell" ependymomas (Fig.11.9). It has been disputed for a long time whether these aspects represented a true oligodendroglial differentiation [1403, 1070] or whether they are secondary aspects [2328, 1385]. Under the electron microscope, these cells show junctional complexes, microvilli, and cilia. They are, therefore, to be considered ependymal [1367].

The intervasal tissue liquefaction may give rise to tissue rarefaction with the formation of GFAP-positive stellate cellular elements. The astrocytic features, however, are not necessarily to be interpreted as secondary.

Myxomatous degeneration, present almost exclusively in spinal locations of the filum terminale, constitutes a regressive phenomenon which is fairly characteristic. It seems to be due to the effect of pressure atrophy, which causes intervasal cell disappearance and hyaline-mucoid degeneration of the vessel walls with the secondary formation of papillary structures. The end process is characterized by the presence of hyalin-mucoid clods, positive on mucin and alcian blue staining, bordered by a thin crown of cuboid or columnar cells. The papilliform aspect seems to be due to swelling of the vessel wall caused by various factors, vascular, mechanical, and so forth, peculiar to the location. Radiated crowns are widely modified: Either the processes are no longer visible because of the swelling of the vessel walls, or they are very long (Fig.11.10). The myxopapillary ependymoma is not, therefore, a type per se, but a type of cellular ependymoma resulting from degenerative changes.

The various regressive events mostly involve the parenchyma away from blood vessels. They may lead to the formation of pseudopapillae resulting from intervascular degeneration with preservation of the cells, forming perivascular crowns. This mechanism is at the basis of the pseudopapillary variety of ependymoma.

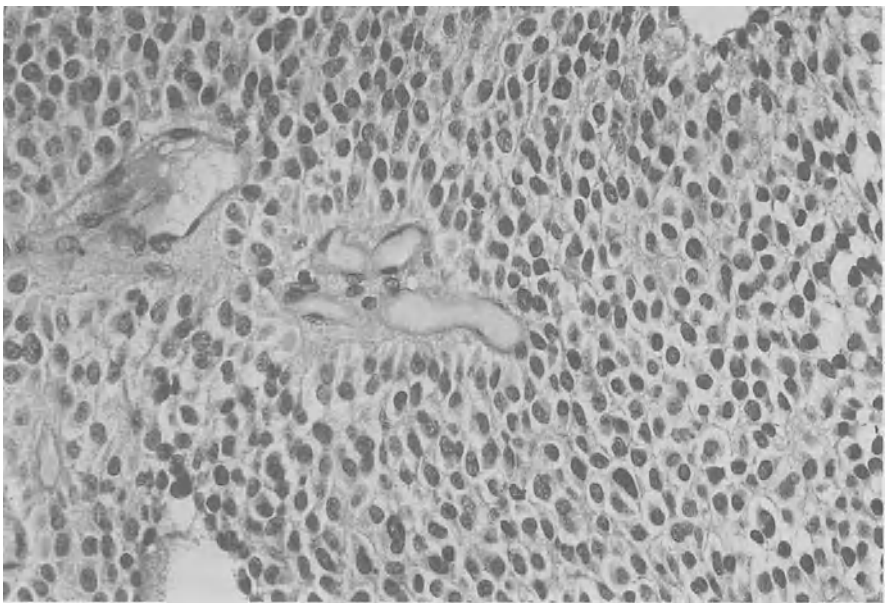


Fig.11.9. Ependymoma, clear cell tumor, H&E, ×400

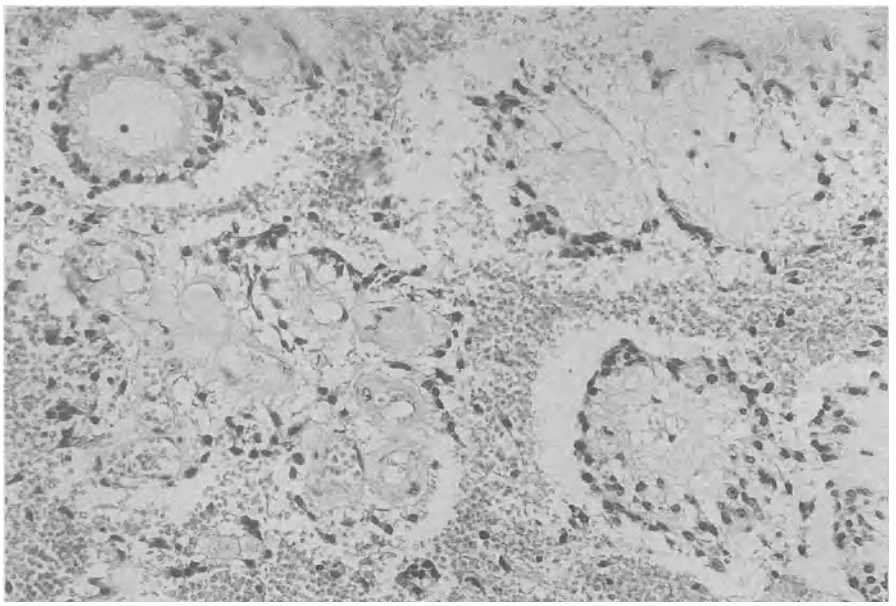


Fig.11.10. Myxopapillary ependymoma, degeneration of the vessel walls and deformed perivascular structures, H&E, ×300

Particularly frequent in this tumor are calcifications, which are sometimes also visible radiologically. In fact, they have been observed on X-radiographs in 30%–40% of cases [370]. Histologically, they are found in 20%–50% of cases [775, 2772, 1784, 2481].

Necroses are very frequent. They may appear as circumscribed necroses with pseudo-palisadings, as in gliomas, as wide areas, or as very small spots, just composed of a few necrotic cells (cellular necrosis) (Fig.11.11).

Positive correlations exist between site, age, and histological appearance. In supratentorial tumors of adults, for example, mitoses (>5 per 10 HPF), the anaplastic variant, oligodendroglial features, and endothelial proliferations prevail. In infratentorial locations, the same oligodendroglial features and perivascular infiltrates are more common. In spinal tumors, few mitoses (<5 per 10 HPF), low cell density, and myxopapillary appearance are more frequent. In children, subependymomatous features in ependymomas and subependymomas occur in the infratentorial location. In relation to age, it is useful to remember that tumors occurring in infants under 1 year old are more often of the anaplastic variety, have mitotic activity (>5 per 10 HPF), and often feature necrosis [2523].

11.1.6 Immunohistochemistry

GFAP is variably positive in ependymomas (Fig.11.12). It is strongly positive in subependymomas, underlining their astrocytic and ependymal character [2903]. In general, this is also true in cells of astrocytic origin [681], mainly in cells of perivascular pseudorosettes, elongated and with "carrot"-shaped processes (Fig.11.12a). In rosettes and canals, staining is usually negative in the luminal pole of the cells and positive in the mesenchymal pole. In papillae, positive cells alternate with negative cells (Fig.11.12b), as can be observed in tanycytic derivatives of the lining of the third ventricle. Reactive as-

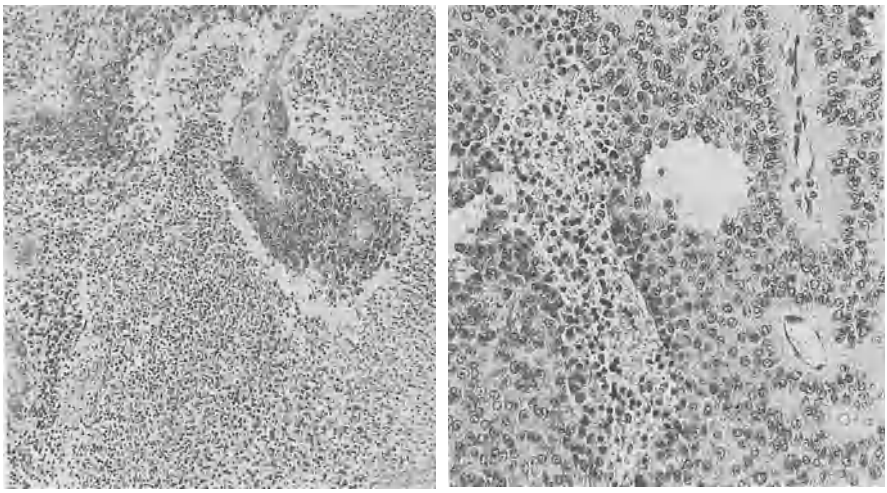


Fig.11.11a,b. Ependymoma: **a** wide necrosis, H&E, ×150; **b** small focal necrosis, H&E ×400

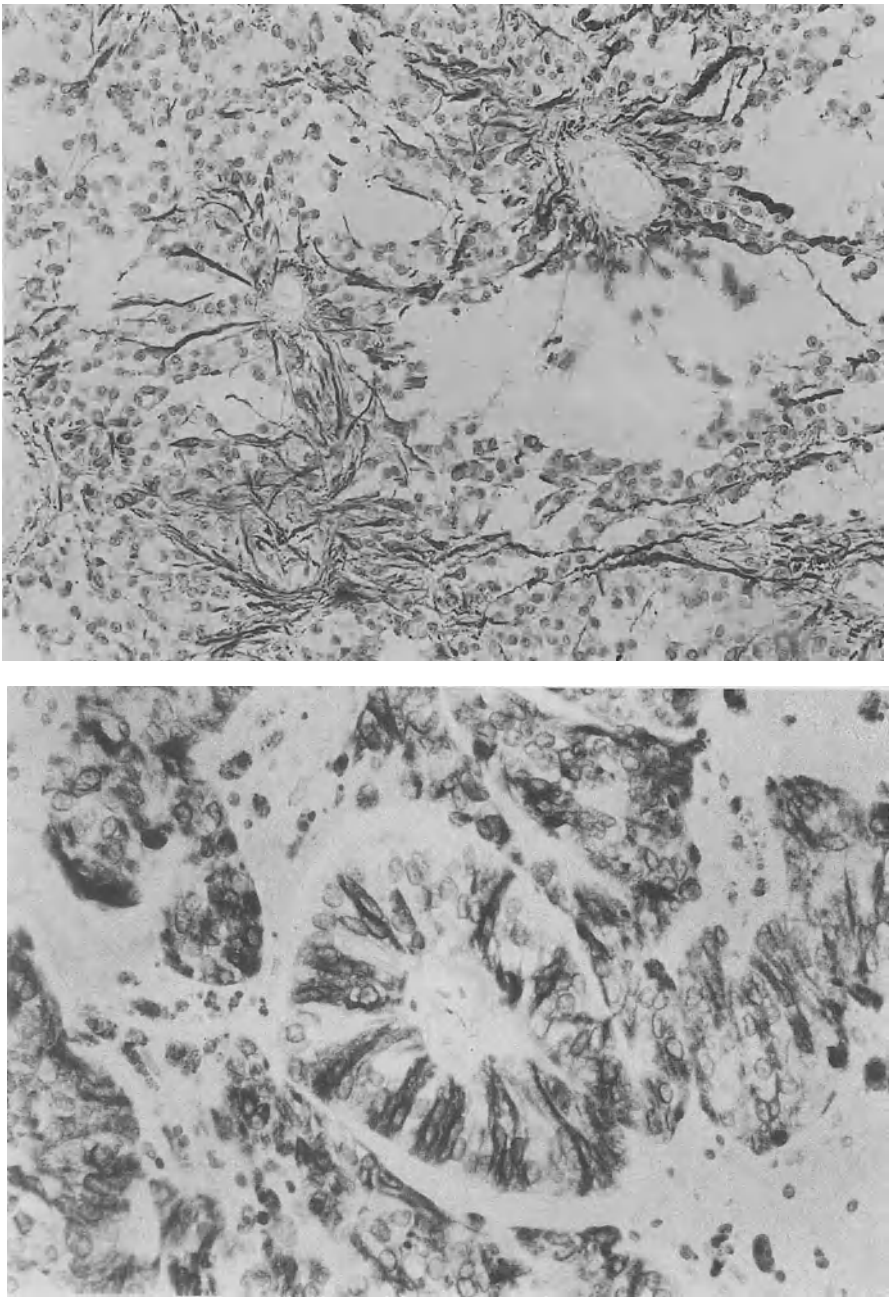


Fig.11.12a,b. Ependymoma: **a** GFAP-positive processes in perivascular pseudorosettes, PAP-DAB, ×300; **b** GFAP-positive cells alternate with negative ones in papillae, PAP-DAB, ×400

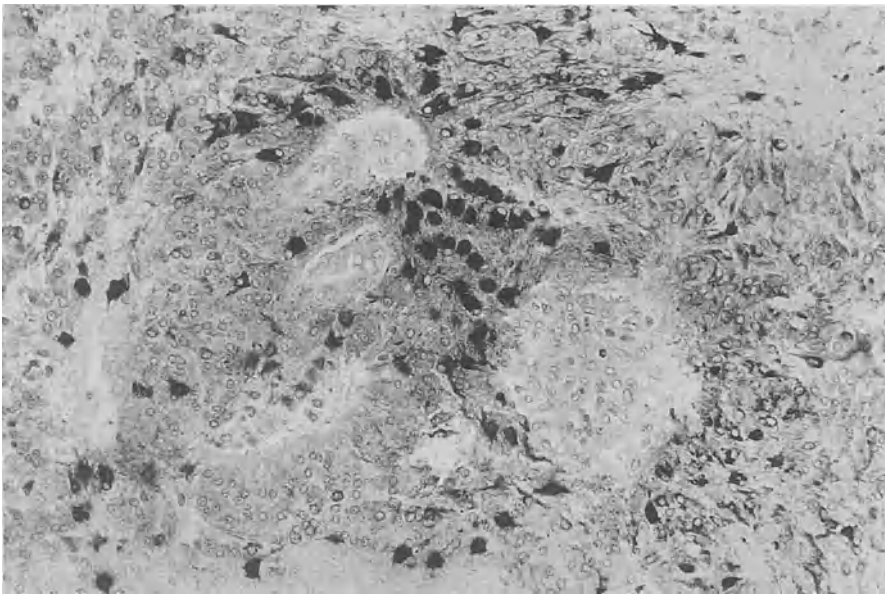


Fig.11.13. Ependymoma, GFAP-positive astrocytes in the tumor, PAP-DAB, ×400

trocytes around or within the tumor, as well as the tumor astrocytes scattered in the tumor or concentrated in areas, are also GFAP-positive (Fig.11.13). The scarce positivity of areas among vessels demonstrates that the tanycytes, possible progenitors of GFAP-positive cells according to some authors [603], only give rise to a small proportion of the cells in ependymomas [681]. Positive, multipolar astrocytes are present. They have received a special interpretation in the formal genesis of the tumor [2923].

The GFAP-positivity in ependymomas has been greatly debated. The findings that intracytoplasmic filaments are present both in normal and neoplastic ependymocytes [2188, 2419, 830], that in culture these filaments show immunologic identity with the astroglial ones [2955], and that normal adult ependymocytes, except tanycytes, do not express GFAP may mean that in tumors the ependymocytes revert to more immature stages and become capable once again of expressing GFAP [2343].

The problem of the relationships between GFAP synthesis in normal and tumor ependymocytes and astrocytes has not been fully clarified. First of all, adult ependymocytes do not contain GFAP [1708, 603, 710, 2923], although they do contain bundles of intermediate filaments [2188] which are similar to astroglial filaments and give a positive reaction for GFAP [2464, 1820]. In man, from the 15th week of gestation to birth, the ependymocytes contain GFAP which they will lose in adulthood. The appearance of GFAP when mitotic activity decreases represents a sign of differentiation [2343]. It is, therefore, possible that in tumor or reactive ependymocytes [482], GFAP is synthesized and visible, while in normal adult ependymocytes GFAP is produced but not in such quantities as to be visible immunohistochemically. Ependymal cells might be capable of assembling more than one type of intermediate filament, as has been demonstrated in astrocytes [2113]. Tanycytes also contain GFAP during development [262], and not all become negative in adult life.

S-100 protein has the same distribution as GFAP [2789, 1423].

The application of immunohistochemical techniques brought the old problem of the transition towards plexus papilloma back to the fore. In this tumor there are foci of

GFAP-positive cells, which suggest its ependymal differentiation (see plexus-papilloma), whereas in ependymomas, in contrast to previous studies [465, 1884], cytokeratin-positivity has been reported [1755]. Also, this finding would be indicative of transition.

11.1.7 Electron Microscopy

In general, the ultrastructural characteristics of ependymoma cells are those of normal ependyma [2825, 284], i.e., the presence of cilia and microvilli on the luminal surface, junctional complexes on the lateral surfaces of the cytoplasm, and no basement membrane on the internal surface (Fig.11.14) [1133]. Junctional complexes have a slit-like shape, with a 200-Å space between the cytoplasmic membranes and with the zonula adherens located in proximity to the microvilli abutting upon a dilated extracellular space. The segments of these membranes are parallel and dense, with condensation of the adjacent cytoplasm. More rarely, zonulae occludentes with an internal space of 100 Å are found near the junctional complex. All these formations are found in well differentiated ependymomas [2805].

The nuclei are large, the nucleoli are visible, the mitochondria are clustered, the endoplasmic reticulum and ribosomes are scarce, and only a few Golgi apparatus are found. Cilia projecting outside the cells and intracytoplasmic cilia are common. Microvilli containing filaments and tubules together with cilia project into an extracellular lumen formed by several cells. This represents a microrosette (Fig.11.15), which has no counterpart in light microscopy [948].

Processes can be found containing IF with or without ependymal features (junctions), which stain immunoelectron microscopically for GFAP (Fig.11.16). They represent either the capacity of ependymoma cells to express IF or the occurrence of astrocytic processes in the tumor.

The presence of two cellular poles, one luminal and the other submesenchymal, seems to be very important [830]. The luminal poles are formed by epithelium with microvilli; the cells are joined by zonulae adherentes, with rare cilia. The submesenchymal or glial poles are formed by parallel processes shaped like a mushroom which ends on a mesenchymal vascular surface. The cytoplasm contains 70–90 Å filaments. At some distance from the mesenchymal surfaces, there are bundles of processes filled with glial filaments, which form the perivascular pseudorosettes. Filaments are also found in the cytoplasm, towards the luminal surface, but here they are less numerous. Large masses of clustered cell bodies without polarity and with astrocytic features are found. The existence of these forms recalls the problem of GFAP expression, i.e., occurrence of tumor astrocytes or gliofibrillogenesis by ependymocytes.

In the myxopapillary ependymoma of the filum terminale, the cells do not express polarity, but their junctions are of the zonulae adherentes type with a cytoplasmic thickening, a 200–250 Å wide space containing amorphous material, or a loose network of filaments [2283, 2700]. Extracellular spaces are formed and delimited by cells containing collagen fibers a basal membrane. At times, microvilli project into these spaces [2283]. Junctions of septate type, typical of the epithelium of invertebrates, have also been described [1155].

Cilia and blepharoplasts are infrequent; however, many cells have atypical cilia. The cytoplasm contains cisternae of the endoplasmic reticulum, ribosomes, mitochondria, glycogen granules and liposomes. The majority of processes contain 70–90 Å microfilaments and 240 Å microtubules. The basal membrane of capillaries forms the internal basal membrane of the perivascular space. The behavior of the basal membranes

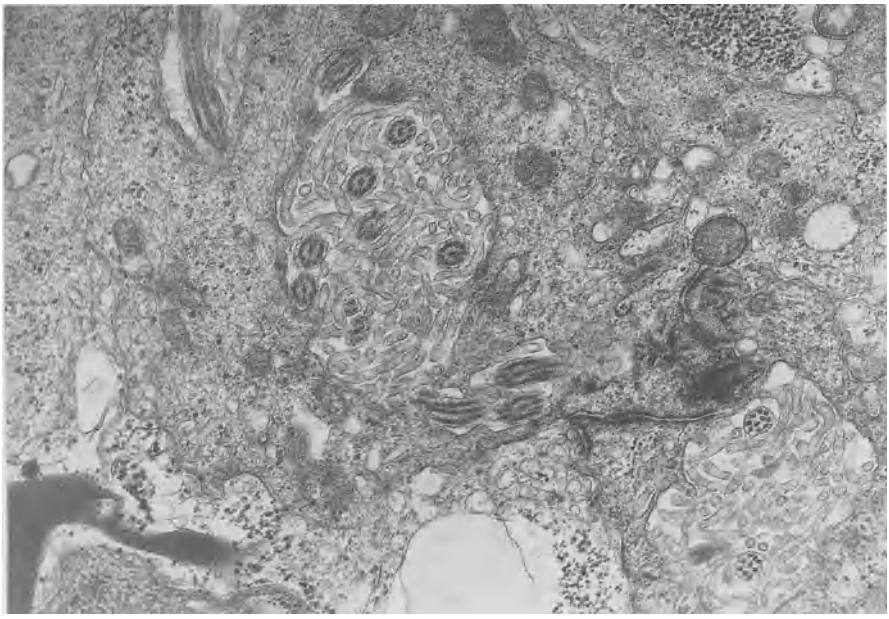


Fig.11.14. Ependymoma, typical ultrastructural features are cilia, microvilli and tight junctions, ×32,000

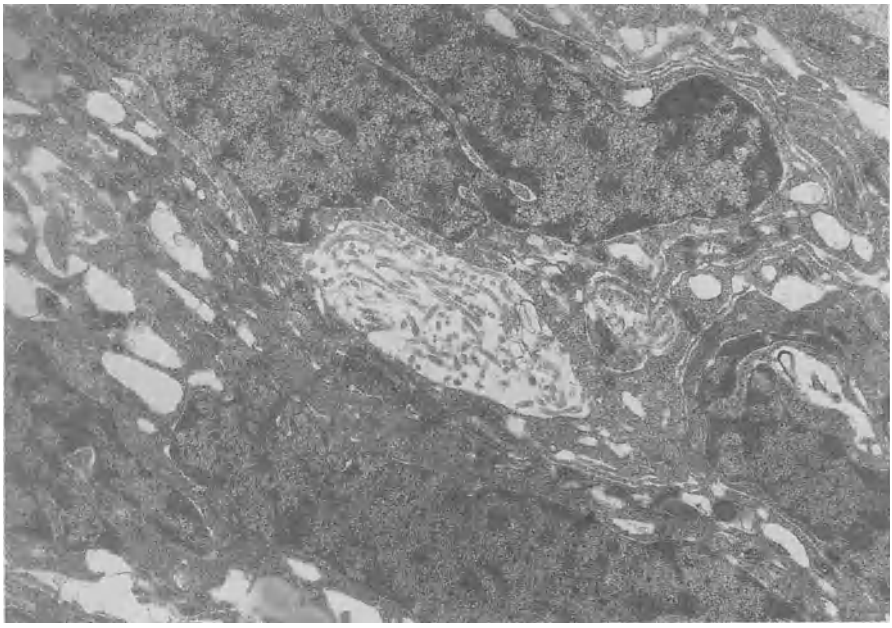


Fig.11.15. Ependymoma, microrosette ×20,000

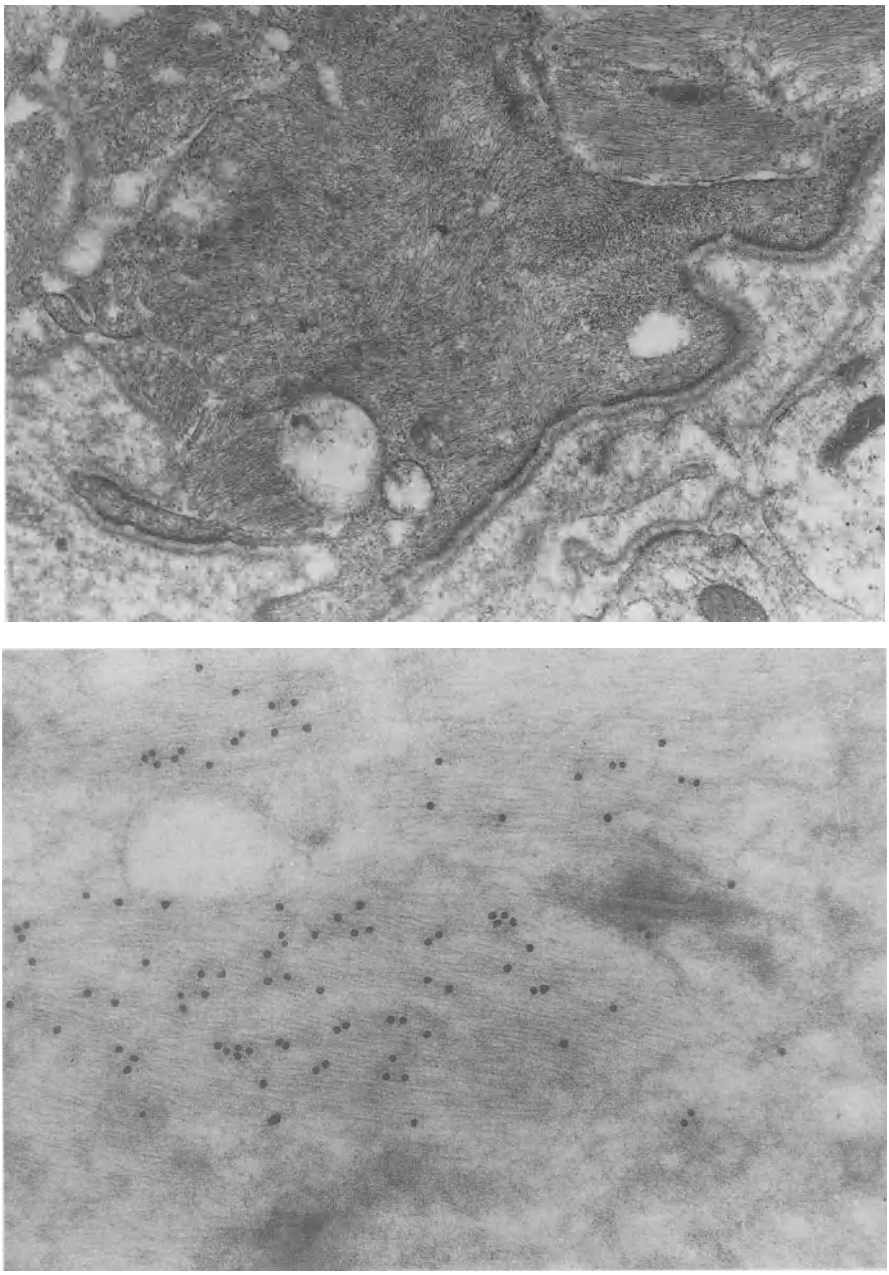


Fig.11.16. Ependymoma: **a** IF coexist with junctional devices, ×35,000; **b** immunogold granules for GFAP on IFs associated with junctions, ×50,000

is peculiar to myxopapillary ependymoma and, together with the paucity of cilia, relates it to the choroid plexus. In fact, in the latter, the cells are separated from the stroma by a basement membrane [644], while ependymal cells do not have a basal membrane towards the neuropil. In myxopapillary ependymoma, the ependymal cells rest on connective tissue instead of lying on the neuropil as in other regions of the CNS.

11.1.8 Anaplastic Ependymoma

The ependymoma is usually thought to be a relatively "benign" tumor with rare malignant forms. Four histological grades of malignancy have been recognized [1405]. In general, a malignant ependymoma is identified because of nuclear polymorphism, high cellular density, necrosis, and endothelial proliferation, as in glioblastoma [2328, 1109]. The existence of an ependymal glioblastoma has also been discussed [1109]. This is to be identified with the ependymal spongioblastoma of Globus and Kuhlenbeck (1944) [943].

The application of "grading" [1405] did not lead to a precise correlation between histological features and survival. It has been regarded either as useless [1506, 794, 3019] or as useful [985, 16]. According to some, a subdivision into three grades on the basis of cell density, number of mitoses, circumscribed necroses, and endothelial proliferations would have a predictive value [2978, 70, 1284].

The malignant variant is characterized by nuclear polymorphism, giant cells, mitoses, and endothelial proliferation, but at least part of the tumor must maintain characteristics typical of ependymoma [2420]. Even by applying these criteria to define anaplastic ependymoma, various authors have found poor [1939] or barely enough correlation with survival [426].

This is not surprising if one thinks that in six out of nine series considered, the number of high grade tumors varied between 40% and 94% [3019]. Evidently, a notable uncertainty in the identification of the malignant variant does exist. The problem is further complicated by the use of the term ependymoblastoma to indicate the malignant variant, instead of a rare tumor with peculiar features of its own [2389], as will be mentioned later.

The identification of malignant tumors has also been tried by means of DNA microdensitometric analysis [1968] and flow cytometry [1606, 2696]. Results have been equivocal, not definitive. The LI after in vivo administration of BUdR has been found to be high in three of eight tumors, but only one of the three had histological features of malignancy, though all three tumors were clinically aggressive [1991].

From what has been said, it can be deduced that there is a great uncertainty in the identification of the malignant variant of ependymoma. First of all, the prognostic significance of its histological features is still being debated. A multivariate analysis of 102 cases [1244] demonstrated that site and age, but not mitotic activity, have a prognostic significance. In the posterior fossa, the prognosis is better in adults than in children; and the presence of rosettes and subependymomatous areas indicate a poor and a good prognosis respectively. These findings, however, have not been confirmed in another series of 62 cases [2282], where the only prognostic element was the presence of microcysts in supratentorial tumors (favorable prognosis). In this series, it has to be noted that cases

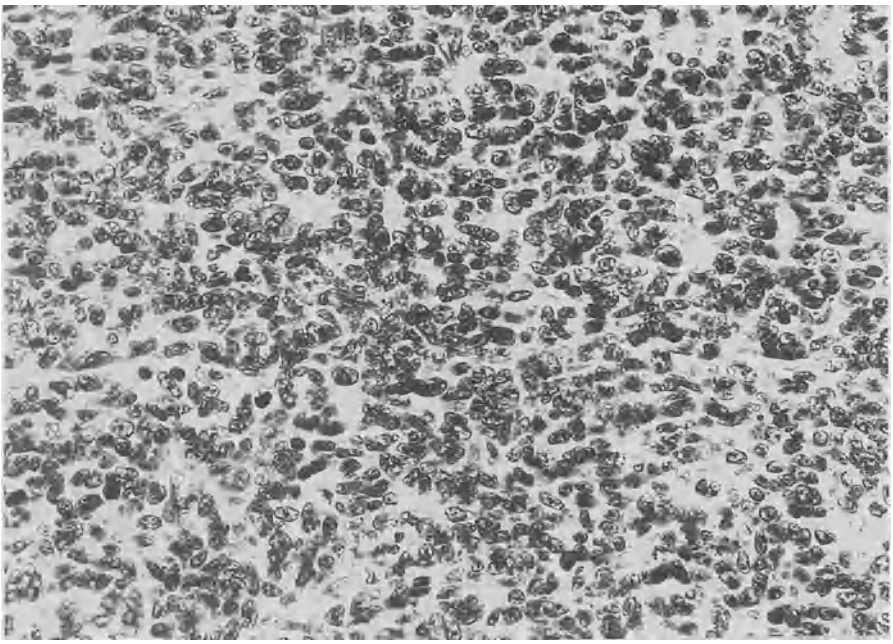


Fig.11.17. Anaplastic ependymoma, very high cell density, H&E, ×400

diagnosed as anaplastic had the same postoperative survival as classic types. Also, in a series of 15 cases diagnosed as malignant on the basis of common histological criteria, the survival was not much different from classic cases [2369].

The reason for this failure may, in part, be the limited number of cases collected in each series, taking into account the different sites of the tumors, the diverse histological features, and the distribution over a wide range of ages. In a large series of 360 cases in childhood [922], posterior fossa tumors with benign histological features showed, paradoxically, a worse prognosis. Histological features associated with a poor prognosis are an abundance of blood vessels, endothelial hyperplasia, mitoses, calcifications, and low cell density. Histological features found in tumors with a good prognosis are astrocytic areas, high cell density, and irregular nuclei. The classic histological variants have no correlation with survival [2354]. In 16 infratentorial ependymomas of childhood, more than 5 mitoses per 10 HPF, large amounts of necrosis, and complete loss of differentiation were indicative of poor prognosis; by contrast, tumors with diffuse expression of GFAP showed a good prognosis [773A].

In a personal series of 298 cases, the malignant variant, diagnosed with the same histological criteria used for gliomas, does not correlate with survival. After multivariate analysis by tumor site, the number of mitoses (>20 per 10 HPF), cell density, and age (<4 years) were prognostic factors in supratentorial tumors. No prognostic factors, with the exception of subependymoma, have been found in infratentorial and other locations [2523]. Only supratentorial cases characterized by a very high cell density (Fig.11.17) and a large number of mitoses (>20 per 10 HPF) showed statistically signif-

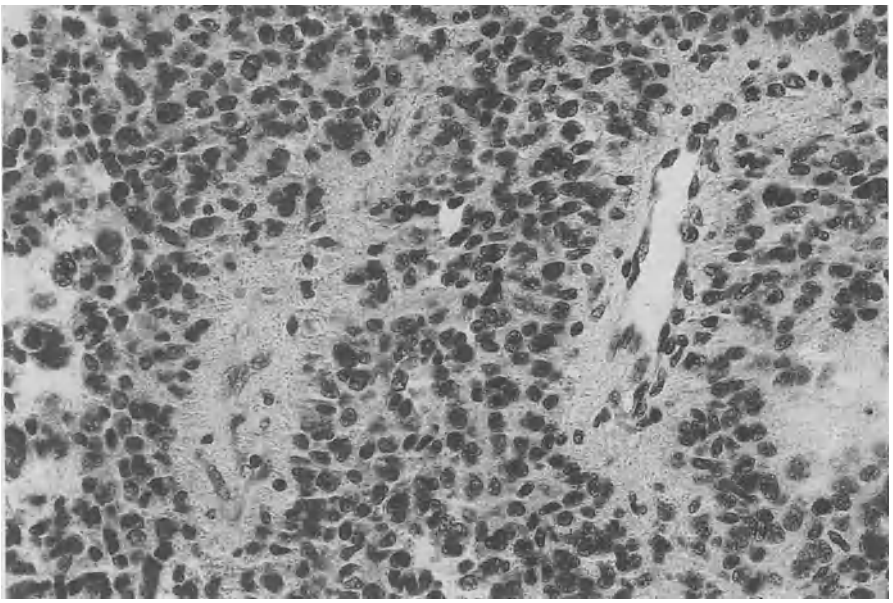


Fig.11.18. Anaplastic ependymoma, incomplete perivascular pseudorosettes, H&E, ×400

icant shorter survival periods [2524]. A high cell density and a large number of mitoses are, on the other hand, the direct signs of malignancy, applying the concepts, today widely accepted, of tumor progression and anaplasia. In these cases, perivascular pseudorosettes are incomplete and barely recognizable (Fig.11.18).

11.1.9 Spread Via the Cerebrospinal Fluid

The frequency of spread via the CSF is extremely variable, from 0% to 60% [2427, 268, 134]. Higher percentages are obviously encountered in anatomically based series [229, 2433]. CSF dissemination is more frequent when tumors are located below the tentorium [2199, 3019] and, it seems, in the more malignant tumors [229, 2433]. It appears, therefore, that the risk of CSF dissemination is higher in malignant infratentorial tumors [1419, 2433, 1533, 473], moderate in malignant supratentorial tumors [1672, 882], and minimal in the remainder, taking into account all the reservations which apply to the term malignant.

11.1.10 Treatment and Prognosis

Treatment of ependymomas is, in the first instance, surgical resection. Although some ependymomas may be totally removed, the 5-year survival after surgery alone is 20% [794, 1939]. Postoperative irradiation (50–60 Gy) prolongs survival up to 40%–50% at

5 years [1307, 1607]. In principle, the prognosis of intracranial tumors is clearly worse than that of tumors of the spinal cord [2638, 1939], even if the survival figures may improve by including subependymomas [1244]. Similar figures are obtained for posterior fossa tumors.

The prognosis of intracranial ependymomas is worse in children [134, 1244, 3019]. Survival rates at 3 and 5 years were 23.3% and 12.5%, respectively, 34.5% and 19.5% for benign tumors and 0% for malignant tumors [501]. In another series survival at 5 years was 51% (without postoperative mortality), with no difference between supratentorial and infratentorial locations, but with a worse prognosis in children under 2 years of age [2199]. In the first year of life the prognosis is very poor, especially for infratentorial locations [1519]. In a personal infant series, age below 2 years was a negative prognostic factor. In a recent series, 3- and 5-year survivors without tumor progression were 46% and 30% respectively. Positive prognostic factors were age greater than 4 years, local radiation dose >45 Gy, and Caucasian race. Factors without influence on the prognosis were the amount of tumor removed, its histological grade, the radiation field, and the chemotherapy used [967]. Tumors usually recur locally.

Taking into account the risk of CSF spread, craniospinal irradiation has been advocated for all high grade tumors [2434]. However, according to some this form of treatment does not seem to ameliorate the prognosis [967], with local relapse remaining the most significant component of failure [968]. Chemotherapy did not help except [1603] in cases with a very poor prognosis. The lack of local control of the tumor remains the reason for therapeutic failure.

A particular problem is the spinal cord ependymoma. It is known that complete surgical removal of spinal cord tumors, using microsurgery techniques, can give excellent local control and survival rates [782, 491]. Postoperative radiotherapy is, therefore, not recommended in such cases. It is recommended, however, in cases of incomplete removal, as improved long-term survival rates resulted at 5 and 10 years 100% and 73% [1481], 87% and 67% [449], and 69% and 62% [3030], respectively. The recommended dose of radiotherapy is 40–45 Gy.

Spinal cord ependymoma may often be totally excised with a very good prognosis with long survival even when the removal has not been complete.

Myxopapillary ependymomas of the cauda equina are associated with a significantly better survival rate than tumors in other sites. They show a mean survival of 19 and 14 years, respectively, after total or partial removal [2695], and radiotherapy has been suggested only when gross tumor remains [2615]. In some cases late recurrences and distant metastases, even with a totally benign histological aspect, have been reported [1826, 2401, 1926, 572]. It is possible that late distant recurrences are due to retrograde seeding, as, for example, in the cases of Davis and Barnard (1985) [572] where the distant recurrences were in the fourth ventricle or in the anterior and posterior fossae.

11.2 Subependymoma

Very often, subependymoma is an asymptomatic tumor, located in close proximity to the ventricular walls, which may be accidentally found at autopsy after the fifth decade. The tumors are small, round or lobulated and localized mainly to the fourth and third

ventricles, but they also occur in the lateral ventricles, septum pellucidum, aqueduct, and spinal cord [826, 272, 2438, 1679, 82]. In the fourth ventricle they originate mostly from the floor and rarely from the roof [1325]. Eight symptomatic cases have been reported [2914] in the cervical spinal cord. They are more rare in the thoracolumbar location [1017].

Asymptomatic tumors are found preferentially in the fourth ventricle. Multiple subependymomas have been described in the fourth ventricle [415] or in association with cerebellar astrocytoma [415] or with plexus-papilloma [2420]. Seven cases were originally described by Scheinker (1948) [2469], while 21 [272] and 36 [415] were reviewed from the literature. Every so often, isolated cases are reported. The term "subependymal mixed glioma" was used because of the contemporaneous presence of ependymal cells and of astrocytes [415]. Subependymoma has been described as characterized by small glial cell groups of subependymal glial type, alternating with areas containing glial fibers. The tumor originates from the subependymal glia [2469]. It cannot be identified with the ependymal spongioblastoma of Globus and Kuhlenbeck [1944], because it is a benign, differentiated, and mature tumor, whereas the latter is a malignant, immature one.

Subependymoma has been considered either as an ependymoma with secondary pressure atrophy [3134] or as a tumor with inactive growth, representing an arrested stage of a benign tumor or an inert lesion, such as for example, a hamartoma [1149, 1478, 2420] It is, however, included in the ependymoma group because of the marked variability of the astroglial component, even though in the nomenclature used by some [826], such as that of "subependymal astrocytoma," the astroglial component is considered to be fundamental.

Besides the hypothesis that these tumors originate from subependymal glia [98, 1951], other proposed origins are from astrocytes of the subependymal plate [2468, 826, 272, 947], from ependymal cells [2420], or from a mixture of astrocytes and ependymal cells [415, 840, 2470]. The tumor has also been considered as a reactive proliferation of the subependymal glia due to hydrocephalus and chronic ependymitis [2420].

Very often, subependymomatous features are found in association with classic ependymomas.

Histologically, the tumors are characterized by clusters of nuclei distributed over a thick fibrillary background formed by cell processes (Fig.11.19). The nuclei resemble those of ependymal cells. In some cases, the processes have a clear arrangement around the blood vessels which recalls that of the ependymomatous pseudorosettes or of astroblasts. Mitoses are rare and calcifications frequent. GFAP staining is usually positive, both in the fibrous bundles and in the cells of astrocytic type [2903, 681].

Vessels are scarce, but often they appear grouped together and show endothelial proliferations, even with mitoses. Sometimes they form a wall. In one case, sarcomatous proliferation started from the vasculature of a subependymoma, forming a sarcomatous tumor [1693].

Electron microscopy demonstrates the presence of characteristics of ependymal cells [98], including blepharoplasts, but also many cells rich in IF with typical astrocytic characteristics (Fig.11.20).

The tumor appears in all age groups. There is generally a long preoperative history, and it may be diagnosed by CT or MRI. Surgically, the tumor may be easily removed from some sites (lateral ventricles), but in others such as the fourth ventricle it is ex-

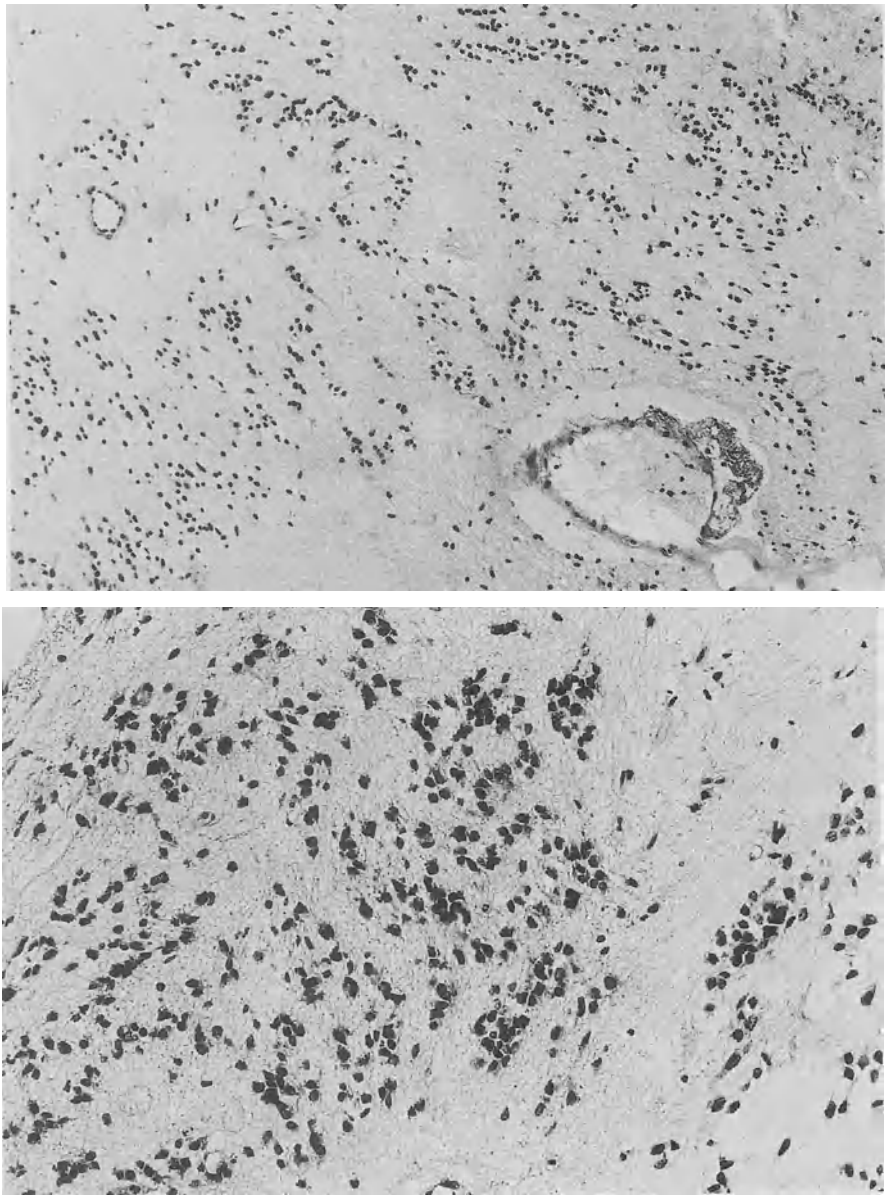


Fig.11.19. Subependymoma: **a** clusters of cells in fibrous fields, H&E, ×150; **b** cluster of cells with intermediate characters between astrocytes and ependymocytes, H&E, ×300

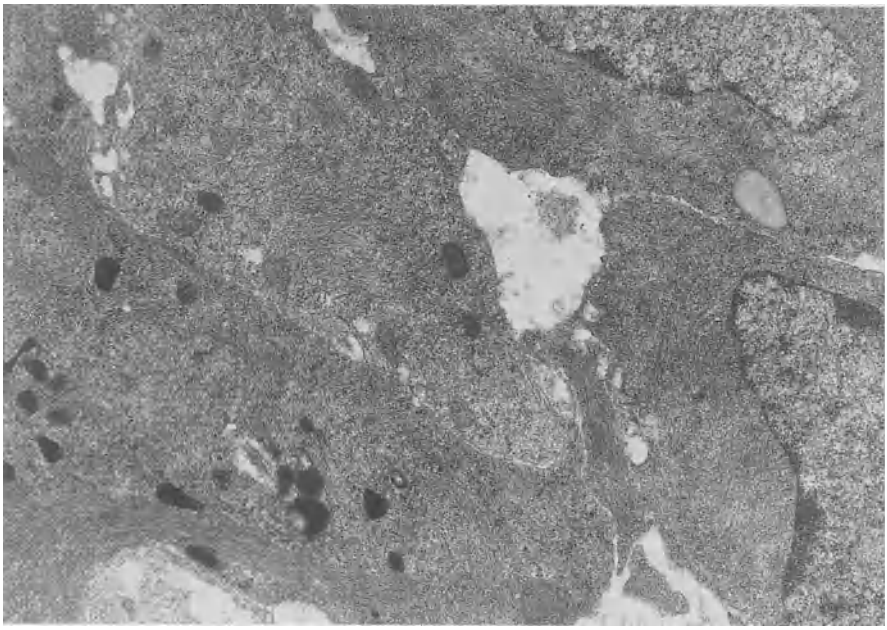


Fig.11.20. Subependymoma, cell processes rich in IFs, ×20,000

tremely difficult or impossible [1325]. In treatable cases, the prognosis is good. The tumor is histologically benign, even if nuclear polymorphism and endothelial proliferation are present. The hypothesis has been put forward that cases with more evident polymorphism and with the highest proliferative index, as judged by flow cytometry, might be more aggressive. This has not been confirmed by survival studies [1808].

Various hypotheses have been put forward to clarify the pathogenesis of this ependymoma variant. Other than the one already mentioned, some believe that the tumor represents an arrested stage of development of the ependymoma [2420]. The hamartomatous hypothesis must also be considered [1149].

11.3 Ependymoblastoma

The term ependymoblastoma has been and is being used to indicate the malignant or anaplastic variant of ependymoma. In reality, in the original concept of Bailey and Cushing (1926) [112], the term was used to indicate a more immature tumor deriving from the so-called ependymal spongioblasts, in contrast to the term "ependymoma" which indicated more differentiated tumors. It must be taken into account that later, in fact, the term was applied to a rare, immature, ependymal tumor, one considered to be a tumor entity [2389]. This is an embryonal-type tumor of the young, which features mitoses in the ependymal rosettes. Other cases have been described [2086, 2246, 1691, 529]. Eleven cases in the literature have been reviewed [1940].

The tumor arises in the first 5 years of life, occurring infra- and supratentorially and also in relationship with the ventricular system. It is large and circumscribed and sometimes has a necrotic-haemorrhagic appearance. In a personal collection of 298 ependymomas, there are 2 cases. Histologically, it is composed of trellises of crowded cells, separated by thin blood vessels. The cells are oval or elongated and poorly differentiated. Numerous mitoses are present. Perivascular pseudorosettes are not present, but there are numerous ependymal rosettes and tubules. The rosettes are formed by multiple layers and feature luminal mitoses. They resemble the Flexner–Wintersteiner rosettes of retinoblastoma and are distinguished from the rosettes of an ependymoma because the latter are not multilayered and have no mitoses. The internal lumen is delimited by an internal membrane. Blepharoplasts are present, but endothelial proliferation is not. The border with the nervous system may be clear-cut or ill-defined due to diffuse infiltration.

The tumors described have been variously treated and carry an average survival of 12 months.

The tumor corresponds to the time when the primitive cells delimiting the neural tube acquire distinctive characteristics of ependymal cells, with the development of cilia and blepharoplasts. Therefore, it shows ependymal differentiation but retains mitotic activity [1940].

In the classification proposed by Rorke [2353], the ependymoblastoma is considered to be a PNET with ependymal differentiation, but in the 1991 WHO classification [1443], it is considered an embryonal tumor.

A congenital case in the sacrococcygeal region in a neonate [1973] and another in the cerebellodiencephalic region [697] have been described.

12 Choroid Plexus Tumors

12.1 Plexus-Papilloma

The plexus-papilloma was the subject of several reports in the last century. After much debate, it was considered to be a tumor entity separate from the ependymomas [2380, 106], put into the group of paragliomas [1189], and then reconsidered as a subgroup of ependymoma [1403, 1405]. It derives from the epithelium of the choroid plexus, which in turn represents the differentiation of primitive neuroepithelial elements which come into contact with the intraventricular folds of the primitive mesenchyme, from which the leptomeninges arise.

12.1.1 Frequency, Age, Site

The plexus papilloma is a rare tumor which is most common in childhood. It has been found to make up 0.6% [542] and 0.6% [3138] of all intracranial tumors. In the personal series, it represents 0.4% of all CNS tumors. It is more frequent in infancy: 3.9% [1802], 2.3% [2839], 2.9% [706], and 3% [2697]. However, the incidence in infancy may be even greater, because some tumors are not recognized in this age group.

Eighty-three plexus-papilloma tumors have been reviewed [1802], 67 from the literature of which 48% appeared in the first decade of life and 20% within the first year of life. Of 19 cases in another series [3041], 12 occurred in subjects less than 20 years old. The age distribution curve has two peaks: one in early childhood and the other in advanced age [3134]. This second peak is due to adult tumors discovered at autopsy.

Plexus papillomas in very early age are probably congenital and relatively frequent. They have been described in children under 1 year old and even in a premature infant [1800, 2853]. There are no significant differences between the two sexes.

The most prevalent sites are the cerebral ventricles, the tumor occurring in the lateral ventricles in 50% of cases, in the fourth ventricle in 34%, and in the third ventricle in 15.3% [2909]. These figures were 40%, 44%, and 16%, respectively, in other series [2225]; in series limited to infantile tumors, they were 72%, 15%, and 10% [706].

The general impression is that tumors of the lateral ventricles are more frequent in children and those of the fourth ventricle in adults [2420].

Tumors of the lateral ventricles generally grow at the trigon region–temporal horn; those of the third ventricle anteriorly; and those of the fourth ventricle caudally along the roof [3134]. Very exceptionally, the tumor is biventricular [1019, 1015]. The tumors, not rarely, may be extraventricular. This is less often due to growth from an ec-

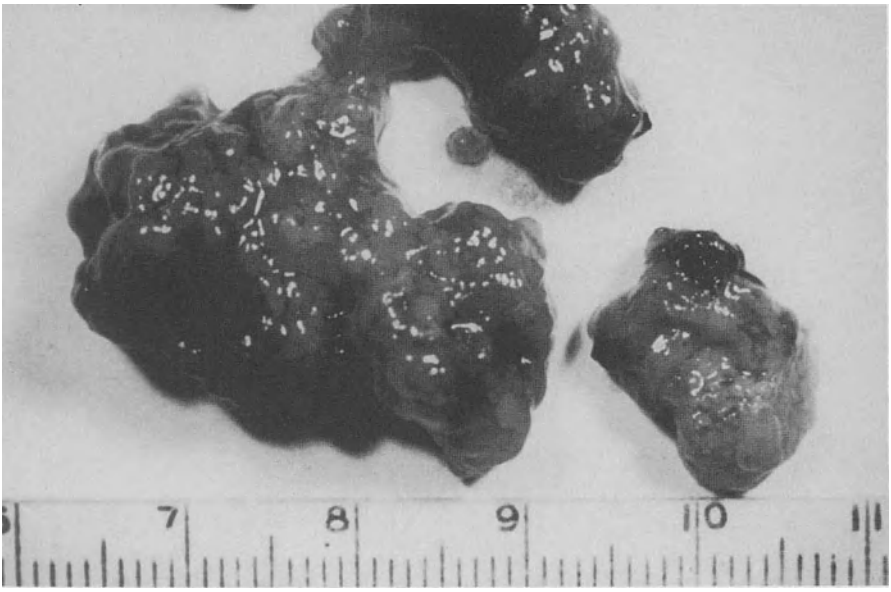


Fig.12.1. Plexus papilloma

topic remnant of choroid tissue [1001, 1335, 2340, 2655] and more often to a protrusion of the choroid plexus through the foramina of Luschka in the pontocerebellar angle [1929].

12.1.2 Macroscopic Appearance

The tumors are globular and blue-gray, and sometimes have a cauliflower appearance (Fig.12.1). They are soft and very vascular. The tumors grow by expanding within the ventricle first, displacing and compressing juxtaventricular structures. They may attain a considerable volume and, upon filling the ventricular cavity, exit from it and invade the nervous tissue.

12.1.3 Microscopic Appearance

Histologically, the structure is very simple because, due to the presence of a large number of villi, the neoplasm maintains the picture of normal choroid plexus (Fig.12.2a). A vascular-connective stroma forms the axes of the papillae, which are covered by a monostratified columnar or cuboidal epithelium (Fig.12.2b). The tumor cells do not have blepharoplasts, a characteristic which distinguishes them from ependymoma. Normally there are no mitoses, but if present, they are indicative of a more aggressive behavior. Among the regressive changes, connective tissue hyalinization and calcification may occur, giving rise to the formation of psammoma bodies.

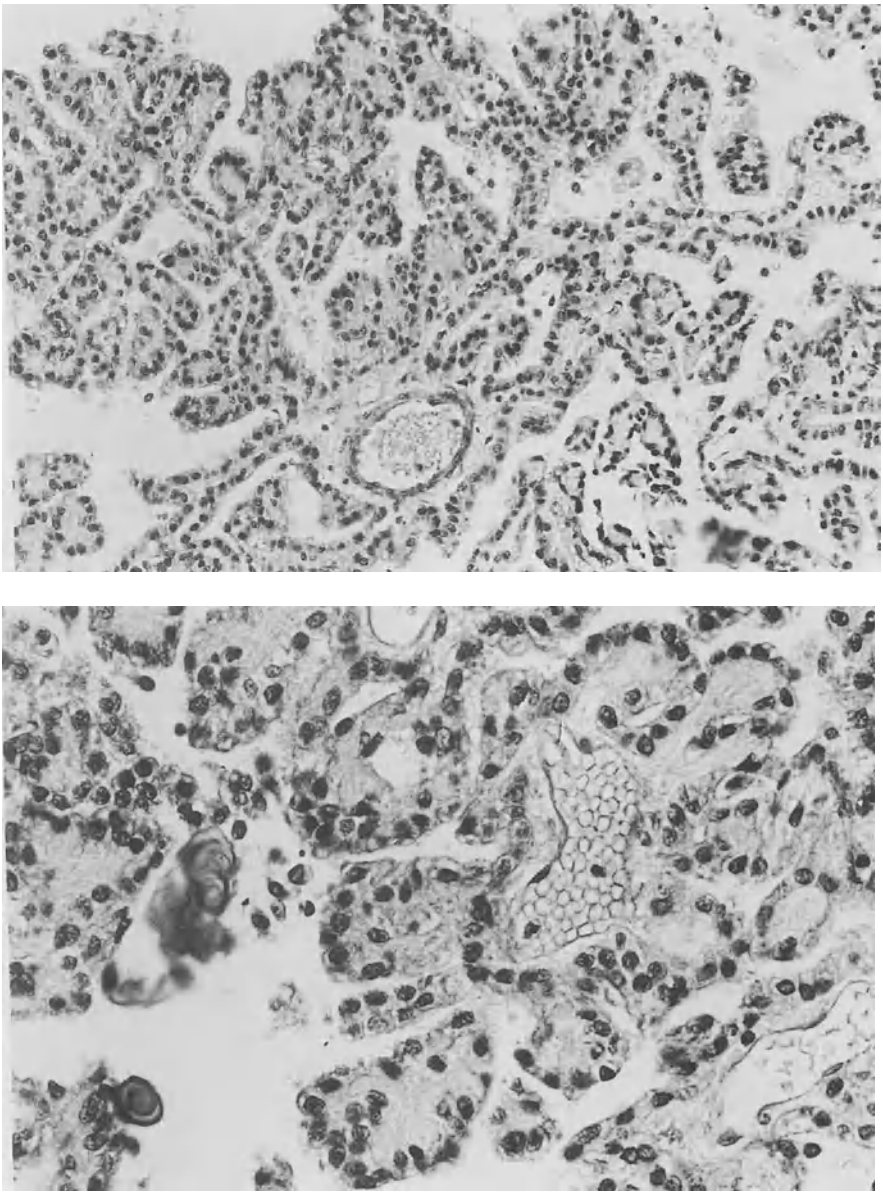


Fig.12.2. Plexus papilloma: **a** general architecture resembling that of choroid plexus, H&E, ×200; **b** structure of papillae, H&E, ×400

Many observations permit one to identify transitional forms between ependymoma and plexus-papilloma. During normal choroid plexus development, the neuroepithelium covers the stromal proliferations running from the leptomeninges into the primitive ventricles, resulting in the formation of papillae. There are not only histological similarities between predominantly papillary ependymomas and plexus papillomas, but also GFAP-positive cells in the latter. When these occur, they represent foci of ependymal differentiation [2398, 2811, 468, 1884, 642]. GFAP-positivity may also be found in the normal choroid plexus. Vimentin and cytokeratin positivity have been reported in plexus carcinomas [642] and in some papillary ependymomas [1755]. Other antigens, such as EMA [642], CEA [468], S-100 [1424], and the antigen recognized by the Leu-7-specific antibody [2180], have been identified immunohistochemically in this tumor. Transthyretin (TTR), claimed to be a specific marker of choroid plexus tumors [1110A], is positive in many cases [2155A, 1147A]. The surface of the microvilli stains with ruthenium and, therefore, contains GAG [1988]. Electron microscopy has demonstrated the occasional presence of a continuous basement membrane and junctional complexes [385, 908, 1812].

The tumor carries a good prognosis, even though local recurrences are not that uncommon [1848]. Metastasis via the CSF does not take place. The associated hydrocephalus results most probably from a combination of CSF overproduction and the very high protein content, at times measured in grams, of the CSF. Surgery is very difficult technically, but today the surgery-related mortality is less than 15%. Survival at 10 years is 88% [706].

12.2 Malignant Variant (Plexus Carcinoma)

A particular problem is represented by malignant degeneration of the plexus papilloma. Cases with the histological characteristics of plexus papilloma but with histologically malignant foci have been reported [2994, 380]. In some instances, this variant of the tumor has been called plexus carcinoma [1216, 804, 2937]. Up to 1951, 30 cases had been reported in the literature [1796]. The main problem related to nomenclature is that the term plexus carcinoma was accepted by some, but not by others. If plexus-papilloma is considered a paraglioma, it would not be correct to refer to its malignant variant as carcinoma [804]. On the other hand, the supposition that plexus carcinoma could be a metastasis to the plexus from a carcinoma of other organs has been presented [1216].

The identification of the malignant variant is difficult and essentially based on the infiltration of neural tissue, the appearance of histological signs of malignancy, the disappearance of the typical regular architecture of the tumor, and the appearance of mitotic activity (Fig.12.3). However, it seems that the prognostic significance of these features is questionable [1848]. In the experience of others, S-100 positivity in less than 50% cells, occurrence of mitoses, absence of TTR-positive cells, brain invasion, and necrotic areas are correlated with a poor prognosis [2155A].

The malignant variant is not frequent [1635] and is mostly found in children or young people [2420]. Differently from plexus-papilloma, plexus carcinoma metastasizes via the CSF [1835], though extracranial metastases have also been reported. This

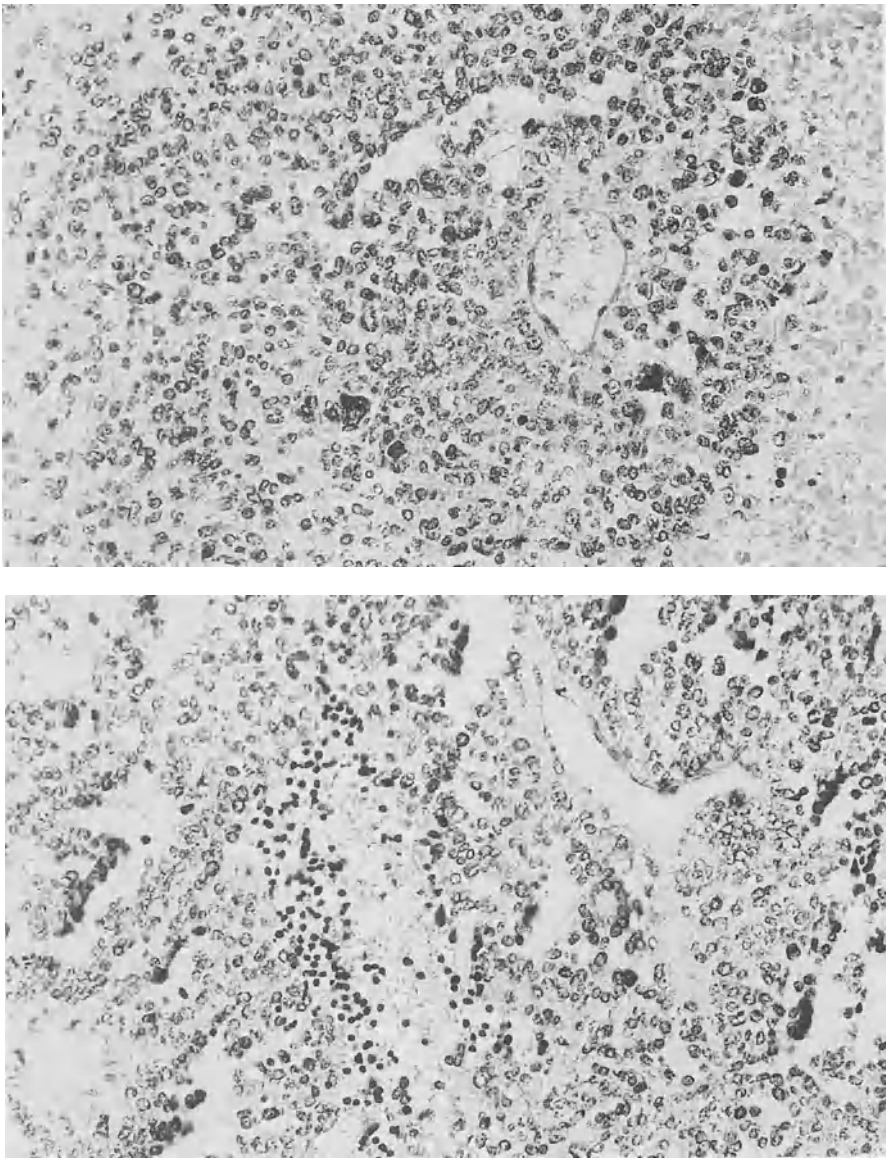


Fig.12.3. Malignant plexus papilloma: **a** nuclear polymorphism and loss of architecture, H&E, ×300; **b** necrosis, H&E, ×300

finding is to be considered in planning the strategy for radiotherapy. Rare malignant plexus papillomas containing melanin have been reported [151, 1563, 236]. The prognosis is generally less good than that with plexus-papilloma. Total surgical removal seems to be followed by prolonged progression-free survival, while adjuvant radiation therapy and chemotherapy are of unproven benefit [706, 2111A].

13 Tumors Composed of Neural Cells

13.1 Ganglioglioma (Gangliocytoma)

Ganglioglioma is probably malformative in origin, often closely resembling a malformation. It is characterized by the presence of both neural and glial tumor cells. The frequency of neural tumor cells is very variable, ranging from tumors in which neural cells clearly prevail (gangliocytomas), to those in which they are very rare when compared with the predominant glial elements. One of the fundamental problems, especially in the latter case, is represented by the recognition of the neuronal elements. This is based, apart from the nuclear and cytoplasmic morphology (vesicular nucleus with evident nucleolus, presence of Nissl's substance, neurofibrils on silver impregnation), on electron microscopic observations (microtubules, dense or light core vesicles, synapses) and on immunohistochemical staining (demonstration of neurofilaments). In the past, many cases were mistakenly diagnosed as gangliogliomas because they contained cells with ganglioid features, as may be found in glioblastoma and other tumors.

One must recognize not only the neurons but also their neoplastic nature. This is possible when the appearance of the neurons is not so much modified by the tumor transformation as to be still recognizable. It must be considered that neurons may belong to the preexisting tissue, as often occurs at the periphery of glial tumors. Practically speaking, the presence of neurons in areas where they are normally lacking, as in the leptomeninges and white matter, or with a distribution different from that normally found, for example, in groups rather than in layers, are useful elements for the diagnosis. The recognition of the neuronal nature of the cells will be progressively more difficult as their appearance shifts towards that of neuroblasts.

13.1.1 Frequency, Age, Site

Ganglioglioma is a rare tumor. In adults, its frequency varies from 0.2% [542] to 0.4% [3138], but in children it has been reported to reach 1.7% [883], 4.5% [2769], or even 7.6% [1315]. The tumor, in fact, is more common in the infantile or juvenile age groups, with the majority of cases occurring in patients under 30 years of age [53, 2420]. The two sexes are almost equally affected.

There are different sites of origin. The tumor more frequently occurs in the region of the tuber cinereum, in the temporal region, and in the third ventricle, but also in the parietal and frontal lobes and in the cerebellum (Fig.13.1). Other sites are less common. Cases in the pineal region have been reported [1225] (Fig.13.2). The tumor may remain silent for a long time, revealing itself with epileptic fits or as an incidental finding dur-

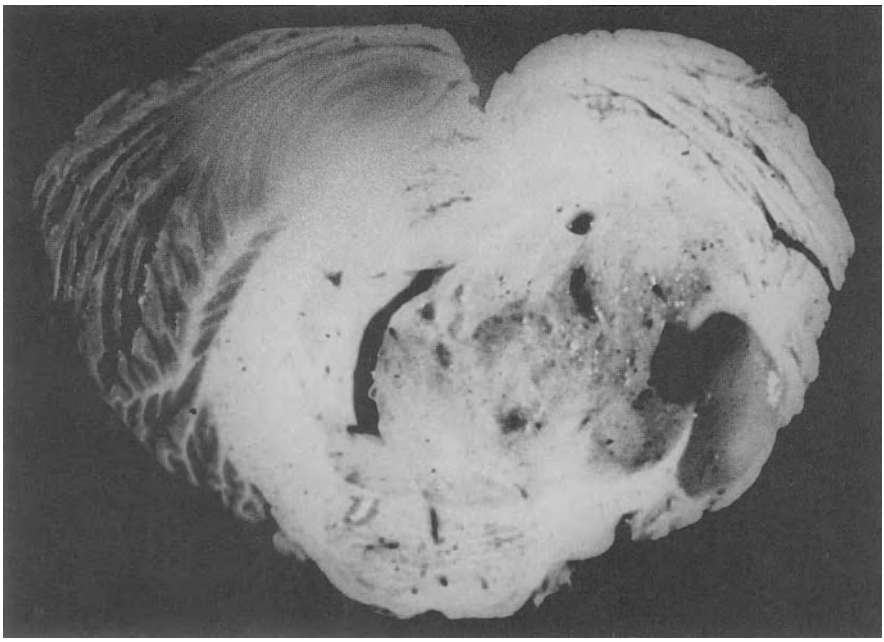


Fig.13.1. Gangliocytoma of the cerebellum

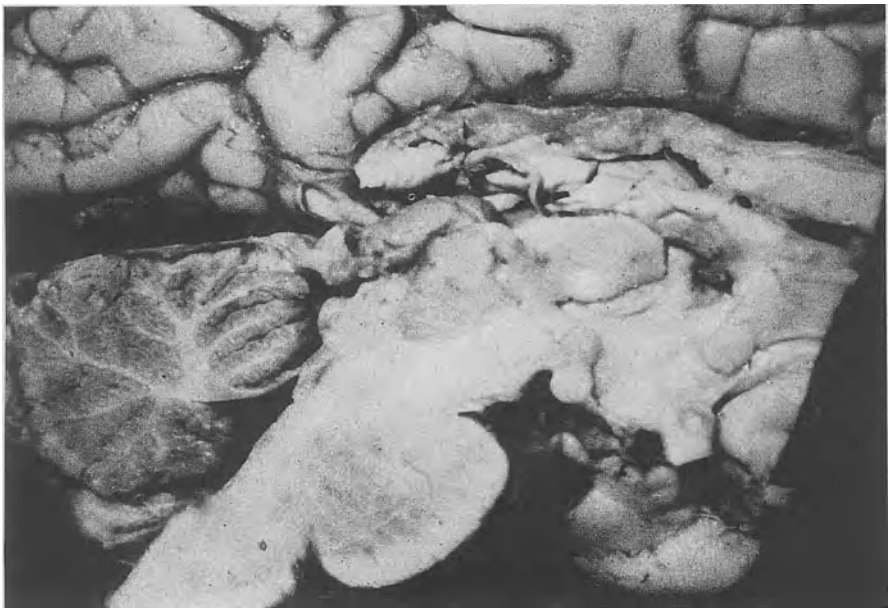


Fig.13.2. Ganglioglioma of the pineal region

ing surgery for temporal epilepsy. An interesting case has been reported of an intramedullary secretory gangliocytoma in a boy developing systemic arterial hypertension during surgical manipulation of the tumor, probably due to catecholamine secretion [99A].

13.1.2 Macroscopic Appearance

The ganglioglioma is usually a small, hard, well circumscribed, grayish-pink tumor. It is often cystic (Fig.13.1) and is sometimes calcified. More rarely, it may be diffuse.

13.1.3 Microscopic Appearance

The tumor is of varied, but generally medium, cell density. It is formed of ganglion cells featuring various changes in both the cytoplasm and the processes. The cells have abnormal processes, are often bi- or multinucleated, and contain normal or irregular Nissl substance (Fig.13.3). Smaller lymphocyte-like cells, at times interpreted as neuroblasts, may also be present. While in pure gangliocytomas the glial component is of the reactive type, in gangliogliomas the glial component is tumoral, astrocytomatous, and often with gemistocytic features. A reticulin component subdividing the tumor into lobules containing clustered ganglion cells may sometimes arise from the blood vessel stroma. Perivascular lymphocytic cuffs may be present. Exceptional cases contain neurofibrillary tangles [1184, 2056] or melanin [1225]. Among the regressive events, the formation of cysts and calcifications are most important. The tumor may extend into the subarachnoid space.

Electron microscopy can confirm the presence of neoplastic ganglion cells, with the demonstration of granules, presynaptic vesicles, and synapses [2339, 2399]. Immunohistochemically, the glial component is GFAP-positive (Fig.13.4b), and the neuronal one is variously positive for NF (Fig.13.4a) and NSE. In some cases, somatostatin, thyrosine hydroxylase, Met-enkephalin, Leu-enkephalin, serotonin, and substance P [2792] have been demonstrated. Yet other studies have shown positivity for VIP [915]. A panel of well-characterized Mabs against neurofilament polypeptides, synaptophysin, and chromogranin A has been proposed for the recognition of neoplastic neurons [635A].

13.1.4 Malignant Transformation (Malignant Ganglioglioma)

A problem of notable interest is that presented by the malignant transformation of these tumors. The cases reported up to now are few. The main difficulty in the recognition of these cases is due to the fact that, if an anaplastic evolution of proliferating cells is admitted, their neuronal character would no longer be recognizable. Therefore, even if malignant forms did exist, they could not be diagnosed. In theory, it is possible to say that malignant forms, related to the presence of neuroblasts, exist, but these are best grouped with neuroblastomas having ganglion differentiation. In general, however, it is thought that anaplastic evolution occurs only in the glial component and in the glioblas-

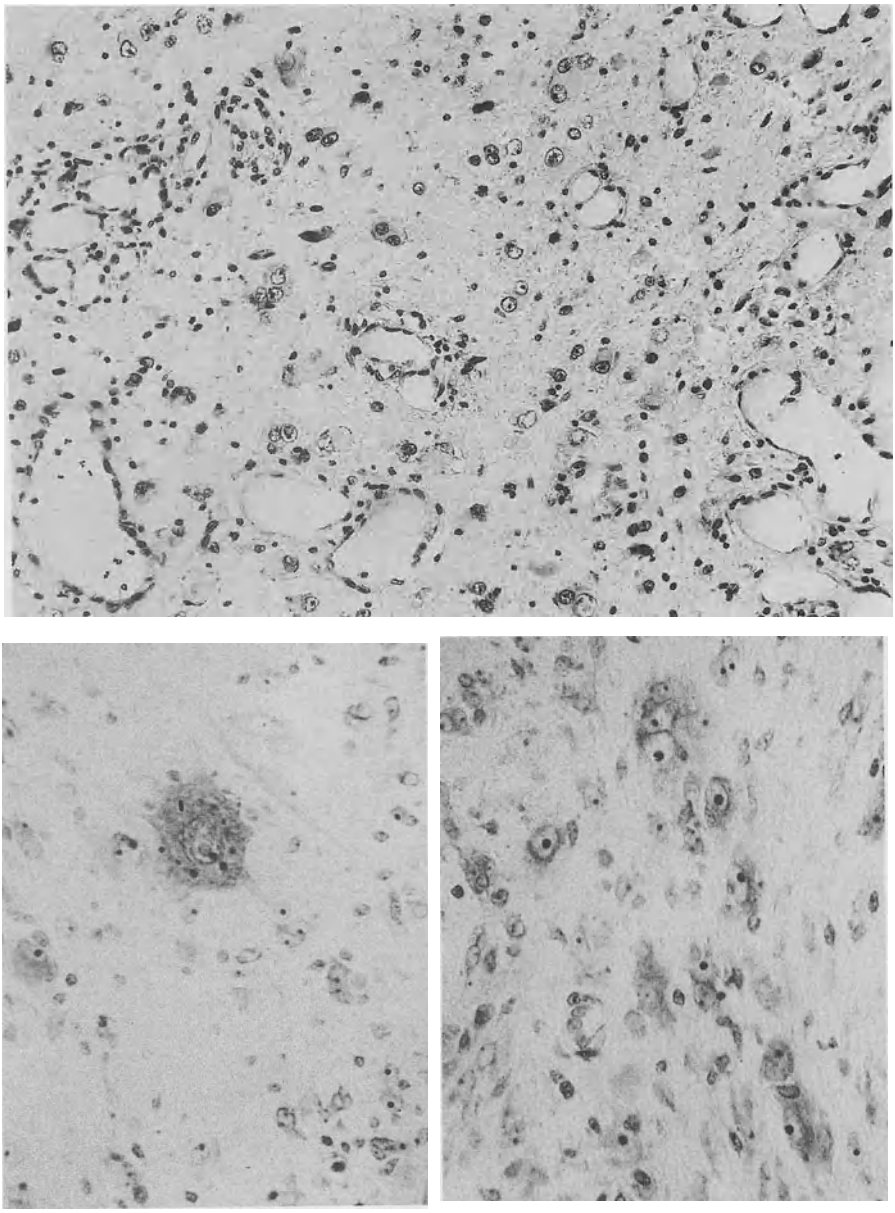


Fig.13.3. Gangliocytoma: **a** deformed neurons and vessels, H&E, ×200; **b**,**c** binucleated neurons and Nissl grains, cresyl violet, ×400 [2486]

tomatous sense [2420]. In one case, the malignant transformation of the glial component led to a glioblastoma 25 years after biopsy [2416]. It must be emphasized that this event is quite rare. In the series of Russell and Rubinstein [1989], it occurred in ten cases. I have never observed an example.

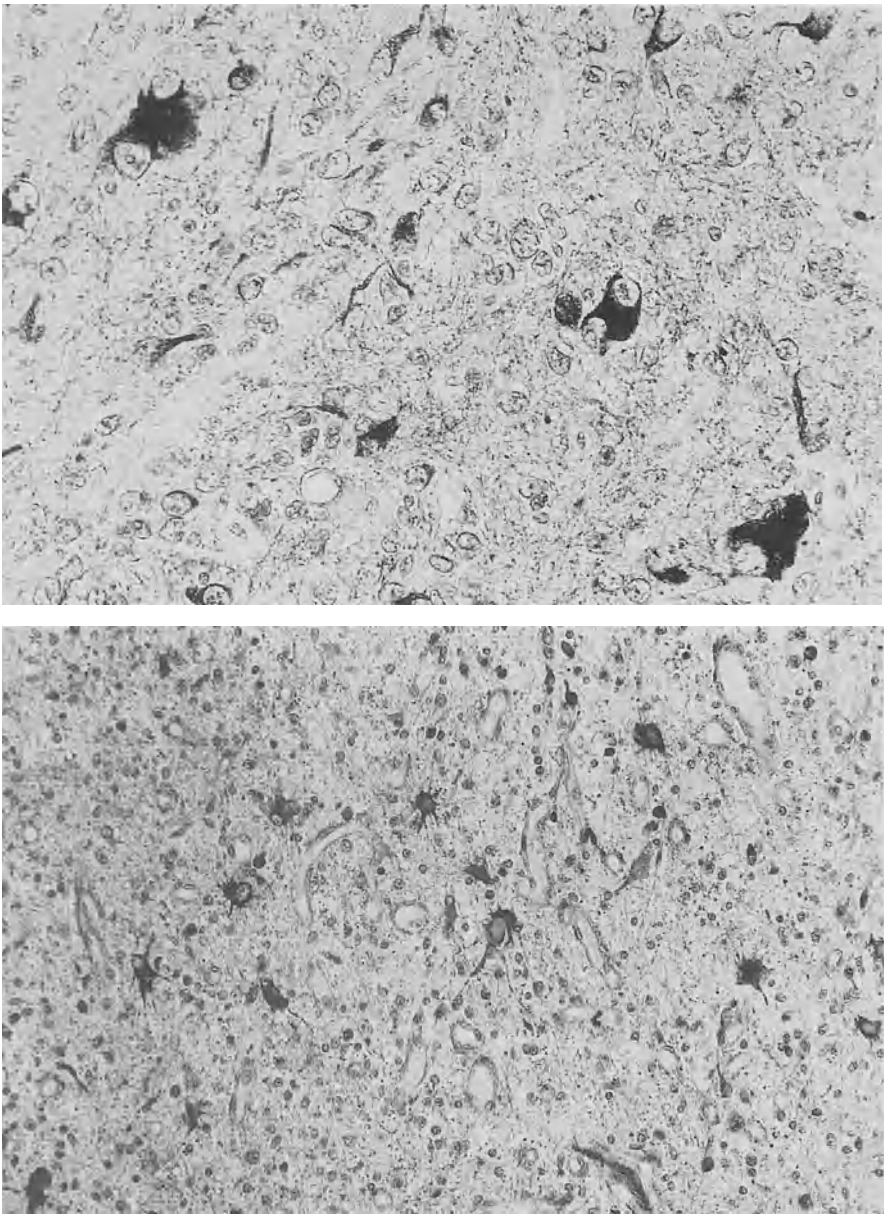


Fig.13.4. Gangliocytoma: **a** neurons evidenced by NF immunohistochemical staining, SM 31 antibody, PAP-DAB, ×300; **b** scanty reactive astrocytes, GFAP, PAP-DAB, ×300

13.1.5 Prognosis

As has already been stated, these lesions are akin to malformations and, in general, are considered as hamartomas, even if the possibility of progressive neoplastic transformation exists. They may be multiple or associated with other malformations such as agenesis of the corpus callosum, various ectopias, etc. The good demarcation which characterizes this tumor, especially when favorably located, permits surgical removal; thus, even though there is no known correlation between its histological appearance and the clinical course, the prognosis is, in general, good and the survival long [1315, 2639A]. Recurrences are frequent, while metastases in the CNS are rare.

13.2 Dysplastic Gangliocytoma of the Cerebellum

A particular type of gangliocytoma of the cerebellum in which the dysplastic character and the affinity to a simple malformation are more evident is considered a separate lesion [1640]. It goes under different names such as dysplastic gangliocytoma, diffuse hypertrophy of the cerebellar cortex or Purkinjoma [447].

Macroscopically, it presents as a circumscribed hypertrophy of the cerebellar folia. Histological examination of the hypertrophic folia demonstrates the existence of an external layer with myelinated fibers and glial cells, a deeper layer with many small cells, and large cells resembling Purkinje cells. The central white matter is reduced or absent. According to Oppenheimer (1955) [2089], who reviewed ten published cases and reported two of his own, the "tumor" results in hypertrophy of the granular layer neurons which send fibers towards the pial surface. This finding has been confirmed by electron microscopy [2243, 770, 2308]. The two cases he reported were associated with ipsilateral leontiasis ossea and foci of ectopic cerebellar tissue. Other cases have been reported, each with its own peculiarities [379, 202]. The tumor is probably hamartomatous in origin. In two cases featuring hypertrophy of the entire hemisphere or of circumscribed areas, the granular layer contained embryonal cells (from which neuroblasts and immature ganglion cells arose) which sent axons into the thickened molecular layer. The white matter practically disappeared.

Reviewing cases from the literature, Hallervorden (1959) [1048] thought that the majority represented malformative lesions in which the hypertrophy of the internal granular layer is secondary to the malformation of the external granular layer. In another review, concerning 36 sporadic and two familial cases [51], associated lesions were found, especially an increase in volume of the skull and/or brain. The genesis of the tumor has also been attributed to a dysontogenetic multivalent leaflet of the median structures of the cerebellum [2882].

13.3 Infantile Desmoplastic Ganglioglioma

A particular variety is found almost exclusively in patients in the first year of life. It is characterized by a marked desmoplastic component and a particularly favorable post-

operative course, and has been called "infantile desmoplastic ganglioglioma." Eleven such cases have been described [2910].

The tumor is preferentially located in the frontoparietal regions. The desmoplasia is due to the involvement of the leptomeninges, which feature an intense desmoplastic reaction. In one case, the astrocytes were seen electronmicroscopically to be covered by a basement membrane [2910]. Tumor cells are GFAP-positive and also contain 200 kDa NF [2420]. The large production of fibrous tissue must be due to meningeal fibroblasts, among which clusters of reactive glial cells can be found [2910]. An alternative interpretation is that astrocytic cells synthesize extracellular matrix proteins. They could produce markers typical of mesenchymal cells through a process of aberrant metaplasia. The formation of cartilage in gliomas has been explained by the same mechanism [1399].

A superficial desmoplastic cerebral astrocytoma has been described in infancy [2812]. It differs from the above mentioned tumor only in the absence of neuronal differentiation. Mixed superficial tumors formed by astrocytes and fibroblasts have been described and called "gliofibromas" [829].

The infantile desmoplastic ganglioglioma differs (other than cytologically) from the xanthoastrocytoma [1395] in that the latter is located in the temporal lobes and arises in older subjects.

13.4 Central Neurocytoma

Under this name are included some para- and intraventricular (lateral ventricles) tumors arising in young subjects, which were previously classified as ependymomas of the foramen of Monro [3140] or as oligodendrogliomas. Several cases have been reported [2159, 3051, 2860, 387A]. The tumor usually originates from the anterior wall of the third ventricle and extends into the corpus callosum and foramen of Monro, at times filling the lateral ventricle.

The tumor is composed of sheets of small, isomorphous cells with a clear cytoplasm and a perinuclear halo (Fig.13.5). They are separated from one another by stromal septa containing capillaries and calcifications [1078]. Homer–Wright rosettes are present (Fig.13.5). In some cases, there is a remarkable resemblance to oligodendroglioma [3051, 2036]; however, some features of neurocytomas, such as more varied nuclei, a more delicate fibrillary background with anuclear zones, and an inconspicuous vasculature permit distinction [1694]. Ultrastructurally, the cells appear to have a clear neuronal differentiation and synapses [1080]. Immunohistochemically, staining for synaptophysin, NSE, Leu-7, and NF is generally positive, whereas that for chromogranin is negative [1080]. In a series of 11 cases [2949], staining for NSE and synaptophysin was positive and on electron microscopy axons, synapses, neurosecretory granules, and microtubules were found. Two cases were also GFAP-positive. It is interesting to observe that, in two cases, there were signs of anaplasia with mitoses, necroses, and endothelial proliferations.

It is undoubtedly difficult to draw a clear distinction between these tumors and central neuroblastomas. Some cases described as central neuroblastomas with a marked

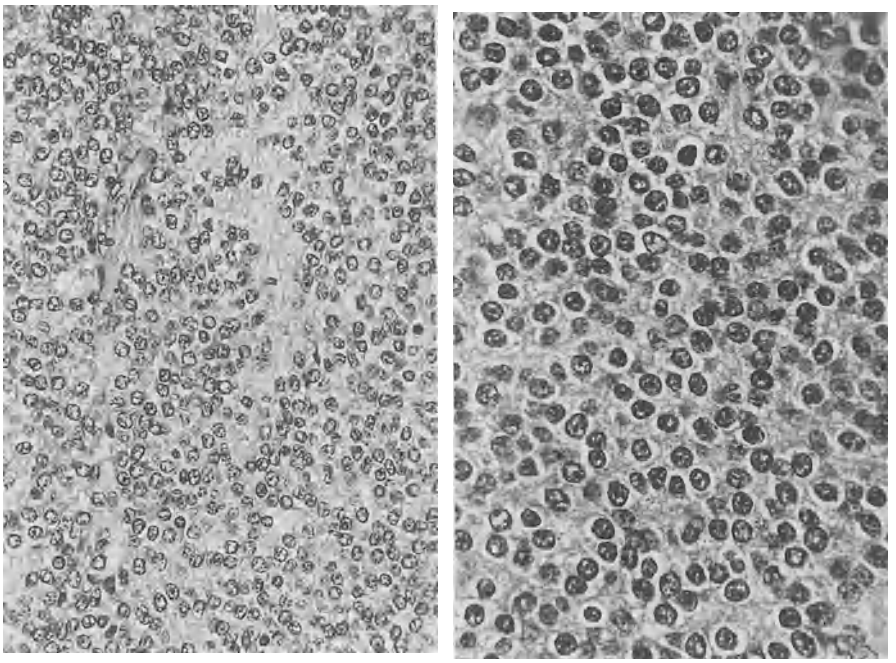


Fig.13.5. Central neurocytoma: **a** typical architecture with "cell-free" islands, H&E, ×200; **b** cell halos, H&E, ×400 (Courtesy of Dr. F. Giangaspero, University of Bologna)

tendency to neuronal differentiation or with mature synapses could, in reality, have been central neurocytomas (see Sect.). In general, a neuroblastoma possesses clear Homer–Wright rosettes and affects younger patients. Neurocytoma cells appear to be intermediate between the immature cells of neuroblastoma and the mature ones of gangliocytoma.

These tumors derive from the subependymal plate of the lateral ventricles, i.e., from residual cells destined to be neurons [2949, 1694], and from gray nuclei of the septum pellucidum and the fornix [1080]. Also a spinal case has been reported [1694]. Neurocytomas follow more benign courses than neuroblastomas and may, in some cases, be cured by excision alone. Malignant courses have been reported [3096A].

13.5 Dysembryoplastic Neuroepithelial Tumors

These lesions are infrequent, often found at surgical exploration as the cause of temporal lobe epilepsy which was untreatable from the medical point of view. They are cortical, multinodular tumors, located in the temporal lobes, occurring in young patients, and diagnosable with CT and MRI. Thirty-nine surgically treated cases with long postoperative survival times have been collected [570].

Histologically, the tumors are formed by nodular foci composed of astrocytes, oligodendrocytes, and neurons. A specific "glioneuronal element" is recognized. It is formed by neurons within a mucoid matrix, accompanied by astrocytes and oligodendrocytes. In the nodular component, a pattern similar to true polar spongioblastoma may be evident. Frank nuclear atypia and glomeruloid capillary proliferations are visible. The lesions may be accompanied by cortical dysplasia [570].

The recent WHO classification [1443] has confirmed this tumor group as an oncotype per se, which was already recognized as hamartomatous [395]. The hypothesis is that these tumors derive from the subpial granular layer during the formation of the cortex.

14 Pineal Gland Tumors

14.1 The Pineal Gland

The pineal gland is attached to the posterior roof of the third ventricle between the posterior and the habenular commissures, and between the pineal and suprapineal recesses. It develops at the beginning of the second month of gestation as an evagination of the diencephalic roof. Concerning function, it is active in the transmission of information regarding the length of daylight, the regulation of reproduction in mammals, and the circadian rhythms. In fish and amphibians, the parenchymal cells (the pineocytes) have a photoreceptor function, transforming light into electrical signals.

In birds, the gland is a photoendocrine transducer transforming light into hormonal signals. In mammals, it behaves as a neuroendocrine transducer, transforming electrical into hormonal signals [97].

The main product of the pineal gland is melatonin, or N-acetyl-5-methorytryptamine. Its synthesis depends on lighting conditions and is stimulated by β-adrenergic sympathetic postganglionic fibers, which in turn are stimulated by darkness. Light has an inhibitory function. Norepinephrine and serotonin are released at the sympathetic endings. The metabolic path begins from plasma derived tryptophane and arrives at melatonin. The stimulation of the β-adrenergic receptors activates adenylcyclase so that the cAMP and N-acetyltransferase levels increase.

The photic stimulus reaches the gland via a complex pathway which begins with the retinohypothalamic tract and then passes to the suprachiasmatic nucleus, but stimuli may also arrive directly from the geniculate body [1919]. The most efficacious wavelength is yellow-green [3079]. Through the lateral hypothalamus and the medial prosencephalic bundle, the stimuli descend in the intermediolateral column of the spinal cord and from here via the preganglionic fibers reach the superior cervical ganglia [381]. The postganglionic fibers reach the gland through the "nervi conari" which pass through the tentorium.

Histologically, the gland, which is present in all vertebrates apart from alligators and armadillos, has a capsule and is composed of lobules separated by connective tissue septa. It contains parenchymal elements, the "pineocytes," and interstitial cells. The former show features of paraneurons [2883] and of elements of the amine precursor uptake and decarboxylation (APUD) system [2160], being positive for NSE and containing secretory granules. They do not have axons but argyrophilic processes which are directed towards the blood vessels, on which they end with club shaped expansions. In the neonatal rat, some features of photoreceptor cells may be found [3121], and this is consistent with the glandular expression of the retinal S antigen [652, 1484]. This is a 48 kDa protein which binds to rhodopsin. It has been found in human fetal and adult pineocytes [2182]. The interstitial cells are GFAP positive astrocytes [1219].

The production of melatonin is regulated by light, and the pineal gland transduces periodic photic stimuli intervening in the temporal organization of various metabolic, physiological, and behavioral processes. It has endocrine and nonendocrine functions [728]. Effects on reproduction and on the thyroid and adrenal glands belong to the former [2296, 2297]. It has no antigonadotropic effects [2296] but influences, via the hypothalamus, prolactin, luteinizing hormone (LH) and follicle stimulating hormone (FSH) production. It may also act directly on the pituitary [2298]. The nonendocrine functions are those affecting locomotion, aggressiveness, analgesia, response to stress, electrical cortical activity and sleep mechanism. They are involved in sleep disturbance, pathogenesis of epileptic fits, hibernation, and thermoregulation [728]. Melatonin acts mainly via the hypothalamus, and it seems that its action is exerted on microtubules [3061]. It also has an influence on

the growth of tumors in general, playing an inhibitory role by its action on mitotic activity and immunocompetence [2298].

Tumors of the pineal gland have to be separated from those of the pineal region, the latter being composed mainly of astrocytomas and germ cell tumors. The true tumors of the pineal gland are rare and represented by pineocytomas and pinealoblastomas, which vary in their degree of differentiation and arise from pineocytes; astrocytomas arise from interstitial astrocytes. Pineocytomas and pinealoblastomas are formed by mature (pinealocytomas) or immature (pinealoblastoma) elements; however, transitional forms between the two exist, so the above-mentioned forms represent the two poles of a spectrum. Their true incidence is not easy to calculate, but it is low: 0.4% according to [3134]. In other series it is 1% in adults and 8% in infants [1168]. Pinealoblastomas have a peak incidence in the first decade of life and pineocytomas, in the third [1120].

14.2 Pineocytoma

14.2.1 Macroscopic Appearance

The tumor is situated at the site of the pineal gland, is well circumscribed, pushes towards the third ventricle, and displaces the aqueduct (Fig.14.1). The pineal gland may be completely destroyed or enlarged. The cut surface is grayish-pink, granular, gelatinous, and cystic or necrotic-hemorrhagic (Fig.14.2).

14.2.2 Microscopic Appearance

The description of the microscopic appearance is drawn from major series of 28 cases and 13 cases [1120, 264]. The tumor cells resemble those of the normal pineal gland. They show a medium density and are arranged in lobules, separated by a delicate stroma and small blood vessels. The cytoplasm may be moderate in amount, with a polar aspect as cells are generally arranged around blood vessels to which they send out delicate processes (Fig.14.3). Mitoses are not invariably present but may be found in variable numbers. Homer–Wright rosettes may be present, and with silver impregnation delicate club shaped processes may be identified.

According to some, the pineocytoma rosettes can be distinguished from the Homer–Wright rosettes of neuroblastomas by their larger and irregular central part and a tendency to become confluent (Fig.14.4) [264]. Upon silver impregnation, tangles of argentophilic processes may be found in the center of the rosettes.

Neuronal, astrocytic, or neuronal and astrocytic differentiations have been described [1120]. Neuronal differentiation may be indicated either by the presence of rosettes or by the presence of neoplastic ganglion cells with atypical processes, Nissl's granules, and so on. The astrocytic differentiation is confirmed by phosphotungstic acid hematoxylin (PTAH) staining or by the demonstration of GFAP. Electron microsco-

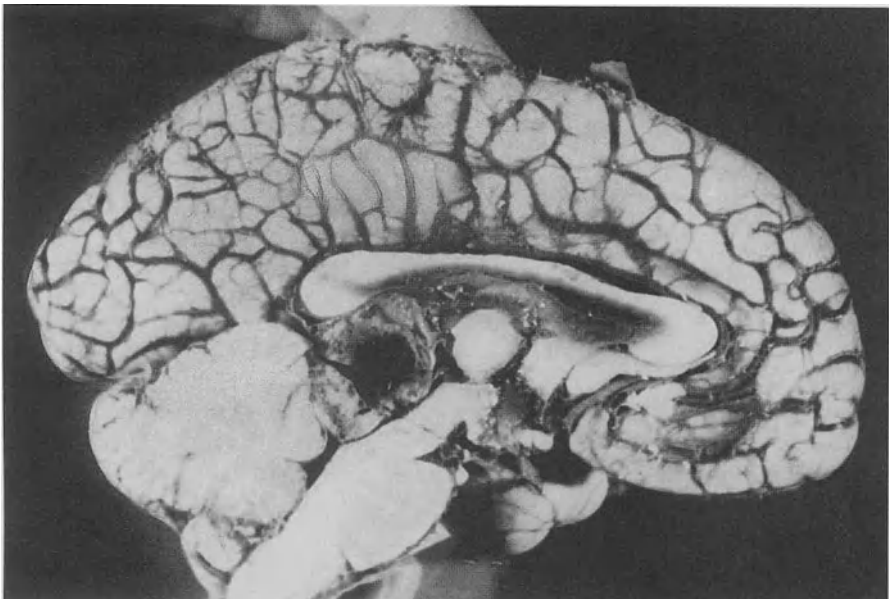


Fig.14.1. Pineocytoma

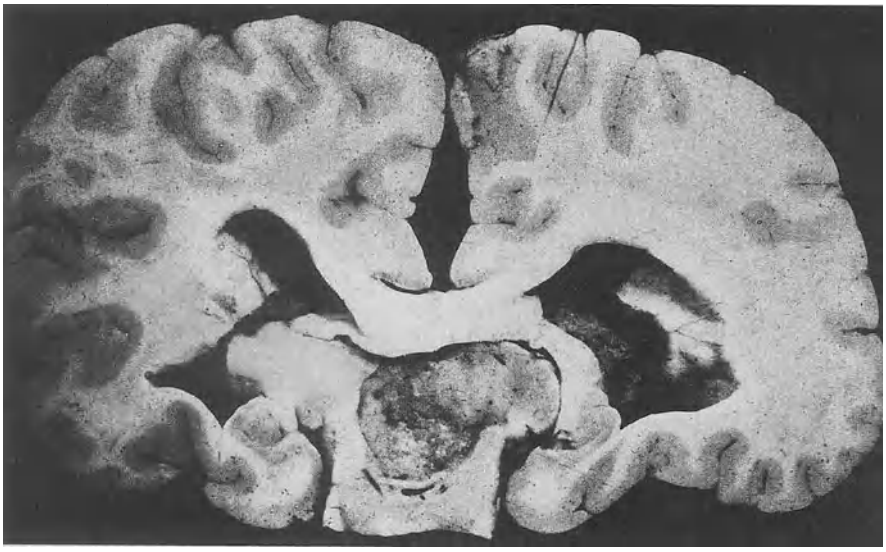


Fig.14.2. Pineocytoma

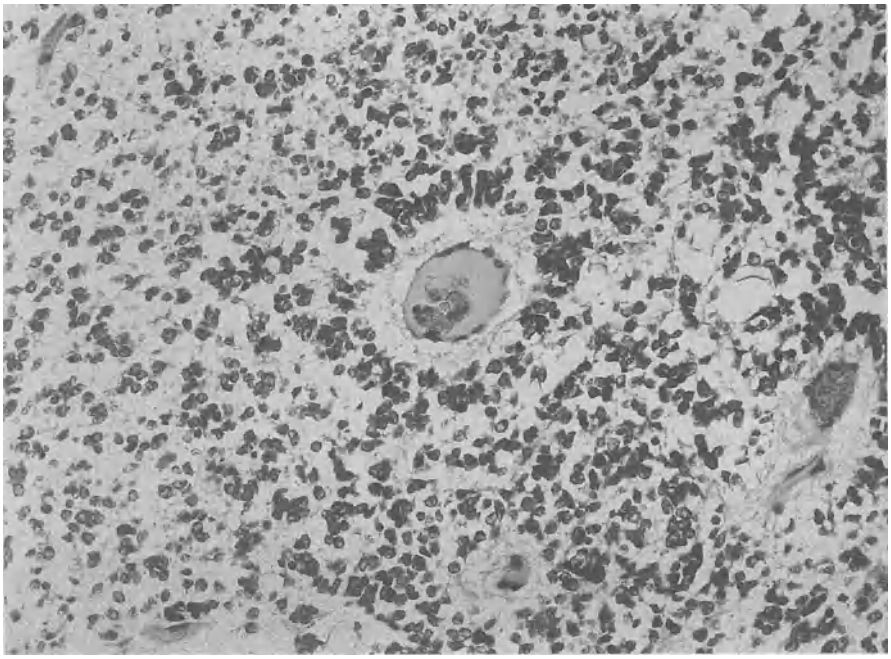


Fig.14.3. Pineocytoma, cells arranged around a vessel, H&E, ×400

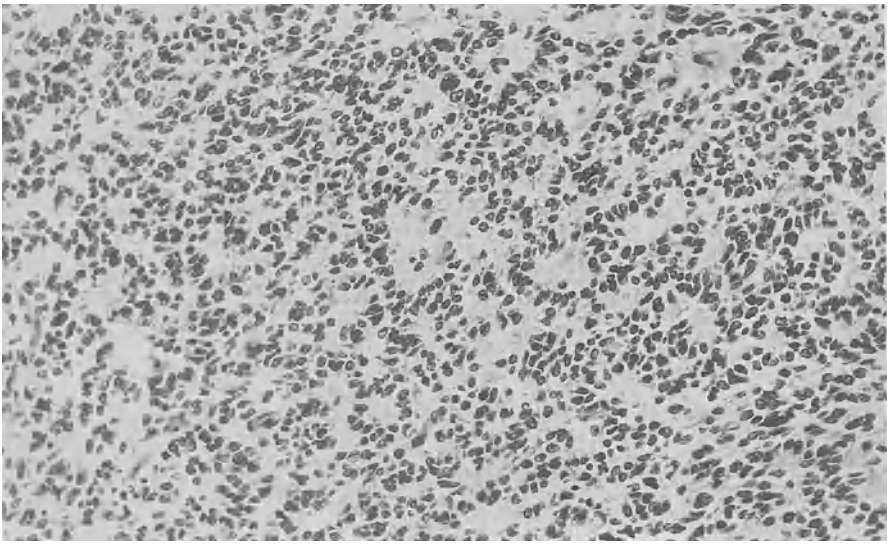


Fig.14.4. Pineocytoma, rosettes, H&E, ×200

py confirms the existence of neuronal characteristics demonstrating, apart from the endoplasmic reticulum, ribosomes and dense core vesicles (Fig.14.5), and in particular microtubule and membranous whorls (Fig.14.6) [1079]. The features, however, are so nonspecific that they may be thought to represent an undifferentiated primitive tumor with some tendencies to differentiate [1770]. Therefore, gangliogliomatous [2403 , 2029] or astrocytomatous [2330, 610, 261] pineocytomas have been described, even with malignant characteristics [1120].

It should be noted that some features, such as the presence of dense-core vesicles, cilia with a 9+0 complex axial filament, synaptic bands, bulb endings of microtubule fascicles, and lightcore vesicles, are similar to those found in an experimental pineocytoma induced in hamsters by human JC papovavirus [2915]. In this tumor, the oncogenesis seems to have simulated the ontogenesis of the gland and have reproduced rudimentary photoreceptor elements.

Pineocytomas must be differentiated from the rare pineal cysts, and this is not an easy task, particularly when small specimens are submitted. Lobules of parenchymal cells are associated with an intense gliosis in the cysts, which are to be considered as nontumoral entities [1445A, 1820A].

14.2.3 Prognosis

The prognosis of pineocytomas is not easy to establish because there are so few in the various series [2103, 695] and because of its difficult delimitation from pinealoblastoma. Also, it is not easy to codify their response to radio- and chemotherapy. Generally, the prognosis is poor and survival does not extend beyond a few years if there is no differentiation, as in pinealoblastomas. If there is differentiation, survival may be prolonged for some years [1120]. Metastasis via the CSF which is easily recognisable, is less probable than in pinealoblastoma. In the experience of the Philadelphia group, infantile pineocytomas tend to be more aggressive than those of adults, the incidence of leptomeningeal seeding is high, and recurrences generally arise within a short time. They advocate, therefore, craniospinal irradiation [547]. However, in the experience of the San Francisco group, leptomeningeal spread is less frequent (one in five), as is local recurrence after surgery and radiotherapy. They advocate craniospinal irradiation only in the presence of documented dissemination [639].

14.3 Pinealoblastoma

14.3.1 Macroscopic Appearance

Pinealoblastoma has ill-defined margins, infiltrates the surrounding tissue and abuts on the third ventricle, and the gland appears to be destroyed (Figs.14.7, 14.8). It has a grayish-pink appearance, is gelatinous, and is sometimes necrotic and hemorrhagic.

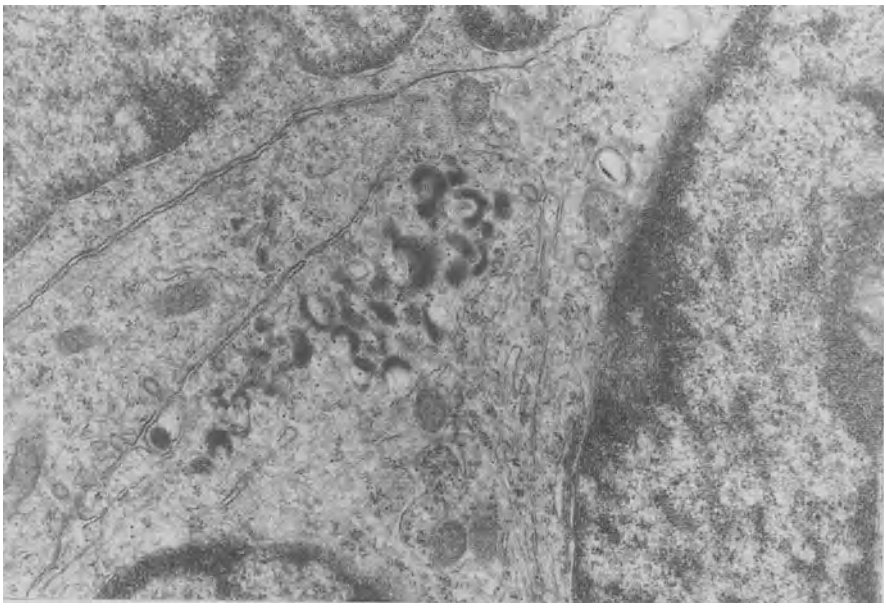


Fig.14.5. Pineocytoma, dense core vesicles, ×20,000

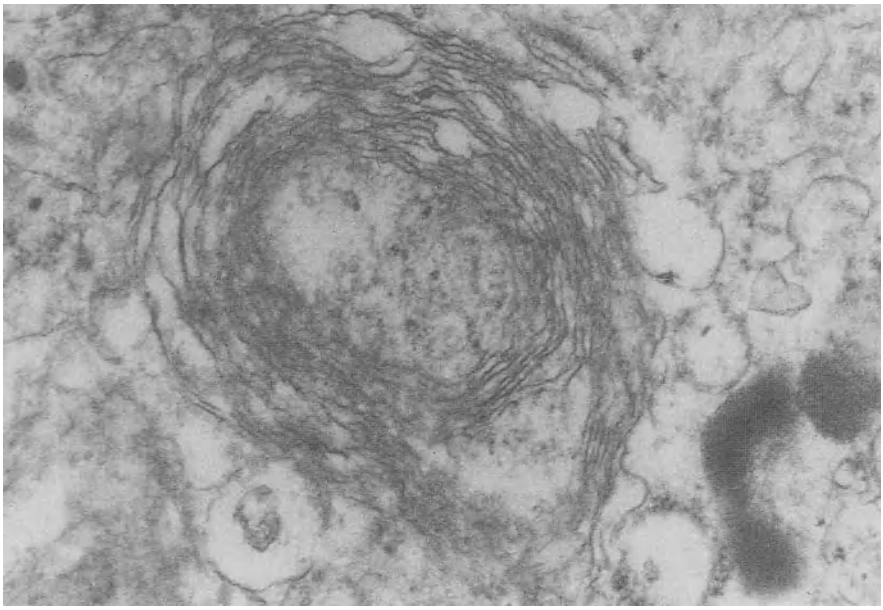


Fig.14.6. Pineocytoma, membranous whorls, ×40,000

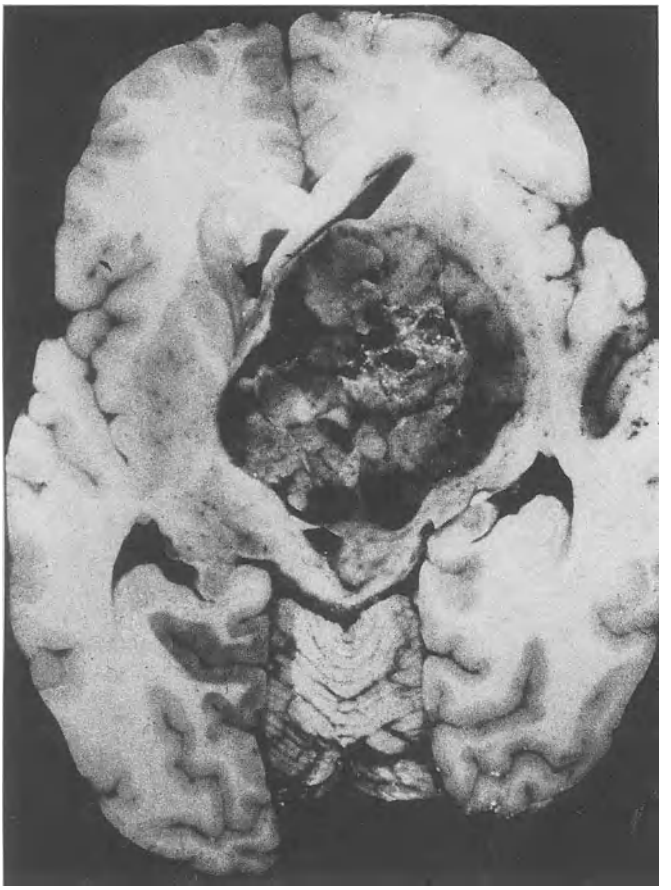


Fig.14.7. Pinealoblastoma

14.3.2 Microscopic Appearance

Histologically, pinealoblastomas have a high cell density and are composed of cells with small, dark nuclei, closely resembling medulloblastoma. Mitoses are frequent, but they may also be absent. The cells may sometimes demonstrate a single, short process with silver impregnation, but they do not have a particular arrangement and form only ill-defined Homer–Wright rosettes (Fig.14.9). According to some, a mosaic effect has sometimes been found, with the formation of lobules in which there are transitional elements in the developmental sense [2420].

Pineocytomatous features may coexist, or transitions between the two tumor appearances may be found. Retinoblastic differentiation can also be present, with the formation of "fleurettes" [2872] and of Flexner–Wintersteiner rosettes, typical of retinoblastoma (Fig.14.10). The fleurettes represent an attempt at differentiation toward photoreceptors [1120, 2720, 264]. Immunoreactivity for S retinal antigen, characteristic of

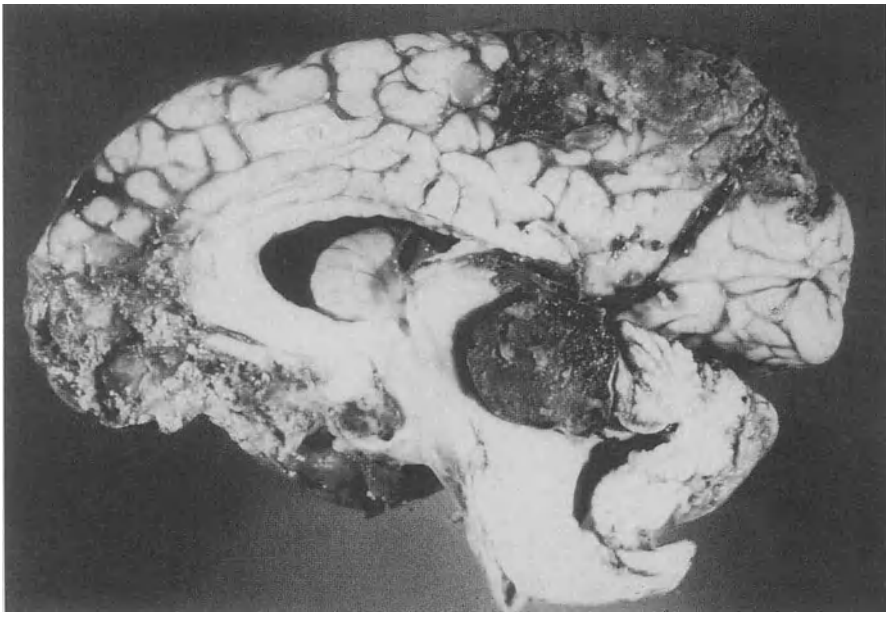


Fig.14.8. Pinealoblastoma

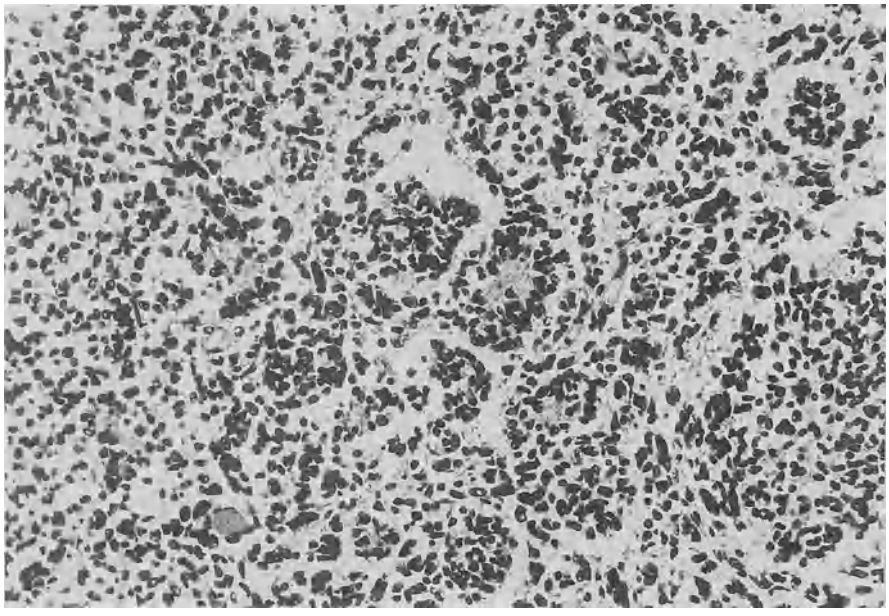


Fig.14.9. Pinealoblastoma, high cell density and ill defined Homer–Wright rosettes, H&E, ×300

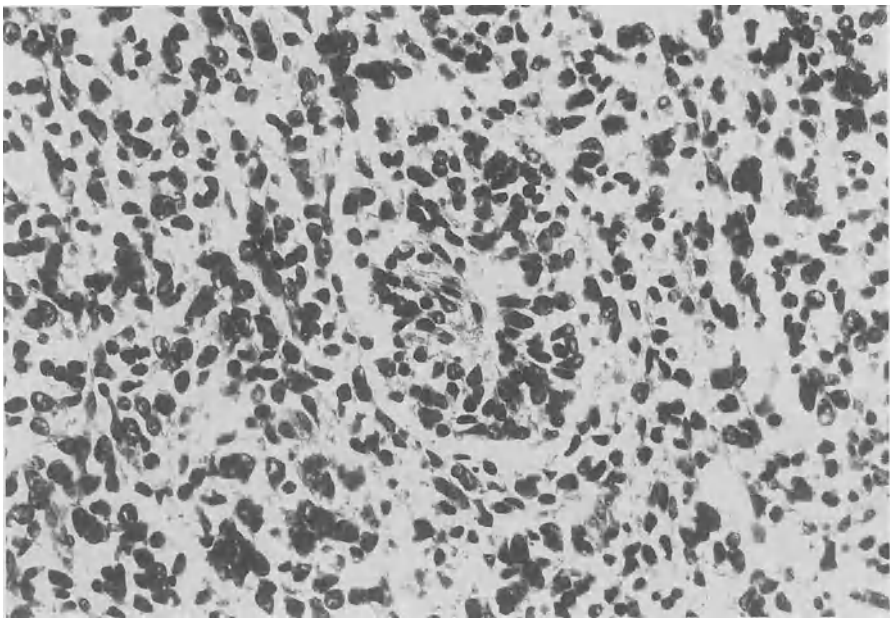


Fig 14.10. Pinealoblastoma, architecture resembling fleurettes, H&E, ×400

retinoblastoma [652], has also been demonstrated in cells of the pineal parenchyma as well as in pineocytomas and pinealoblastomas [2182, 531].

Neuronal differentiation has also been described in some cases [1120, 2681, 2344, 2073], and in one case retinoblastic differentiation and ganglionic and glial elements were seen [2681]. It is not yet clear whether the astrocytic elements are derived from the astrocytes of the pineal gland or represent multipotential differentiation of pineocytes, although the second hypothesis seems more probable [2420]. The same concept can be applied to cells with neuronal features, which might derive from normal neurons of the gland and not be a product of differentiation [1075].

Melanotic deposits have been described [191, 1120, 2533], which correspond to normal findings in the gland during development. In another case, rhabdomyoblastic features were also described, together with neuroblastic, ependymoblastic, and retinoblastic elements, which can be explained by the close topographic relationships between the neural crest and the neural tube at the level of the prosencephalon [2533]. Necrosis, hemorrhage, and calcification in the tumor may be found, but there is never endothelial hyperplasia.

Electron microscopic examination has been carried out in only a few cases. In one, analogies with photoreceptor elements of the pineal gland of inferior vertebrates were found [1456].

In the tumors of the human pineal gland, neither melatonin nor the enzyme which synthesizes it (hydroxyindol-O-methyltransferase) have been immunohistochemically found.

14.3.3 Prognosis

Metastasis via the CSF into the ventricles and subarachnoid spaces is common in pinealoblastoma [1476, 2103], and the prognosis is dismal [1168], although long-term survivors have been reported [2885]. Because of the paucity of cases, it has not been possible to glean precise clinical statistics from surveys. Similarly, it is difficult to evaluate the efficacy of treatment procedures such as radio-and chemotherapy [547].

14.3.4 Trilateral Retinoblastoma

Cases featuring an association between bilateral retinoblastoma and pinealoblastoma have been described in children. This goes under the name of "trilateral retinoblastoma" [100], and it is hereditary, while solitary pinealoblastoma is only exceptionally familial [1621]. Retinoblastoma may unusually be unilateral in this syndrome. Up to date, 30 cases have been reported [2420]. The association has a special significance in the context of pineal tumors, demonstrating the photoreceptor origin of the cells which undergo neoplastic transformation.

In very rare cases, a variant of the trilateral retinoblastoma, a retinoblastoma-like tumor in the supra-or parasellar region, has been described [100, 1426]. In one [2569], it was undifferentiated and exhibited immunohistochemical positivity for the S retinal antigen.

15 Embryonal Tumors

15.1 Medulloepithelioma

Medulloepithelioma is an extremely rare tumor which, according to Bailey and Cushing (1926) [112], is a primitive and multipotential tumor par excellence. It was fully described later [2862], and up to now almost 30 cases have been reported. The tumor recounts the architecture of the primitive medullary epithelium and its capacity to differentiate. In a personal collection, there is one such case.

It is a tumor of infancy, usually located in the hemispheres, but it has also been described in the posterior fossa [190, 2455, 254] and in the cauda equina [1354].

Macroscopically, it appears as a circumscribed, grayish, hemorrhagic, necrotic or cystic tumor.

Histologically, it features papillae and tubules formed by columnar or cuboidal cells which simulate the neural tube (Fig.15.1). There is a PAS-positive limiting membrane, of doubtful nature, on the luminal surface and an external limiting membrane, which is strongly PAS-positive and rests on a delicate connective tissue. Mitoses are frequent and found close to the lumina of the tubules.

The tumor is capable of differentiating toward neuroblastic, ependymal, astrocytic, or oligodendrocytic lines and sometimes in all directions [2473, 254].

Four cases have been the object of an accurate immunohistochemical study with a panel of antibodies and antisera [353]. It has been observed that, apart from the medullary primitive epithelium, there are neuroblastic, ganglion, astrocytic, ependymoblastic and ependymal areas; in one case, even an area of polar spongioblastoma was found. The primitive medullary cells were found to stain positively for GFAP, vimentin, and class III β-tubulin. It is important to note that vimentin marking was positive in ependymoblastic areas and in ependymal rosettes. The stroma is of variable consistency and contains blood vessels. It is susceptible to metaplasia, as in one case in which there was formation of cartilage, bone, and striated muscle [88], to the point of suggesting a mixed mesenchymal and neuroepithelial origin.

The differential diagnosis has to include ependymoma, malignant plexus-papilloma, and teratoma. The diagnosis is difficult when differentiation signs are poor or lacking. The biological behavior is that of a malignant tumor with spread to the subarachnoid spaces [2216], and extraneural metastases [2907] have also been reported.

15.2 Medulloblastoma

Medulloblastoma was separated off as a distinct tumor entity by Bailey and Cushing and given the name of "spongioblastoma cerebelli," which was later modified by the same

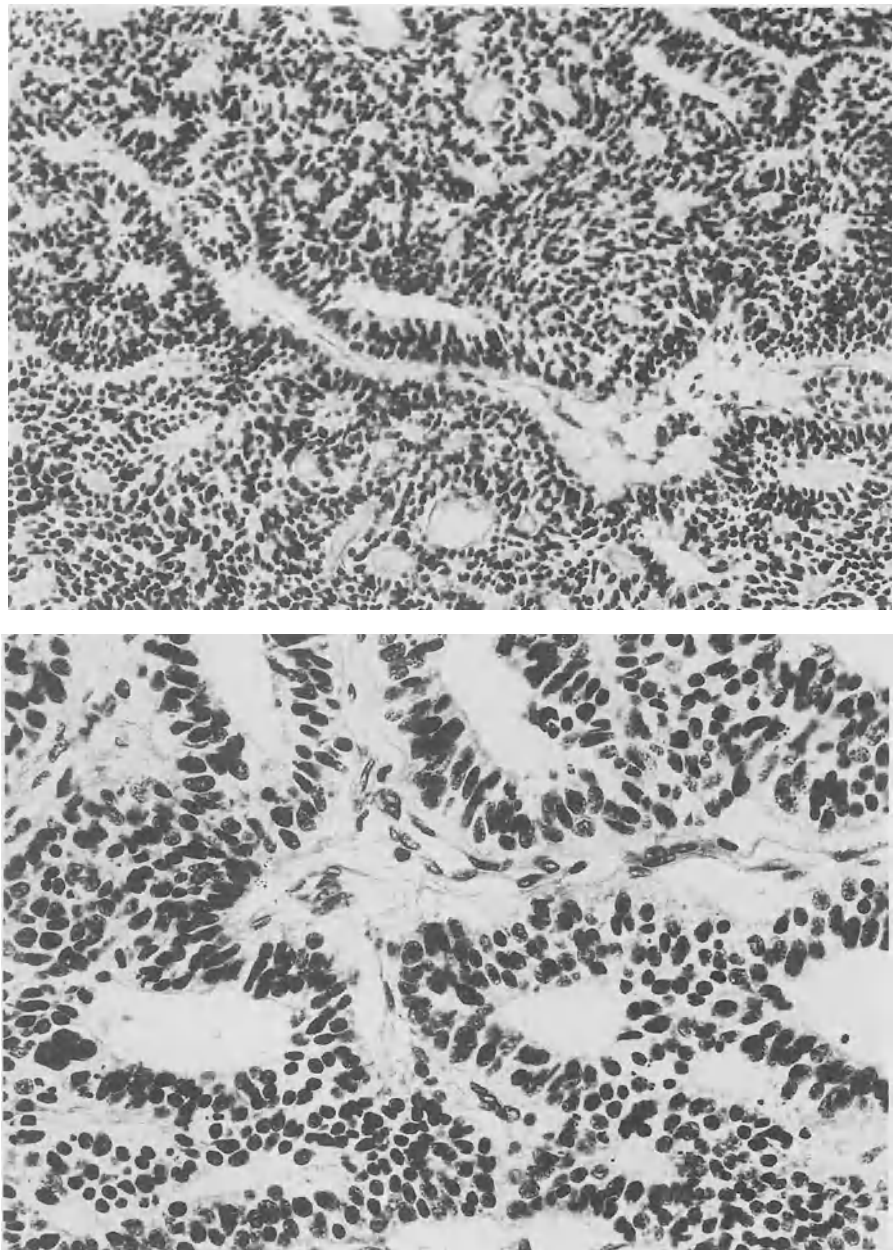


Fig.15.1. Medulloepithelioma: **a** general architecture with tubules and rosettes, H&E, ×200; **b** columnar and cuboidal cells of tubules, many mitoses, H&E, ×400

authors [1925] into "medulloblastoma cerebelli," to avoid confusion with other known tumors with the same label. It was later variously defined, for example as a neurospongioma [2382], an isomorphous glioblastoma [1189], or a granuloblastoma [2738], reflecting the various opinions on its origin. The tumor is generally considered to be formed by immature and undifferentiated elements, which are capable of differentiating toward glial and/or neuroblastic lines.

15.2.1 Frequency, Age

It arises frequently, representing about 4.2% of all CNS tumors [3138]. In infancy, it is much more common, with values of around 20%–25%. In the posterior fossa, it is almost as frequent as cerebellar astrocytoma. There is a slight prevalence in men [2329, 3134, 2486]. The incidence peak is found between 7 and 12 [3138] or 5 and 10 years [2486]. Medulloblastomas are rarely found over the age of 50 years [80, 442]. Patients with laterally located medulloblastoma are older [2402].

Congenital cases have been described [1004, 160, 49, 1416]. The incidence is 1 /200,000 children per year. Environmental factors of etiological importance have been sought but not found. It was noted that the increase in incidence of this tumor in the years 1954–1958 was associated with the use of polio vaccine contaminated with SV40 virus [751].

Familial occurrence of medulloblastoma has been reported [2845].

15.2.2 Macroscopic Appearance

The tumor usually arises in the vermis and presents as a soft, gray-pink mass, sometimes with evident necrosis. At times, it is so soft that it can be aspirated during surgical intervention. In some cases, especially if the tumor arises in the cerebellar hemispheres, it may be very hard and involve the meninges which appear thickened (Fig.15.2). Expanding into the cerebellum, the tumor may invade the roof of the fourth ventricle and grow, filling the ventricle (Fig.15.3). It may grow up to the aqueduct or block the foramina of Magendie and Lushka. Locally, it infiltrates the cerebellar cortex but may fungate into the subarachnoid spaces and then re-enter the cerebellum, including wide portions of the cerebellar lamellae.

15.2.3 Microscopic Appearance

The tumor is characterized by a very high cell density (Fig.15.4a). The cells are relatively isomorphous or moderately polymorphous with a roundish or elongated shape, a scanty, sometimes pear-shaped cytoplasm, and a small apical process or with a double panache at the sides of the nucleus. The nuclei are hyperchromatic. Mitoses are very frequent (Fig.15.4b) and very often atypical, more so than appear on superficial examination (Fig.15.4c–f). The more common pathological findings are given by pictures like "laggard chromosomes," "three group metaphase," etc. [2496]. Quantitative data dem-

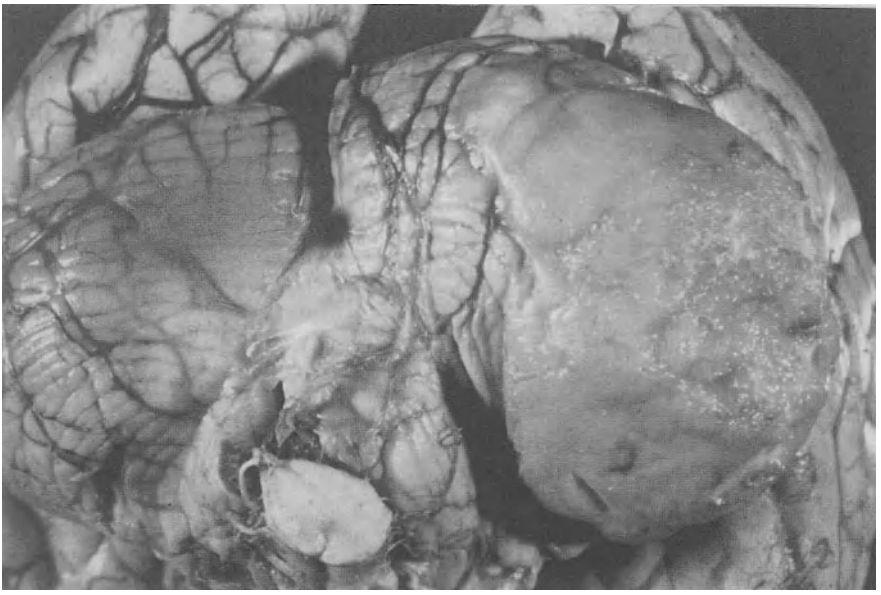


Fig.15.2. Medulloblastoma of the cerebellar hemisphere

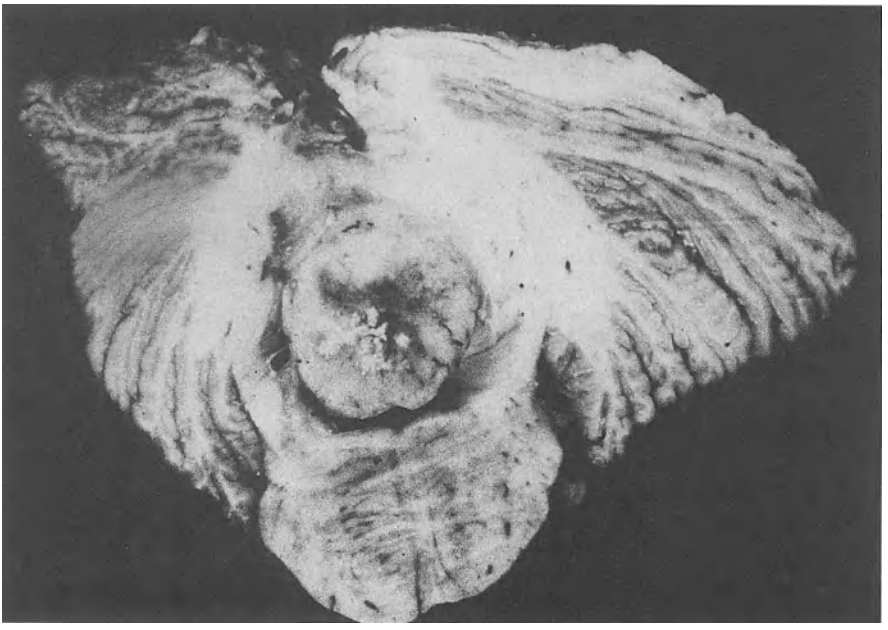


Fig.15.3. Medulloblastoma of the vermis filling the fourth ventricle

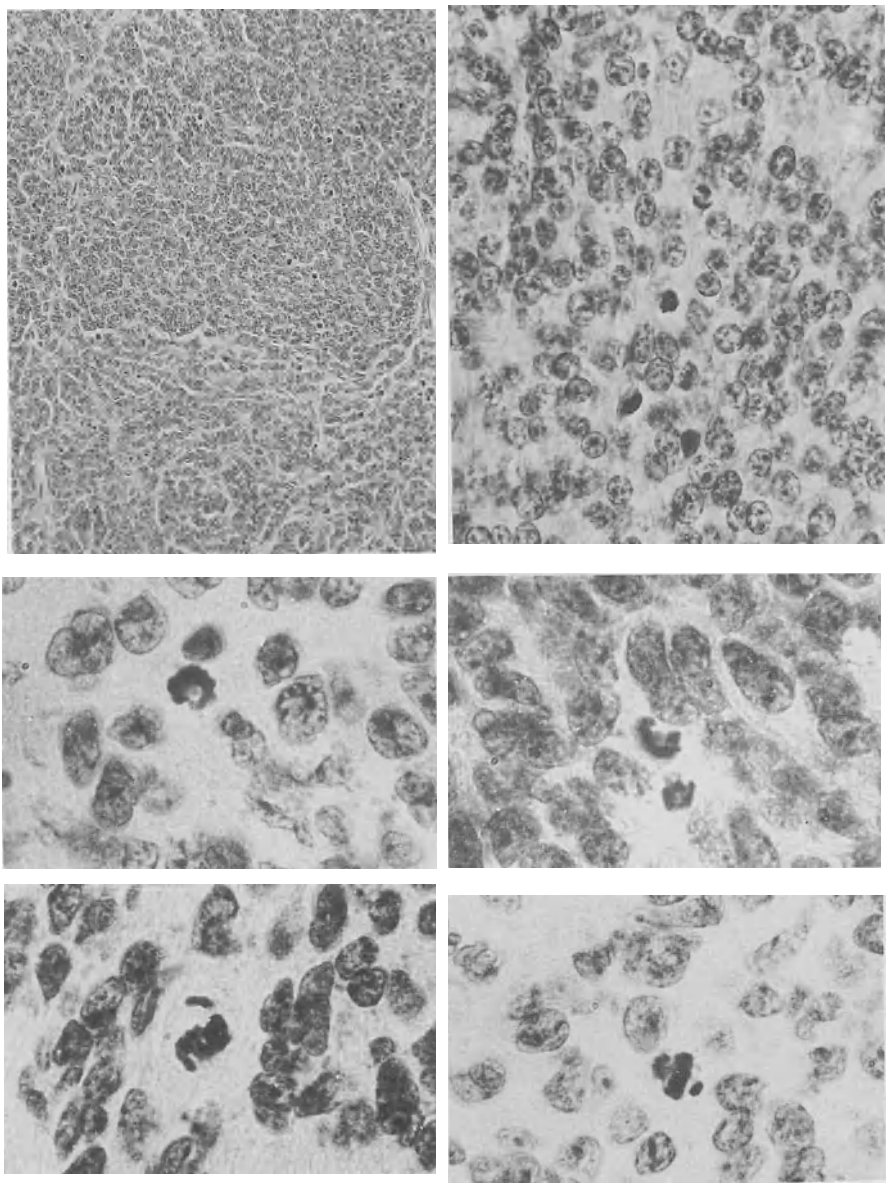


Fig.15.4a–f. Medulloblastoma: **a** isomorphic cells with high density, H&E, ×200; **b** frequent mitoses, H&E, ×400 ; **c,d** C-mitoses; **e** laggard chromosomes; **f** three-group metaphases mitosis, carmalum, ×1000 [2486]

onstrate that 25% of mitoses are abnormal and that 30% of these are bizarre [2563]. The nuclei in general are relatively isomorphous, but occasionally some polymorphism is observed, and sometimes there are true monstrous nuclei [1109, 2881], located particularly along the stromal septa which separate the tumor lobules (Fig.15.5a).

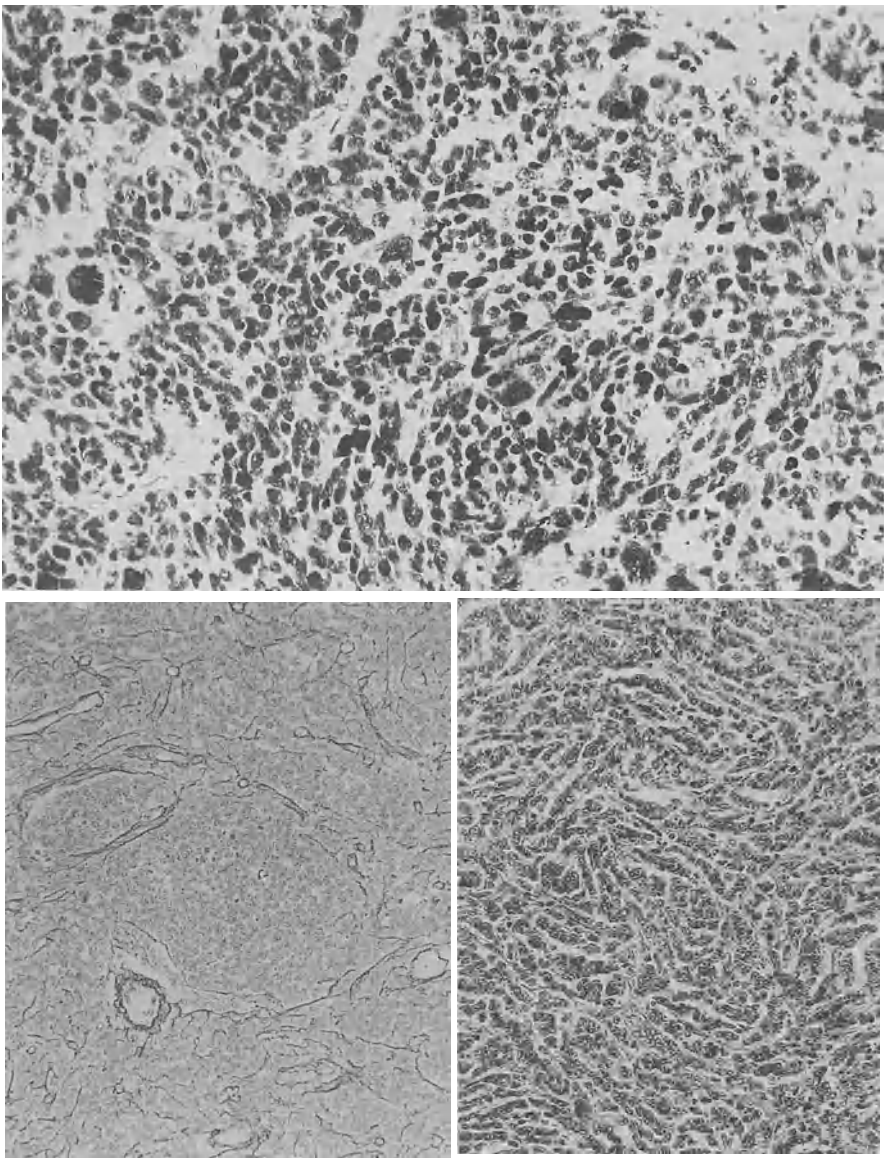


Fig.15.5a–c. Medulloblastoma: **a** polymorphous nuclei, H&E, ×400; **b** tumor lobules delimited by reticulin fibres, Gomori, ×200; **c** cords of tumor cells in the desmoplastic variant, H&E, ×200 [2486]

Cases with cells and nuclei of larger dimensions are not rare. The tumor tends to have a lobular structure, and the lobules are separated by reticulin septa connected with blood vessels (Fig.15.5b). The cells tend to form pseudorosettes, which are known as Homer–Wright rosettes (Fig.15.6a). They are composed of cells arranged around a fi-

brillary center similar to those of neuroblastoma. Necroses appear as small, circumscribed foci which at times exhibit hypercellularity at their border or even pseudo-palisades. Small calcifications may be present. Lymphocyte-like nuclei, which correspond to cell necrosis or to pathologically arrested mitoses, are found throughout the tumor(Fig.15.6b,c). The DNA of these cells appears to be "denatured" [2496]. The vascularization of the tumor is scanty when considered in the light of its speed of growth. It consists mostly of blood vessels of small caliber. There are, at times, larger vessels, but thrombosis is usually lacking and endothelial proliferation is moderate. However, at times the stroma is particularly represented: Blood vessels show thickened walls containing proliferating nonendothelial cells or even intraparietal proliferations of tumor cells (Fig.15.7a).

15.2.3.1 Desmoplastic Variant

A variety of medulloblastoma is known as "desmoplastic." It is characterized by growth of the tumor in the meninges so that the tumor acquires a circumscribed appearance and an increased consistency. The location is often lateral. Cords of tumor cells (Fig.15.5c) are formed which run in parallel with thick, abundant collagen and reticulin fibers (Fig.15.7b,c). In another mode of subarachnoid growth comparable with the "cerebellar arachnoid circumscribed sarcoma" [792], tumor cells are arranged as mosaics in roundish areas devoid of reticulin but surrounded by rich reticulin strands to simulate reactive follicles of lymph nodes (Fig.15.8). These go under the name of "pale areas" or "pale islands" (Fig.15.9). Given the importance that the desmoplastic variety has in the biology of the tumor, it is necessary to emphasize that a type of vascular desmoplasia has been recognized [2353], when there is a particular richness in the stroma, even when the meninges are not involved.

Cerebellar neuroblastoma, a variant characterized by lobules of cells immersed in a thin Bodian-positive network and hence formed by neuritic prolongations, has been described (Fig.15.10b) [2626, 2158, 3086]. The nuclei are vesicular and contain an evident nucleolus, a sign of neuronal differentiation (Fig.15.10a); sometimes even mature neurons are present [1350, 2419], especially at the edges of the lobules. The distinction between the so-called cerebellar neuroblastoma and the desmoplastic variant of medulloblastoma is not easy because there is not a clear cut separation between the areas described above and "pale areas."

15.2.3.2 Melanotic Medulloblastoma

Rarely, and only in children, a pigmented variety has been described [806, 2402, 2767, 191, 238, 665, 648], characterized by cells containing melanin pigment. In general, it is thought that these tumors, usually with neuronal differentiation, derive from the neural crest as the melanotic progonoma, but in contrast to this neoplasm they are malignant.

15.2.3.3 Medullomyoblastoma

Another variety, containing striated muscle tissue, is known as medullomyoblastoma. Muscle fibers, sometimes abundant, are positive for desmin and myoglobin and under polarized light show the characteristic striations (see Chap. 21). It is thought that the

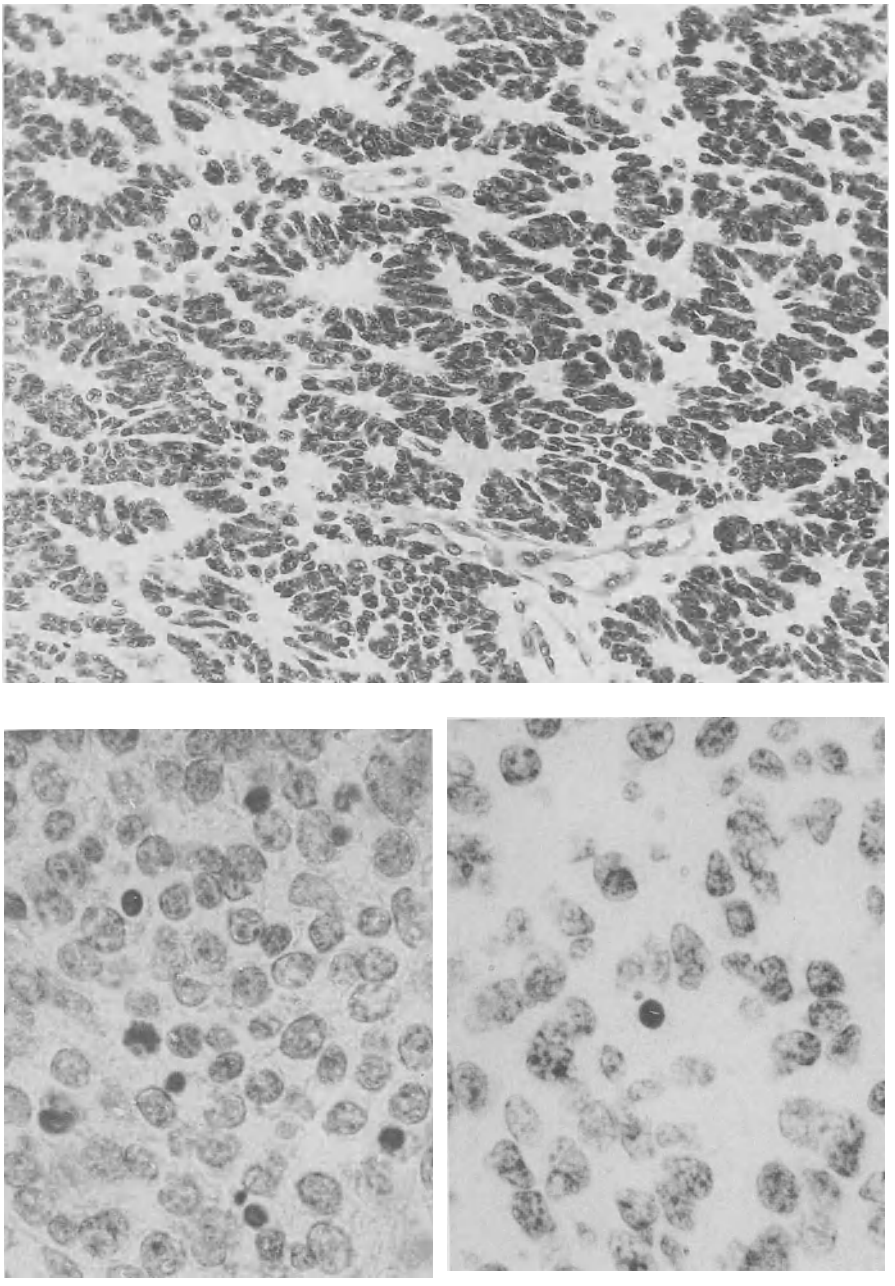


Fig.15.6a–c. Medulloblastoma: **a** Homer–Wright rosettes, H&E, ×400; **b,c** lymphocyte-like nuclei, Carmalum, ×1000 [2486]

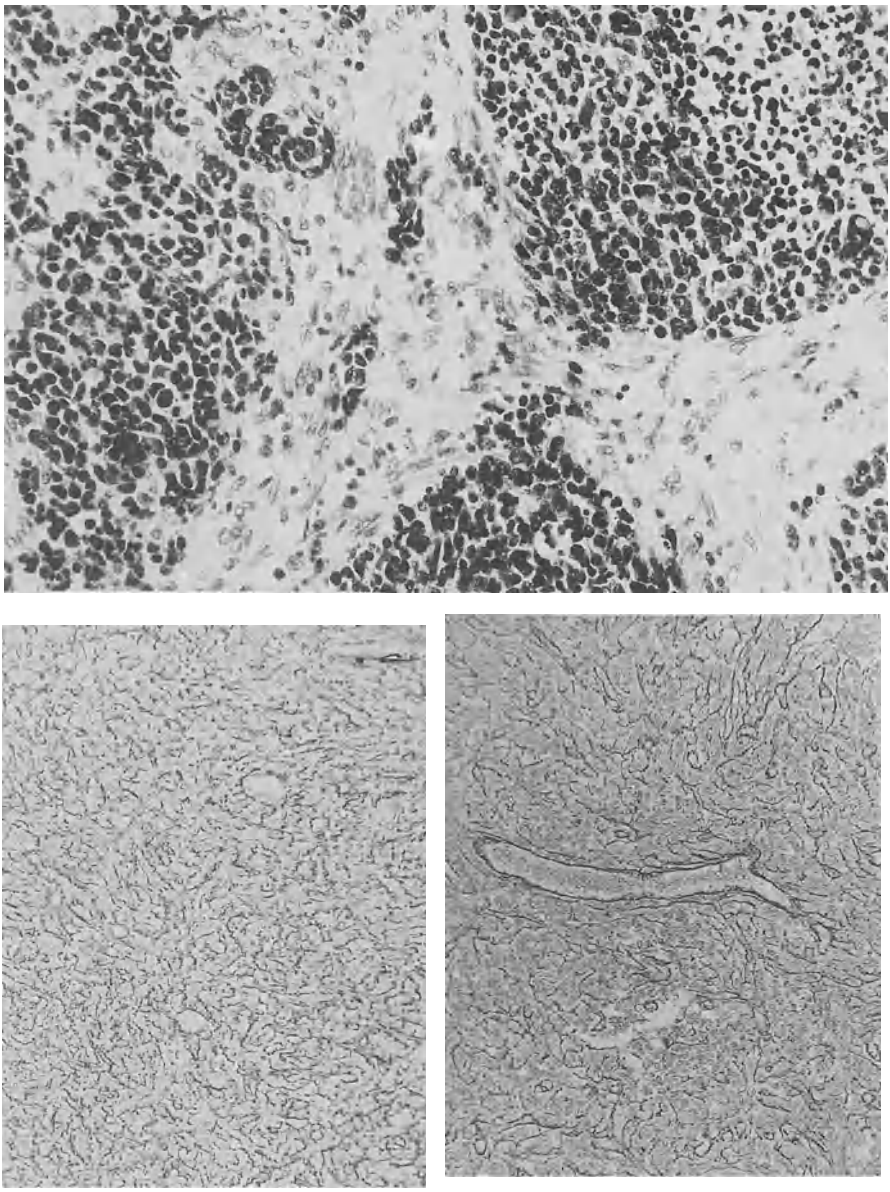


Fig.15.7a–c. Medulloblastoma: **a** hypertrophic stroma with proliferated vessel walls, H&E, ×300: **b**,**c** desmoplastic variant with abundant reticulin network, Gomori, ×200 [2486]

rhabdomyoblastic component derives from the ectomesenchyme, i.e., from the neural crest. The observation that rhabdomyoblastic differentiation occurs in transplants in nude mice from a permanent cell line of a classic medulloblastoma would suggest a neuroectodermal derivation [919], as has been observed in experimental cultures of gliomas [1615, 1272].

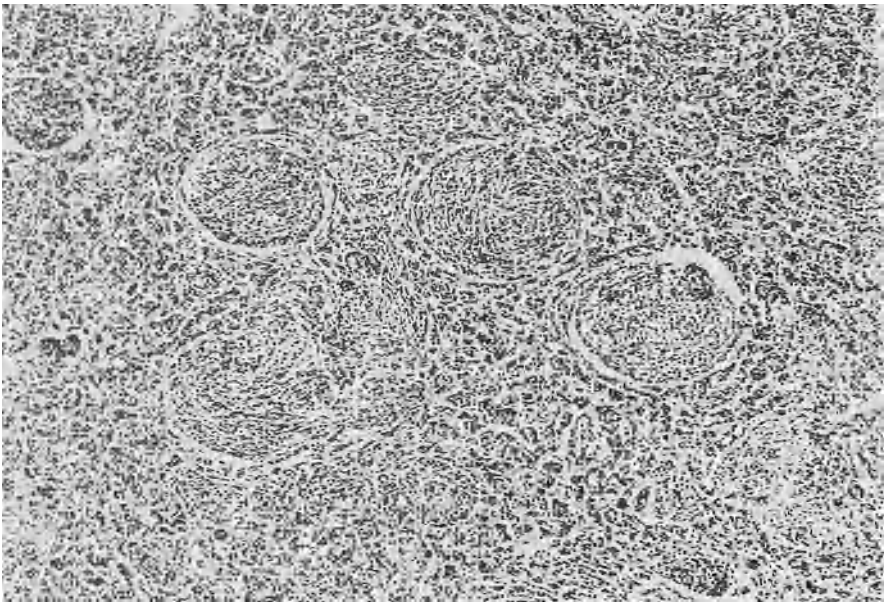


Fig.15.8. Medulloblastoma, follicles in subarachnoidal growth, H&E, ×200

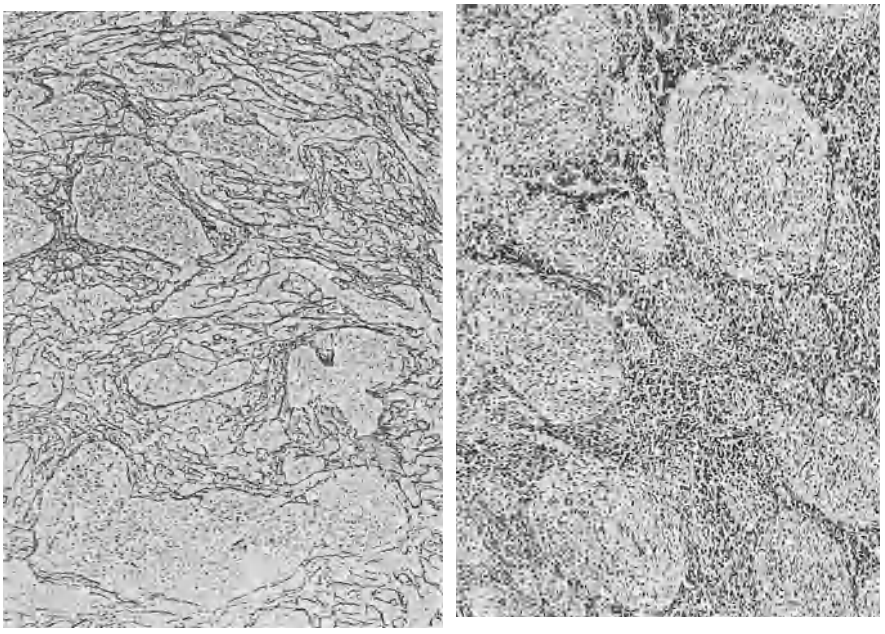


Fig.15.9a,b. Medulloblastoma, pale islands **a** delimited by reticulin, Gomori, ×300; **b** with Bodian staining, ×300

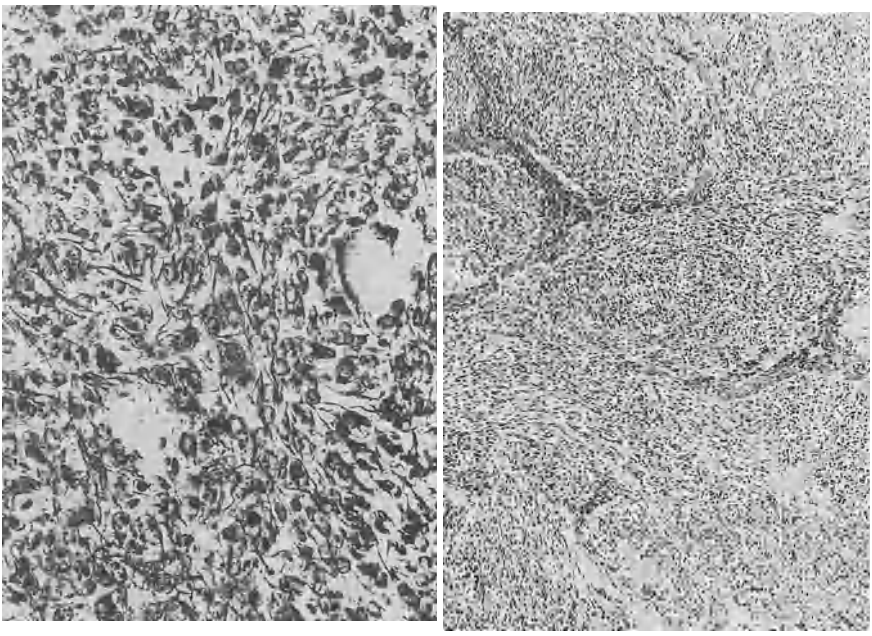


Fig.15.10a,b. Medulloblastoma: **a** cells with short positive processes, in neuronal differentiation, Bodian, ×400; **b** general aspect of differentiated tumors, also called cerebellar neuroblastomas, Bodian, ×150

15.2.4 DNA Content and Pathology

On the basis of microfluorimetric and flow cytometry studies, medulloblastoma has been found to be composed of diploid and, more rarely, of tetraploid cells [1201, 1606, 1938, 2856]. Desmoplastic tumors usually have a diploid DNA content. From chromosomal analyses, it has been found that diploid and, more rarely, almost tetraploid cell lines prevail [1584, 212].

Cytogenetic data have been, up to now, limited to a few cases (see Chap. 4). The most common change is the presence of isochromosome 17q [196 , 365]; other common changes involve chromosome 1, 6q, 11, 16q, 17p, or 22 [2891, 2254, 207]. Chromosome 17p contains the gene for p53, which is another gene suggested to be a recessive cancer gene [1833].

15.2.5 The Problem of Differentiation

This problem has been debated for half a century and regains strength with each new application of techniques capable of unveiling the glial or neuronal nature of the cells. Basically, it has to be established whether medulloblastoma is an undifferentiated tumor, i.e., formed by primitive, undifferentiated, neuroepithelial cells, or if neuronal and/or glial differentiation takes place. Fifty years of histology, electron microscopy, in vitro culture, histochemistry, and histoenzymology studies have demonstrated, on the one hand, the existence of neurons or neuroblasts and astrocytes

and, on the other, that these were, respectively, included in the tumor proliferation, reactive to tumor invasion, or the product of cell differentiation. The whole problem has been reviewed by us up to 1975 [2486]. In the epoque of immunohistochemistry and molecular biology, the debate has gone on with further data, obtained with sophisticated procedures. With immunohistochemical methods, it is possible to demonstrate within the tumor GFAP-positive, and hence glial, cells [603, 619, 712, 2903, 581, 2923, 1756, 2126, 926, 2509, 2526, 1116, 341].

Depending on the evaluation expressed by various authors on the GFAP-positive cells as tumor or reactive, the incidence of astrocytic differentiation in medulloblastoma has been found to be minimal or absent [467, 2509, 2526], in 50% [2344] or in an even higher percentage of cases [2126]. On the basis of shape, location, and distribution, criteria have been devised to identify GFAP-positive cells as reactive astrocytes or as tumor cells, and hence the expression of glial differentiation by the tumor [1756]. No clear-cut, absolute results have been achieved, the definition of GFAP-positive cells as tumor (Fig.15.11b) or reactive (Fig.15.11a) remaining the result of interpretation [530]. In more recent series, it seems that astrocytic differentiation does not occur in more than 10% of cases [1523, 341].

The finding of GFAP-positive cells in the desmoplastic growth is in favor of glial differentiation [1116]. However, opinions are divergent [467, 2526]. Of particular importance is the finding of GFAP-positive astrocytes in the "pale islands" (Fig.15.12a) [1116, 1358], especially at the border of the reticulin rim, which should resolve the matter because the "pale islands" are only found in the subarachnoid growth and also in the metastases [2402]. However, the doubt that these structures or at least part of them are related to inclusions of healthy cerebellar tissue has not been completely ruled out [2519]. The problem of glial differentiation in medulloblastoma has a theoretical basis, because the external granular layer of the cerebellum does not seem to give rise to neurons and glia, but only to neurons [531, 613], and there is no doubt that medulloblastomas arise from it [1333, 2396]. However, other structures may give rise to medulloblastoma and are capable of differentiating toward glia before neurons [1638], i.e., the internal granular layer in the roof of the fourth ventricle, which forms the external granular layer, due to dorsal and lateral migration. Medulloblastoma may, therefore, originate in different embryonal periods with different histological features and at different ages of patients [2396]. Under this profile, cases of congenital medulloblastoma are very important (see above). In two recent cases, it has been possible by extrapolating from the growth curves to date the beginning of the tumor to between the 15th and the 24th weeks of i.u. life [1132], which is the period of the highest histogenetic activity of the cerebellum and in which the cells of the external granular layer are not yet engaged in becoming neurons. The fundamental fact remains that up to now the best demonstration of glial differentiation of this tumor is obtained in culture [1112]. An event that is difficult to ascertain must still be considered, i.e., that glial progenitors are present in medulloblastoma, which still do not express GFAP. In cultures of a medulloblastoma, it has been demonstrated that GFAP expression may be induced in GFAP negative cells by adding dibutyryl cyclic adenosine monophosphate (dBcAMP) [1766]. This demonstration is a good point in favor of the existence of glial differentiation in medulloblastoma but still does not give sufficient guarantees as to the real existence of glial tumor cells not expressing GFAP, but capable of doing so. Differentiation toward an oligodendroglia line has also been considered, given the presence of "honeycomb" cellular features (Fig.15.12b) as in oligodendroglioma [2402]. These features may sometimes be found but could be the expression of degenerative events. They have also been interpreted as foci of neuronal differentiation [341].

The demonstration of neuronal differentiation is better substantiated, if it can be excluded that elements with neuronal characteristics are to be interpreted as normal, included elements, an event which is not at all infrequent, given the mode of growth of medulloblastoma. Electron microscopy data indicating neuronal differentiation are not any more reliable than those indicating glial differentiation [369], even if in some cases electron microscopy has unequivocally demonstrated the neuroblastic nature of the tumor, to the point that these cases were called "cerebellar neuroblastomas" [729, 2626, 1136, 2158, 3086]. Recently, neurite-like processes containing longitudinally oriented microtubules united by "adhesion plaques" have been observed. As in embryonal neurons, they are rich in microtubules and poor in NF. This would explain the low reaction with the corresponding antibodies. As differentiation proceeds, the NF increase, and the neurite-like processes elongate, forming the "pale areas," already described [1358]. From the immunohistochemical point of view, mono- and polyclonal antibodies against NF have not always been used with con-

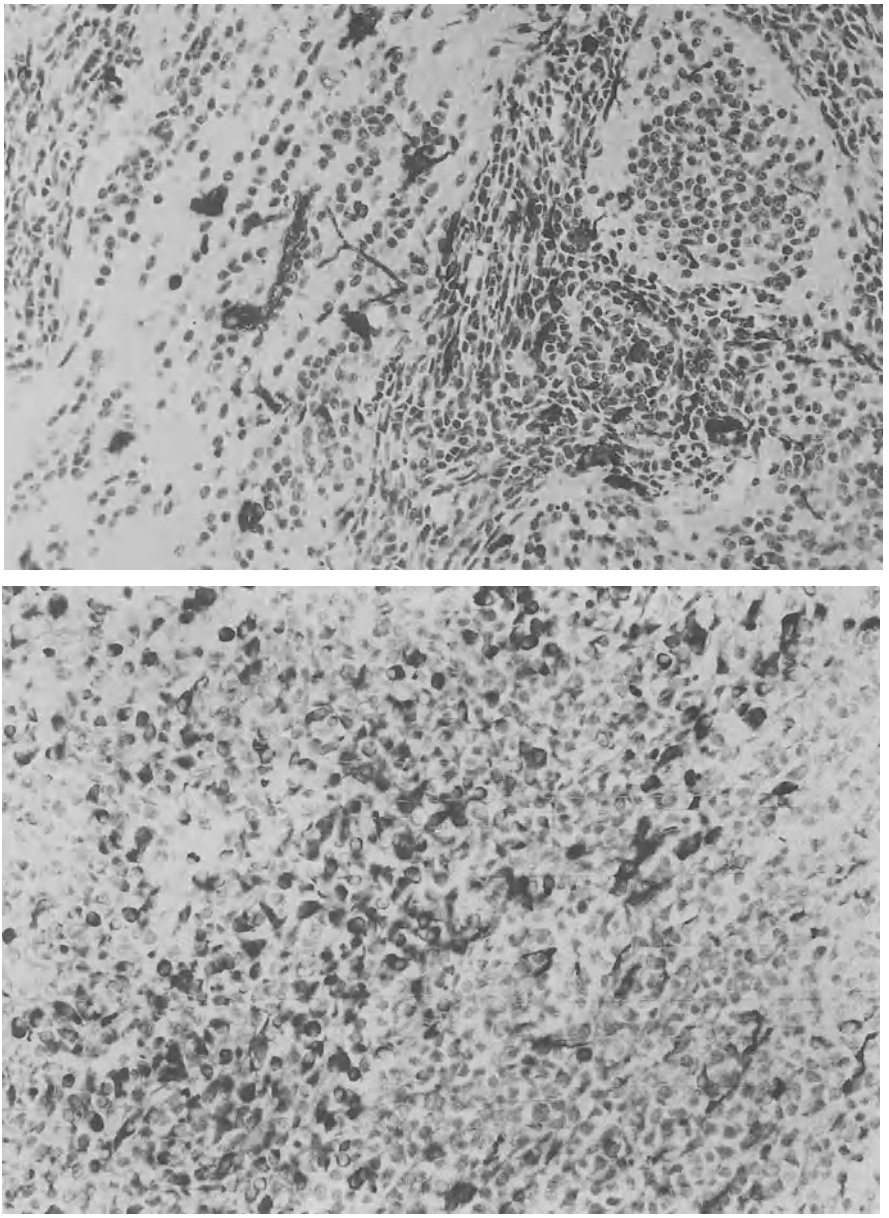


Fig.15.11a,b. Medulloblastoma: **a** GFAP-positive cells of reactive nature, PAP-DAB, ×400; **b** GFAP-positive tumor cells, PAP-DAB, ×400

cordant results [2344, 831, 2924, 341]. In general, the antibodies highlight mature neurons when they are already visible by common histological methods, and therefore, one may be suspicious of their being normal, included neurons. Depending on technical limitations, frequently only neuronal processes can be demonstrated. NSE has been demonstrated to be present sometimes, but it is

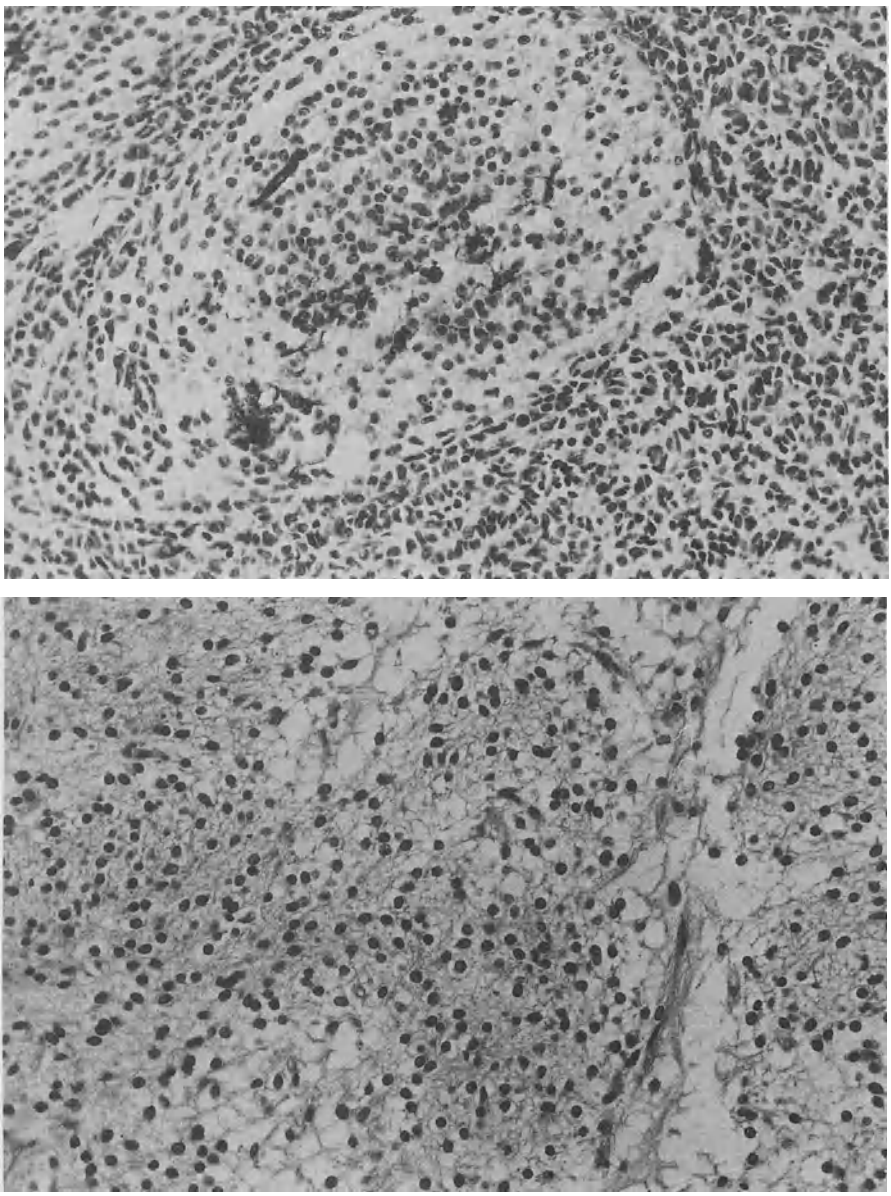


Fig.15.12a,b. Medulloblastoma: **a** GFAP-positive cells in a pale island, PAP-DAB, ×400; **b** oligodendroglial-like aspect, H&E, ×300

not completely specific for neuronal neoplasias [1042, 2939]. The conclusion must be made very cautiously; however, it is possible to highlight positive areas which correspond to areas with histological signs of neuronal differentiation [926, 341]. The positivity for synaptophysin (Fig.15.13) seems rather more reliable. It has been demonstrated in medulloblastoma [982, 2574], but more de-

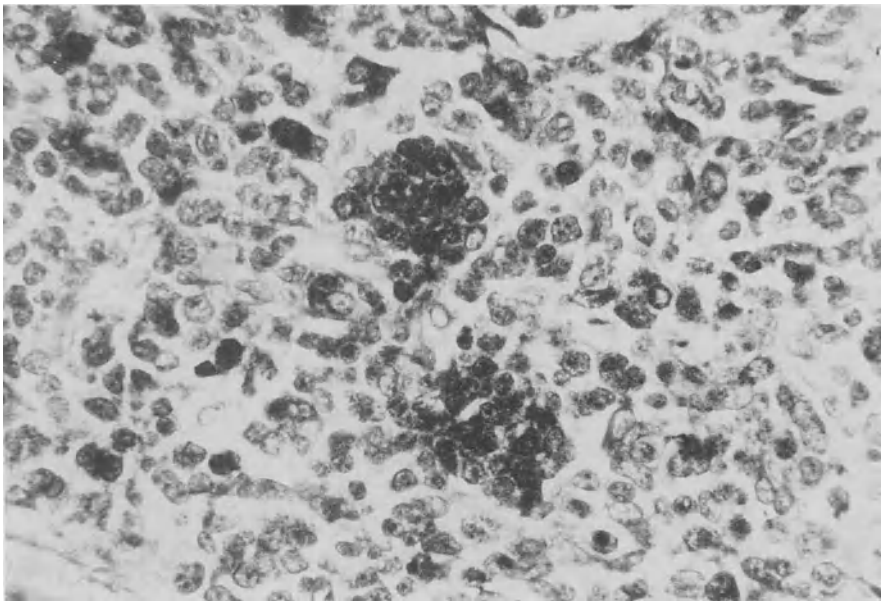


Fig.15.13. Medulloblastoma, synaptophysin positivity, PAP-DAB, ×300 (Courtesy of Dr. F. Giangaspero, University of Bologna)

tails are needed. Still more dependable seems to be the demonstration that the pale areas are the site of positivity not only for NSE but also for tubulin [1358]. Recently, the presence of "synaptic ribbon" type structures, which occur in photoreceptor cells and pineal neoplasms, has also been reported [1112], in line with the immunohistochemical demonstration of photoreceptor molecules [1485, 2181]. Some 35% of medulloblastomas contain the S retinal antigen (S.Ag), thus appearing capable of a differentiation toward photoreceptors [2177].

Recently, reliable data on the immunohistochemical demonstration of differentiation antigen toward neuronal, glial, or even neuroendocrine lines have become available [1914, 983, 1066]. Interesting studies were carried out on permanent cell lines, of which four are still continuing. Phenotypic analysis demonstrated that in two of the lines there is a glia-like phenotype [1832, 1273], and in two it was neuron-like [831, 832, 1091]. In the latter, neurofilament subunits of high and medium but not of low molecular weight are produced [2869, 832]. The possibility of rhabdomyoblastic differentiation has already been mentioned [919].

Medulloblastoma is therefore a truly heterogeneous tumor [913]. In every day experience, the neuronal differentiation does not seem questionable, since cells with neuroblastic or neuronal features are visible in many tumors with hematoxylin–eosin or Bodian staining, especially when in greater number than normal for the cerebellum. Homer–Wright rosettes, which in reality are pseudorosettes because they do not have a real central cavity, are usually accepted as a sign of neuronal differentiation, because of the analogy with the structures in sympaticoblastomas. The problem of differentiation in medulloblastoma is, therefore, still under discussion, but the occurrence of differentiation is today beyond doubt, especially that toward the neuronal line. It has been demonstrated that there is a similarity between the cytogenetic stages of cells in neuronal differentiation and medulloblastoma cells [2866]. Specific polypeptides such as microtubule associated protein (MAP) and NF subunits are similar. In a review of 330 cases, neuronal differentiation was immunohistochemically observed in 60% of cases compared with 13% of the glial one calculated by GFAP-positive staining [1442].

As for the experimental induction of medulloblastoma, JC virus, a human DNA virus of the genus *Polyomavirus*, has been shown to induce medulloblastoma in hamsters. The infected neona-

tal cells in the external granular layer migrate towards the internal layer and carry the signal of JCV large T mRNA. The origin of the tumor could thus be in the cells of the external granular layer [1987].

15.2.6 Prognosis, Recurrence, Metastasis

Medulloblastoma grows by infiltration and frequently metastasizes in the nervous system. Metastases normally occur via the CSF and are usually found in the arachnoid, in the vertebral canal, between the spinal roots, in the cauda equina, and on the ependymal surface of the ventricles. Sometimes they may even occur against the flow of CSF. For this reason, the cytological examination of the CSF has taken on a particular importance, especially in relationship to the prognostic evaluation and treatment. Medulloblastoma, together with glioblastoma, is also the neuroectodermal tumor which most frequently metastasizes outside the CNS [371], probably because of the disruption of the BBB [1936]. Preferred sites are bones (vertebrae, femur, pelvis), lymphnodes, liver, and lungs [2392, 1448, 1839].The bony location is responsible for the possible pancytopenia [2708]. The tumor may also infiltrate nearby structures by contiguity, with intradural spread [1280].

The prognosis of medulloblastoma is poor, if not treated, as is that for local recurrence after surgical removal. More than 50 years ago, in the series of Cushing (1930) [539], operative mortality was 32% with an average survival of 5.5 months. Today, 50% of treated patients survive 5 years. Treatment consists in surgical removal, irradiation, and chemotherapy, articulated in diverse protocols of multimodal therapy on the basis of which maximum survival periods of notable duration are obtained [1482, 1578, 230, 738, 2790]. The radiotherapy scheme foresees a tumor dose and an adjunctive prophylactic irradiation to the spinal cord and cerebrum. However, although this regimen may result in a cure, given the clearly aggressive character of the therapy, deleterious effects on intellectual and somatic development and on the endocrine and hematological functions may appear [676, 1181, 938]. The problem of therapy of medulloblastoma is thus more complex than that of malignant gliomas of adults.

The dissemination of the tumor via the CSF, even against the flow, has rendered necessary irradiation not only of the tumor focus but also of the brain and spinal cord. One must note, however, that while supratentorial irradiation is responsible for the endocrine and neuropsychological sequelae, the probability of supratentorial metastases is only 8% [1578].

On the basis of Collins' law [479], according to which the period of risk of recurrence is equal to the age at the moment of appearance of the tumor plus 9 months, survival beyond this period is equivalent to cure. Actually, for medulloblastoma there are recurrences well beyond this period. A large number of studies have been dedicated to the identification of prognostic factors, which are essentially age, sex, extent of surgical resection, extension of the neoplasia, histological features, and radio- and chemotherapy. First of all, it appears, not without contradictory data, that an age over 3–5 years and the female sex lead to a better prognosis: 60% against 40% survival at 5 years [183, 2133] or a longer disease-free interval [378]. The extent of the surgical removal is an important factor, because total removal seems to lead to longer survival [2256, 2133, 2852 , 1256], but not everyone agrees on this point [378].

The radiation dose to the posterior fossa is also the subject of controversy: while for many authors a dose of 50–55 Gy leads to better survival [183, 1482, 2133, 1607], for others there are no differences vs a dose of 40–50 Gy. Given the frequency with which tumor spread occurs in the subarachnoid spaces, the entire craniospinal axis is usually irradiated. The trend today is to lower the dose to the cerebrum in order to reduce the negative sequelae already mentioned [1046].

The prognostic importance of the histological factors is extremely controversial. Individual histological signs do not seem to be important, but some associations are, for example, necroses and numerous mitoses [1482]. The favorable prognostic significance of the desmoplastic variant as compared with the classic one, on which many agree, is the object of discussion [1847, 416, 2133]. In striking contrast are the results of studies on the prognostic influence of histological signs of differentiation. For some [2104] they did not have any importance, while for others, 72% of patients with such signs were still disease-free after 5 years [378]. In recent series, tumors with neuronal differentiation do not appear associated with a better prognosis [1442], whereas tumors with GFAP-positive tumor cells seem to lead to a longer survival [959].

The efficacy of chemotherapy is still under discussion [2102, 2111]. In general, it retards but does not prevent recurrence.

The best results are obtained in association with radiotherapy and in recurrences. In association witht the postoperative radiotherapy, polychemotherapy (CCNU, vincristine, procarbazine and prednisone) appeared to be efficacious in poor-risk patients (small children, large tumors invading nearby structures, incomplete resection, presence of metastases), even though systematic toxic effects are significant (34 ; 738 ; 2790). In recurrences, various chemotherapeutic agents have been shown to be effective, both singly (high dose methotrexate, cyclophosphamide, cisplatin, carboplatin) [34 ,2102] and in combination. Among the latter are 8-drugs-in-1-day [2167], CCNU, vincristine and cisplatin [1604]. Studies are in progress concerning the possibility of reducing the radiation dose to the neuraxis and delaying radiotherapy in small children by preirradiation chemotherapy [1505 , 2102].

15.3 Neuroblastoma

Neuroblastoma is a rare, primitive, hemispheric tumor which arises in children under 5 years of age; 26% of sufferers are children under 2 years old [166]. Up to 1976, 12 definitive cases had been reported [1191]. Subsequently, single cases have periodically been described, and now their number is over 80 [872].

15.3.1 Macroscopic Appearance

The tumor is rather large, well-circumscribed, hard, grayish-white, often cystic, and sometimes necrotic or hemorrhagic. It is located (in decreasing order of frequency), in the frontal, parietal-temporal, and occipital areas [1191].

15.3.2 Microscopic Appearance

The tumor is formed by densely packed cells with a hyperchromatic nucleus and numerous mitoses, so that it resembles medulloblastoma (Fig.15.14a). Three varieties have been distinguished [1191]. In the classical one, the stroma is scarce and limited to blood vessels. The tumor may have a clear-cut limit toward normal nervous tissue or infiltrate diffusely. Homer–Wright rosettes are present, as are sometimes mature ganglion cells (Figs.15.14b, 15.15) (ganglioneuroblastoma). In the transitional variety, the amount of connective tissue is greater, and this is responsible for a lobulated appearance, while Homer–Wright rosettes and mature neurons are less frequent. In the desmoplastic variant there is a compact network of connective tissue with marked lobulation, while Homer–Wright rosettes and mature neural forms are even less frequent. Numerous reactive astrocytes are present around the tumor. The abundant stroma (Fig.15.16) derives both from the meninges and blood vessels; calcifications are frequent.

The histological identification of this oncotype is not easy, unless it is possible to demonstrate ganglion and neuroblastic cells and Homer–Wright rosettes, which may be absent or present in variable numbers. If these signs are lacking, the differential diagnosis, especially vs. ependymoma, may be very difficult. In some cases, a palisade arrangement similar to that of polar spongioblastoma has been described [1191, 158, 1566, 2070].

Under the electron microscope, the presence of NF, microtubules, dense core vesicles, synaptic vesicles, junctions, etc. is diagnostic [99, 2309, 962, 2158, 2070]. It is possible that some of the neuroblastomas, at least those in which neuronal differentiation and the presence of mature synapses extend through most of the neoplasia, could be better labelled as central neurocytoma.

Immunohistochemistry is not of great help, unless an evident neuronal differentiation is present. Positivity for 68-kDa NF has been reported [2344, 1400]. An increased amount of urinary and CSF catecholamines has also been noted [99], but the finding has not been confirmed [166]. Cases with differentiation also toward glia have been described [2161, 99, 2431, 564, 2344, 2859], which may support the hypothesis of an origin from a multipotential cell also capable of differentiating toward glia.

15.3.3 Prognosis

The tumor often spreads via the CSF. Rare cases with extracranial metastasis have also been seen. The prognosis of these tumors is not easy to assess both because they are rare and because of the diverse treatment modalities applied. Prognosis is usually not good, but survival data are distributed over a wide range of periods, i.e., 3 years in 60% of cases and 5 years in 30% [166]. There does not seem to be a relationship between the histological variety and survival [166], even if the cystic forms appear to have a better prognosis [170]. Every so often, cases with a particularly long survival are reported [2859]. Local recurrence, arising in 40% of cases [170, 2420], and metastases along the CSF pathways are the causes of death. The influence of radio- and chemotherapy seems doubtful.

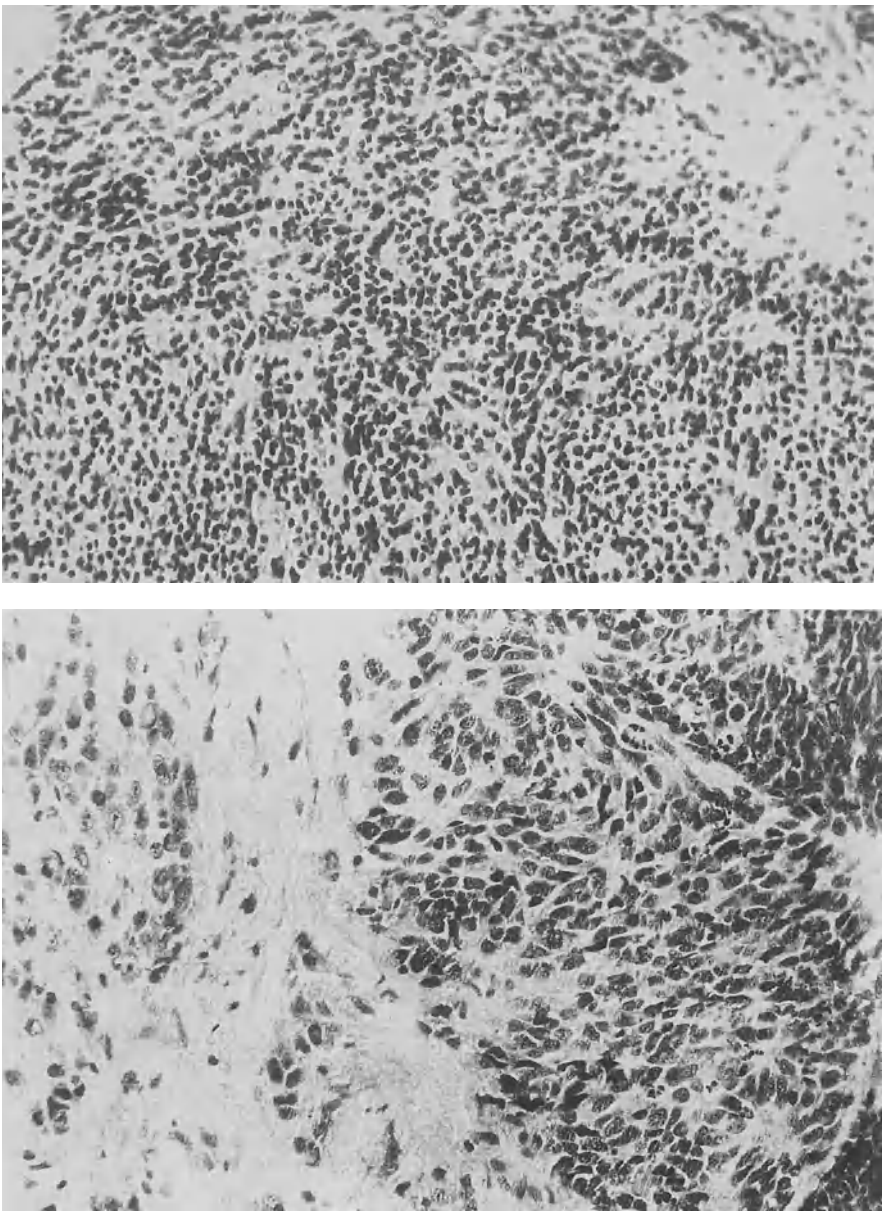


Fig.15.14a,b. Neuroblastoma: **a** densely packed cells with hyperchromatic nucleus, H&E, ×200; **b** Homer–Wright rosettes and a group of differentiated neurons, H&E, ×400

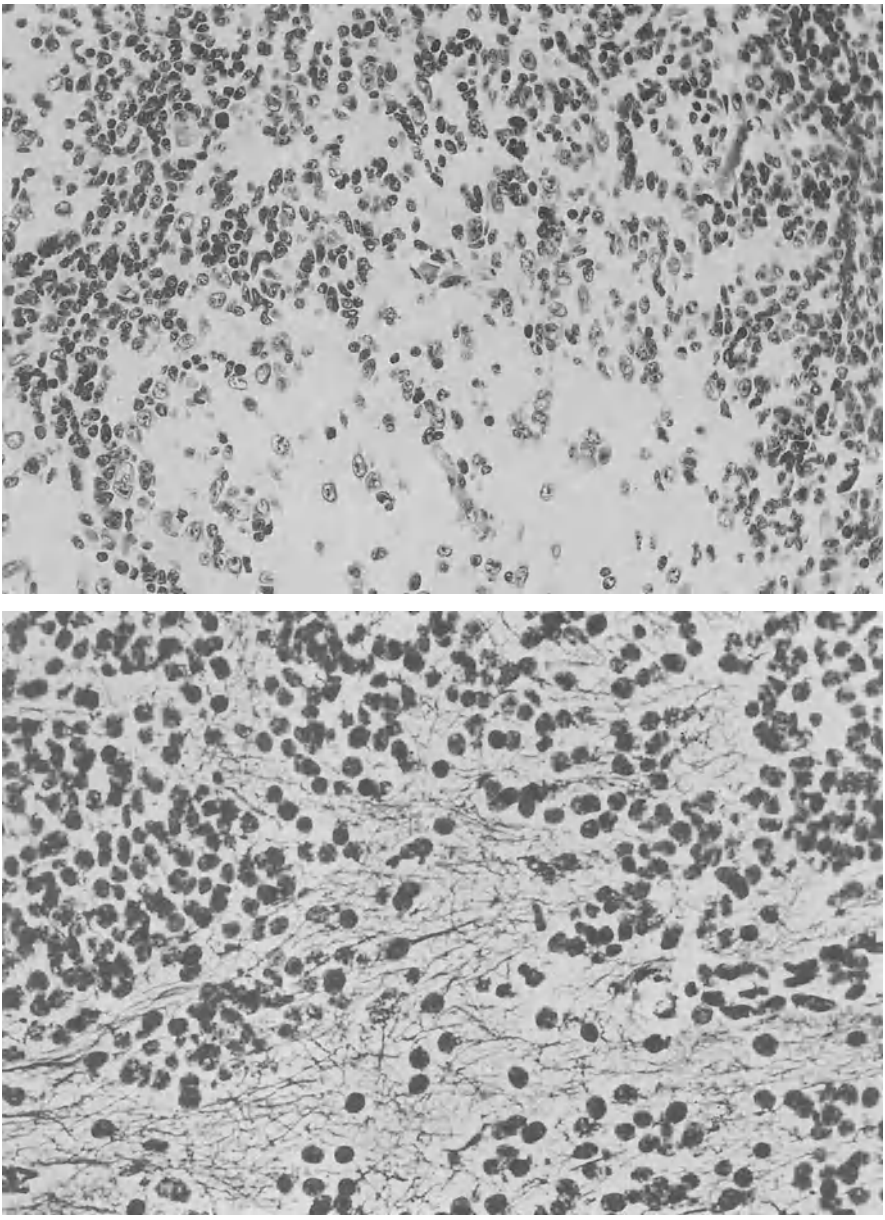


Fig.15.15. Ganglioneuroblastoma: **a** neuroblasts and differentiated neurons, H&E, ×300; **b** differentiated neurons, Bodian, ×300

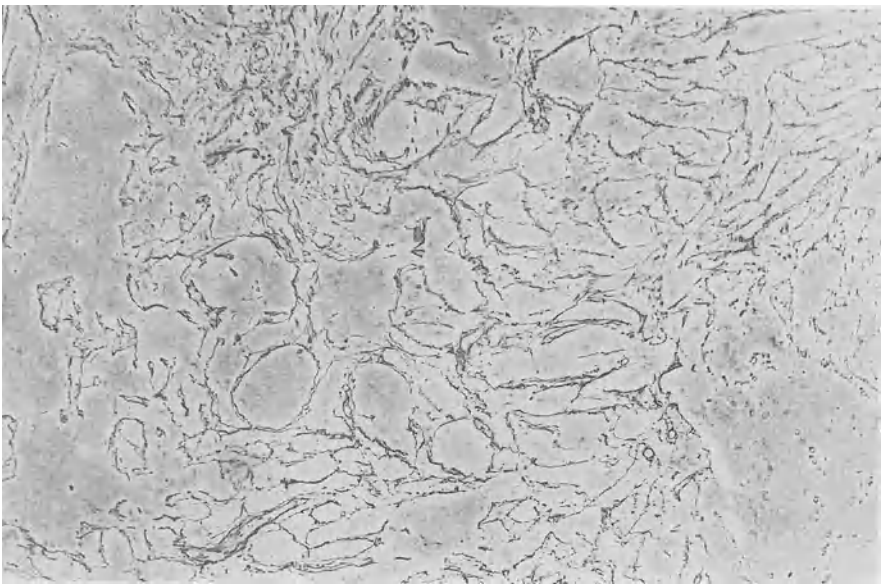


Fig.15.16. Neuroblastoma, hypertrophied stroma, Gomori, ×200

15.4 Polar Spongioblastoma

The term "polar spongioblastoma" has been used in the literature to indicate two types of brain tumors. One is the spongioblastoma group of Zülch (1956) [3134], which corresponds to pilocytic astrocytoma [2420], and the other is the so-called primitive polar spongioblastoma described by Russell and Cairns (1947) [2414] and by Russell (1955) [2413] as a malignant brain tumor arising in the neighbourhood of the ventricular system mainly in childhood and adolescence. A few examples have been reported from different locations: the cerebellum [1910 , 2729], mesencephalon [2414], fourth ventricle [2414], diencephalon [584], frontal lobe [1288], temporal lobe [2415] and spinal cord [2665, 2548] (Fig.15.17).

Histologically, the tumor is composed of poorly differentiated cells with nuclei arranged in a parallel fashion forming typical palisades (Fig.15.18). Cellular layers and groups are separated by a vascular-connective stroma. The cells have a polar shape and delicate fibrils. The authors who originally described the tumor thought that the cells were undifferentiated, but capable of differentiating toward glia or oligodendroglia. The cells are GFAP-negative.

The controversy about this tumor revolves about whether it is a real entity or simply a particular form of glioma. In the cases so far published, besides the spongioblastic aspect there was also an astrocytomatous aspect [576, 2548, 2729] or an oligodendrogliomatous one [2388]. Those who believe the tumor is an entity consider the latter aspects as differentiations of an immature tumor. The nonbelievers think that, on the contrary, the spongioblastic aspect is an epiphenomenon.

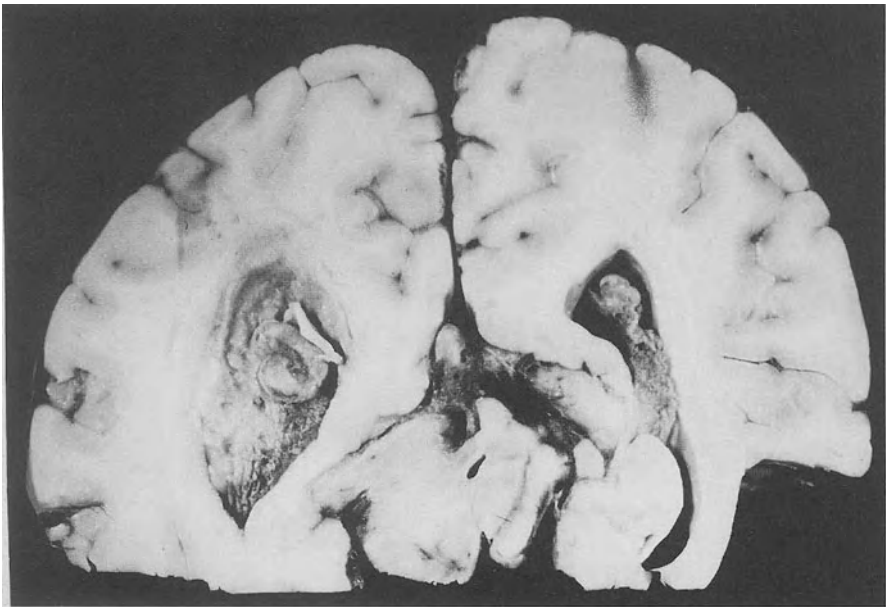


Fig.15.17. Tumor in the temporal region, diagnosed as polar spongioblastoma

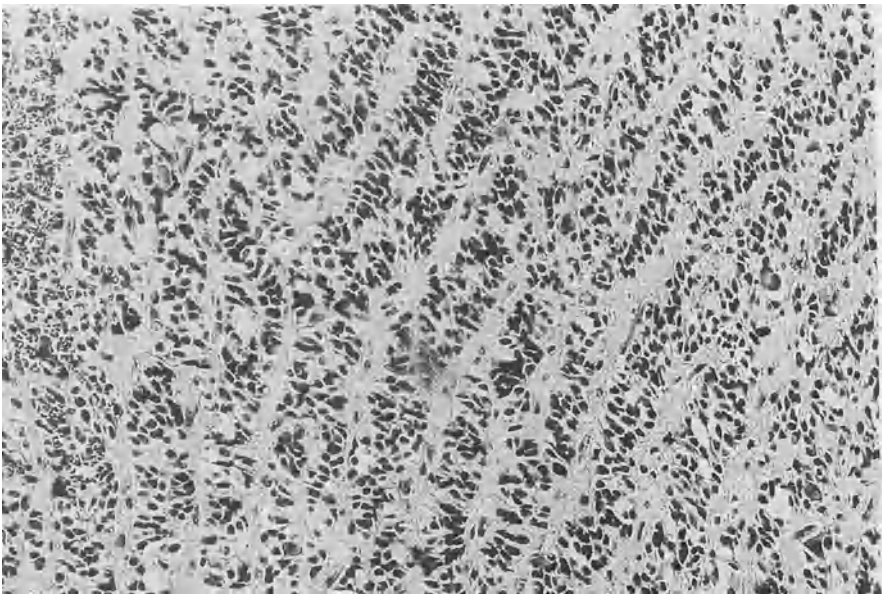


Fig.15.18. Polar spongioblastoma, typical palisades, H&E, ×200

In some neuroepithelial tumors, such as cerebellar astrocytomas, (Fig.15.19a), ependymomas (Fig.15.19b), oligodendroglioma (Fig.15.20), and even medulloblastomas, areas with palisadings or rhythms of nuclei can be found. Palisadings have also been described in neuroblastomas [1566 , 158], but there they are separated by reticulin bundles [1191]. In the personal series (2525B), two cases with a typical spongioblastic aspect were found. Both tumors were located deep in the temporal lobe, of a 12-year-old child and a 51-year-old woman. Delicate fibrils were evidenced by PTAH; GFAP was negative and vimentin was positive, which might have some relevance to the immaturity of the tumor. Calcifications were present as well as mitoses and circumscribed necroses. The tumor behaved malignantly and both patients died 3 years later. In one case, the tumor showed (under the electron microscope) characteristics of a neuroblastoma with microtubules and dense core vesicles (Figs.15.21, 15.22); in the other, after serial sections a typical ependymomatous aspect was found in a circumscribed area of the tumor. A case with clear-cut neuroblastic characteristics was reported recently [1288], and neuroendocrine aspects have been observed in another instance [584].

Palisadings are not uncommon in neuroepithelial tumors, where they represent the secondary architecture. In a few instances, the polar spongioblastic aspects may represent the primary architecture and characterize the extension of the tumor. This happens mostly with neuroblastomas and ependymomas to which the so-called polar spongioblastoma belong.

15.5 Appendix: Tumors of the Retina

Embryologically speaking, the retina originates from an extension of the primary cerebral vesicle. From the complicated anatomy of the invaginated optic cup, two important features must be stressed which have a prominent relationship with tumors arising from this structure. First of all, there are the pigmented elements of neuroepithelial origin, interposed between the layer of cones and rods and that of the choroid; other pigmented elements, of mesenchymal origin, are those of the choroid layer. The rod and cone layer corresponds to the ventricular ependyma. It may react to pathological processes, forming rosettes. Beside neurons, which are the photoreceptor cells, the retina contains glia cells which are represented by Müller's cells and by stellate astrocytes.

15.5.1 Retinoblastoma

Retinoblastoma originates from immature retinal cells and is the most frequent malignant ocular tumor in childhood. The average age of the patients at clinical diagnosis is 18 months [2384]. Very important to note is that the tumor is heritable in 40% of cases. It is heritable in all cases where it is bilateral and in 10%–15% of unilateral cases. Conversely, all nonheritable cases are unilateral.

Molecular genetic studies have demonstrated that the tumor results from two mutational events (see Chap. 2). In the heritable form, the first mutation on the RB gene is

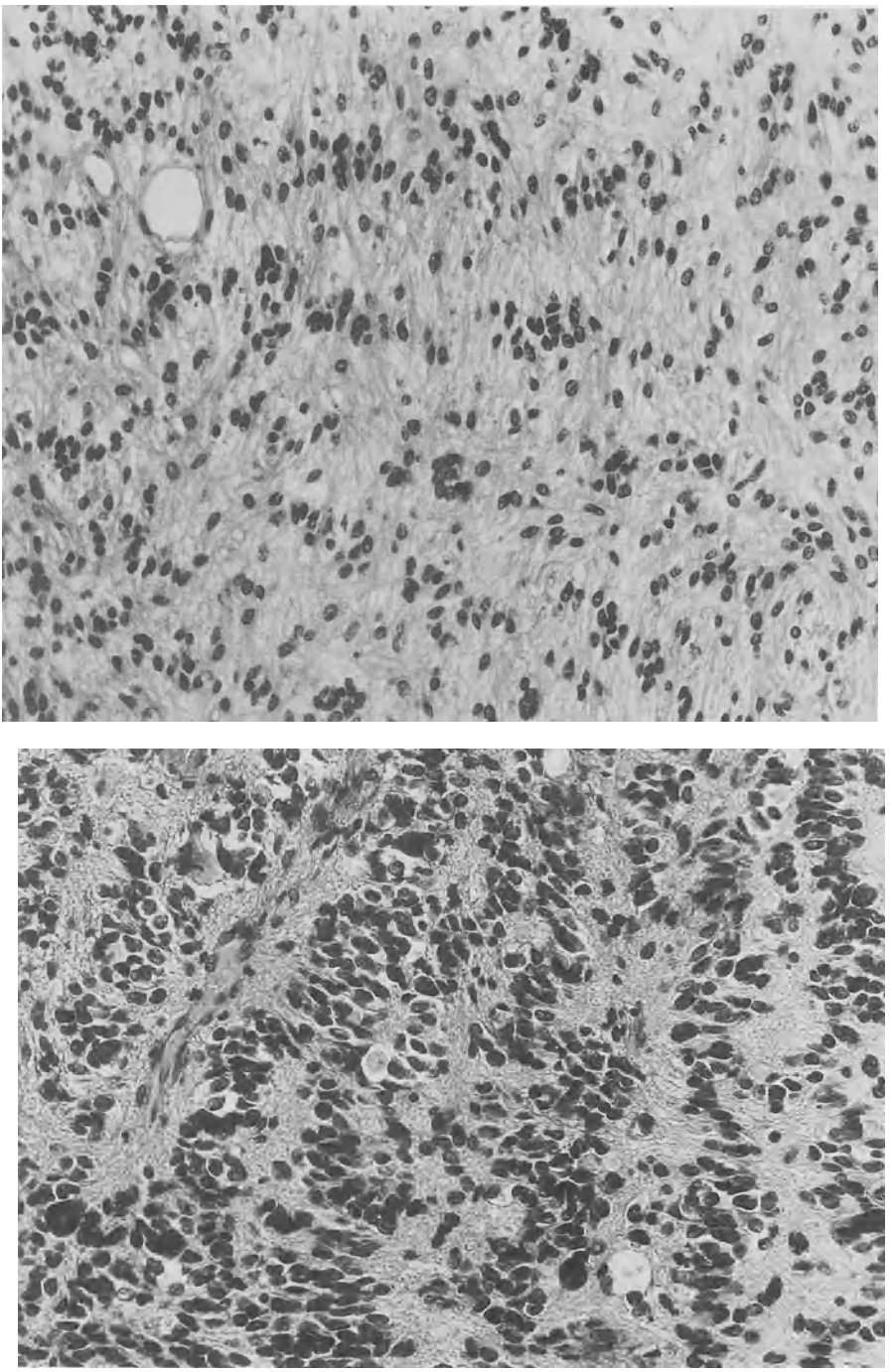


Fig.15.19. a Stepladder rhythms in pilocytic astrocytoma, H&E, ×300. **b** Stepladder rhythms in ependymoma, H&E, ×300

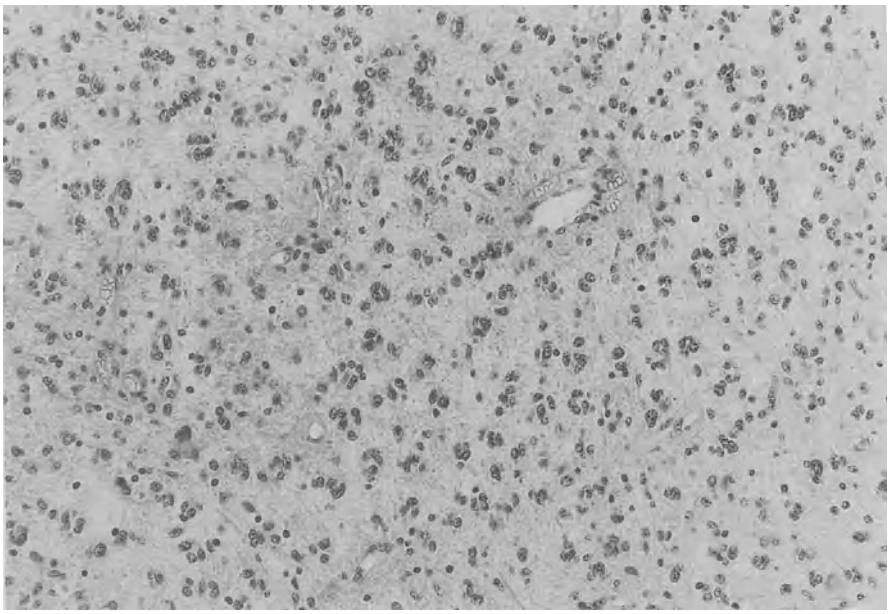


Fig.15.20. Cell rhythms in oligodendroglioma, H&E, ×300

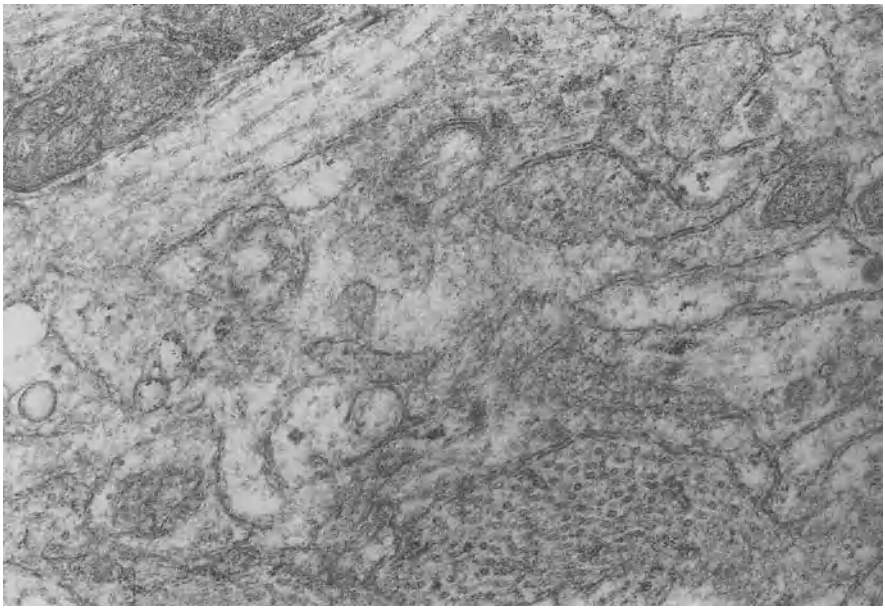


Fig.15.21. Polar spongioblastoma, interdigitating cell processes and microtubules, ×40,000

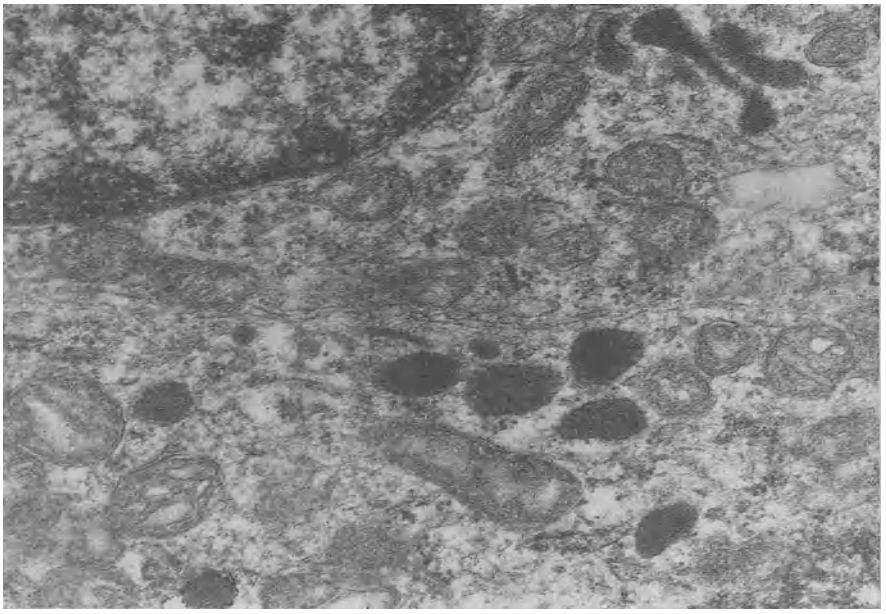


Fig.15.22. Polar spongioblastoma, dense core vesicles, ×40,000

transmitted by the germinal cells, while the other occurs in the somatic cells; in the non-heritable form, both mutations occur in the somatic cells, the first before birth and the second after birth [1782].

Secondary malignancies may develop in the heritable group of patients, represented mostly by osteogenic sarcoma, in 15%–20% of patients after a mean interval of 11 years [6]. A debate arose about the possibility that such malignancies could be due to the radiation therapy.

Another association of bilateral retinoblastoma is that with pinealoblastoma, the so called trilateral retinoblastoma.

Macroscopically, the tumor appears at an early stage as a white nodule in the posterior part of the retina. It grows by detaching the retina or forming masses in the vitreous chamber. Finally, the globe enlarges, and the tumor may extend through the sclera.

Microscopically, the tumor reveals a high cell density. The cells are round or oval with scanty cytoplasm and large nuclei. Many mitoses are present. In most cases, rosettes are found (Fig.15.23): Cells, often in mitosis, are arranged about a lumen to which stretch the cytoplasms covered by a membrane stained with PTAH. Fleurettes may develop [2872] as a sign of photosensory differentiation, formed by long processes traversing a membrane side by side. Occasionally, Homer–Wright rosettes can be found.

A matter of lasting debate is the occurrence in the tumor of a glia differentiation. Some interpret the GFAP-positive glia cells occurring in the tumor as reactive gliosis [2183], whereas others believe that they are an expression of a glial differentiation [2827]. The real occurrence of such differentiation still remains controversial [2420]. Electron microscopy demonstrated photoreceptor differentiation, fleurettes, cilia with a

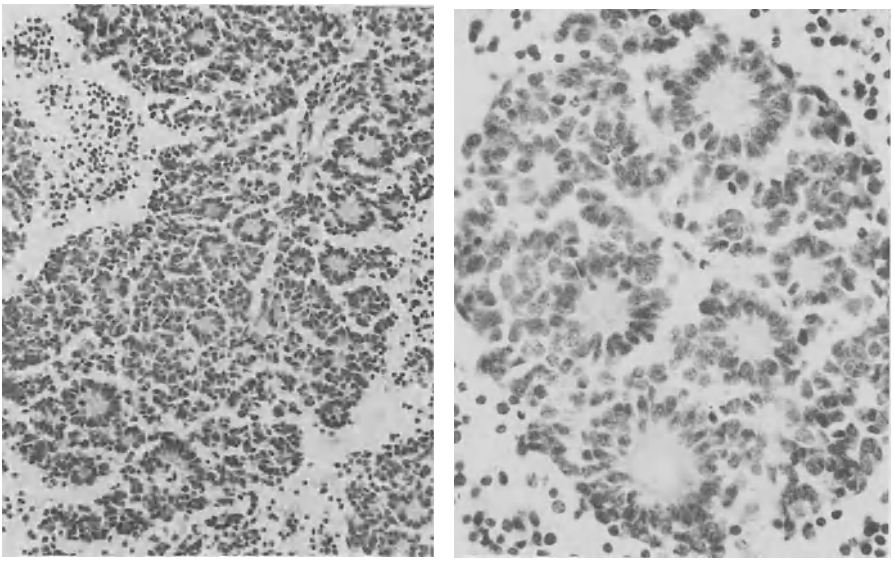


Fig.5.23a,b. Retinoblastoma, typical rosettes, H&E, ×200; ×400

9+0 pattern, synaptic ribbons, and dense core vesicles but was unable to settle the controversy about glia differentiation [23].

The same interpretation given to the GFAP-positivity, i.e., as due to reactive glia cells, could be applied to the positive staining for S-100 protein observed by some [1436] and anti-Leu 7 [2183]. The positive staining for NSE, found by many, must be considered with reservation because of the poor specificity of this marker. Flexner's rosettes were positive for 68- and 210-kDa subunits of NF [2457]. Also positive is the staining for S-antigen in rosettes, fleurettes, and isolated cells [653, 2183], as well as for rhodopsin [654].

Retinoblastoma cells have been grown in culture, and some established cell lines are available. Data on the cell kinetics show high values for the LI.

Retinoblastoma is a malignant tumor, but in most cases the treatment is highly effective: The cure rate is almost 90% [23]. Distant metastases are rather rare. Also rare, but possible, is its spontaneous regression.

16 Glomus Tumors, Paraganglioma

Paraganglia have been divided [2991] into sympathogenic chromaffin and parasympathogenic nonchromaffin. The former derive from the adrenal medulla, the so-called free paraganglia, and some intraneural or intraganglionic chromaffin cells, from which chromaffin paragangliomas such as pheochromocytoma arise. The latter are represented by collections of epithelioid cells situated on the blood vessel wall in relation to the vagus and glossopharyngeal nerves. They go under the name of carotid, jugular, tympanic, vagal, aortic, and supracardiac paraganglia. Related tumors are glomus tumors or nonchromaffin paragangliomas or "chemodectomas" [1969]. An objection to the last nomenclature is that there has been no definitive demonstration of chemoreceptor function in these tumors [939]; thus the term paraganglioma which may be specified as functioning or nonfunctioning, is preferable.

It is possible to demonstrate biogenic amines using formaldehyde-induced fluorescence in all the paraganglia.

16.1 Site, Age

They are rare tumors. Some have been described as located in the head and neck [2558, 475, 1100] with 160 cases having been reported up to 1957 [1451], whereas spinal tumors are very rare, only 11 cases having been described up to 1984 [1890, 1617, 1185, 2896, 2419, 1553, 228, 1677, 2542, 2818, 1243].

Another seven cases have been successively presented [245], of which three were epidural and four intradural. Only five tumors have been described in the cauda equina, and some in the orbit [2031, 2927, 2153]. In general, the sites along the cerebrospinal axis at which the tumors have been reported include the pineal gland, the pituitary gland, and the cauda equina. They often appear at multiple sites, and sometimes in other members of the family. The age of predilection of these tumors varies between the fourth and the sixth decades of life. Females are more often affected.

16.2 Microscopic Appearance

Histologically, they are characterized by tufts of roundish or elongated cells with abundant eosinophilic cytoplasm, immersed in a connective stroma rich in blood vessels

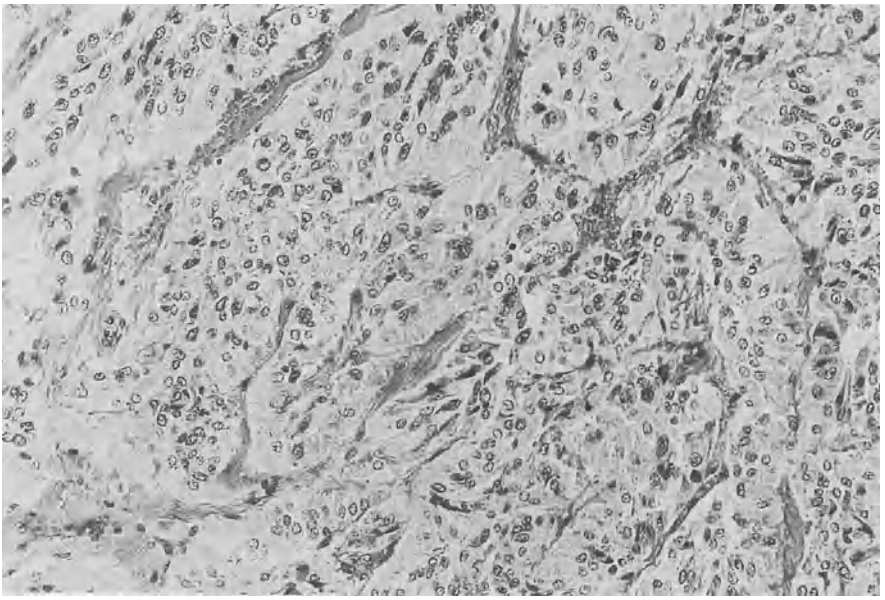


Fig.16.1. Paraganglioma, lobules and cords of roundish cells delimited by a connective stroma, H&E, ×300

(Fig.16.1). Three types have been described [1591]: a typical one with an "organoid" arrangement in which the cells are enclosed between vascular and sinusoidal channels [939]; an adenomatous type with features closer to epithelium; and the angiomatous type with particular prominence given to the vascular network. On this histological appearance there is agreement among various authors [1451, 2841, 2206]. The main cells of a juxtacarotid chemodectoma cultured in vitro are bipolar, one of the poles being nuclear and the other cytoplasmatic, as in histological preparations [500]. The cells may give off a process which grows in a way similar to an axon; they do not actively migrate, but the body shows pulsatile contractions. Cells with cytoplasmic argyrophilic granules situated at the periphery of the lobules have been observed in many tumors. In culture, however, these cells are not easily recognized. Bundles of nerve fibres related to the blood vessels are present in these tumors, but they are not observed in culture.

The argyrophilic cells of the tumor are thought to be similar to those of the gastrointestinal tract and may secrete serotonin. This would agree with the fact that the histological structure of the organ is that of a highly specialized neuronal photoreceptor. Under the electron microscope, dense core vesicles and secretory granules are recognizable [1243].

Rare cases containing melanin have been described, two in the uterus [2815] and one in the orbit [2153]. Positive staining for GFAP and S-100 protein in sustentacular cells was found in many cases of 65 adrenal and extra-adrenal paragangliomas and was correlated with a good prognosis [7A].

16.3 Prognosis

Paragangliomas grow slowly but may invade the surrounding structures, especially the blood vessels. They may also show extracranial extension [2631] or compress the brain stem and cerebellum. Rarely, extracranial metastases are observed [3058, 1586, 2367].

The elective treatment is surgery, even though a complete resection is rarely possible because of the invasiveness and location of the tumor. The tumor often recurs [2286]. Radiotherapy as primary or postsurgical treatment leads to contrasting results [81, 2644, 1415, 1878]; it does not "sterilize" the tumor [2701]. In cauda equina tumors, the prognosis is good in the case of total removal, unless lymph node involvement and distant metastases appear [2300].

17 Tumors of the Cranial and Spinal Nerves

17.1 Neurinoma (Schwannoma)

This tumor has been given various names, due to the various cells of origin proposed. Some authors have postulated a fibroblastic origin for the tumor cells, while others have proposed an origin from Schwann cells. The term "fibroblastoma perineurale" was coined by the former authors to indicate an origin from the fibroblasts of the perineurium [1745, 2169], although later on the derivation was thought to be from the endoneurium [2813]. The term "neurinoma" or "neurofibroma" was used by other authors [1190] to underline its neuroectodermal nature. The term "neurilemmoma" has been used to emphasize its origin from Schwann cells [2746]. Today, there are no doubts as to the origin of these tumors, and the most frequent label is neurinoma in Europe [3134] and schwannoma in the USA [2420].

It should be noted that the two theories on the origin of the tumor are not mutually exclusive: From the basic concept of "mesectoderm" it is possible that the primitive neural crest gives rise to both Schwann cells and mesenchymal perineural cells [1026], and observations on the mesenchymal origin of Schwann cells have been made [757].

The problem of the relationship between neurinomas and neurofibromas, especially when multiple as in von Recklinghausen's disease, is somewhat complex. For the latter tumors, investigators have been divided between a mesodermal (fibroblasts originating from neural connective tissues) and an ectodermal (origin of the tumors from Schwann cells) interpretation. Today the last one is generally accepted.

17.1.1 Frequency, Age, Sex

Neurinomas represent around 6.8% of all brain tumors, but at the spinal site they are more frequent than meningiomas, representing 25% of all tumors [3138]. Neurinomas of the peripheral nerves are very rare.

They more commonly occur in the fourth and fifth decades, and the average age is slightly lower for spinal tumors. Neurinomas are truly rare in childhood.

There is a greater incidence in women.

17.1.2 Site

The most frequent site of origin is the cerebello-pontine angle, followed by the spinal cord. In the former, the tumor arises from the eight nerve, more precisely from the ves-

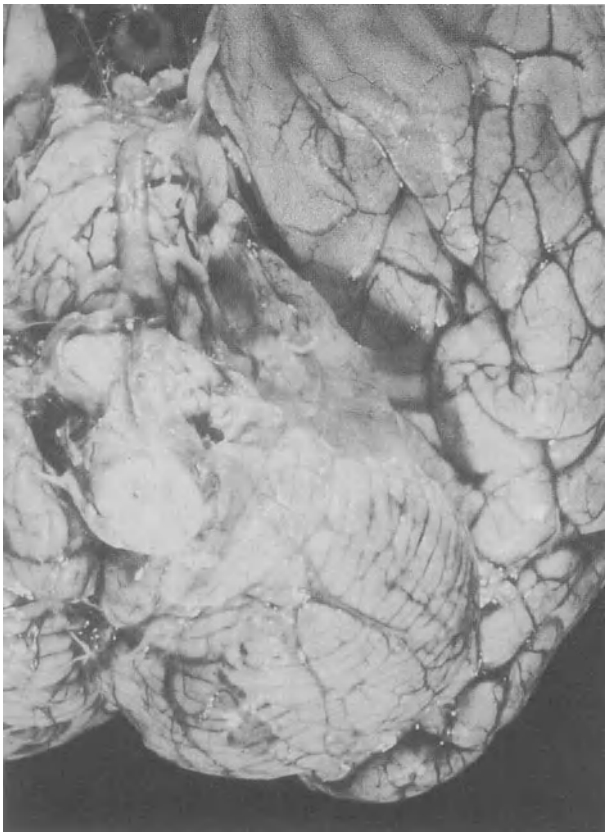


Fig.17.1. Neurinoma, tumor bed in the cerebello-pontine angle

tibular component, close to or in the ganglion of Scarpa. It then involves the acoustic component, the facial nerve in the internal acoustic meatus [1107, 1108, 1058], and spreads into the cerebello-pontine angle (Fig.17.1). The tumor may burrow into the medulla, pons, or cerebellum (Fig.17.2). It may extend inferiorly to the foramen magnum, and superiorly through the tentorium. It usually engulfs the fifth and sixth cranial nerves. The tumor is usually unilateral but can occasionally be bilateral, normally in the context of neurofibromatosis.

More rarely, neurinomas may arise from other cranial nerves. The most common site is the trigeminal or the Gasserian ganglion, but most of these tumors occur in cases of neurofibromatosis. Isolated neurinomas of the fifth nerve have been reported by various authors, and 61 cases, personal and from the literature, were reviewed in 1960 [2527]. Further cases have been described since [259]. Those arising from the ganglion, the majority, are usually kept separate from those of the roots.

Neurinomas of the seventh nerve are next in order of frequency. They may arise from the intracranial portion of the nerve [858, 165, 1595], but more often they develop from the intratemporal part, and even extratemporally and extracranially. Forty cases

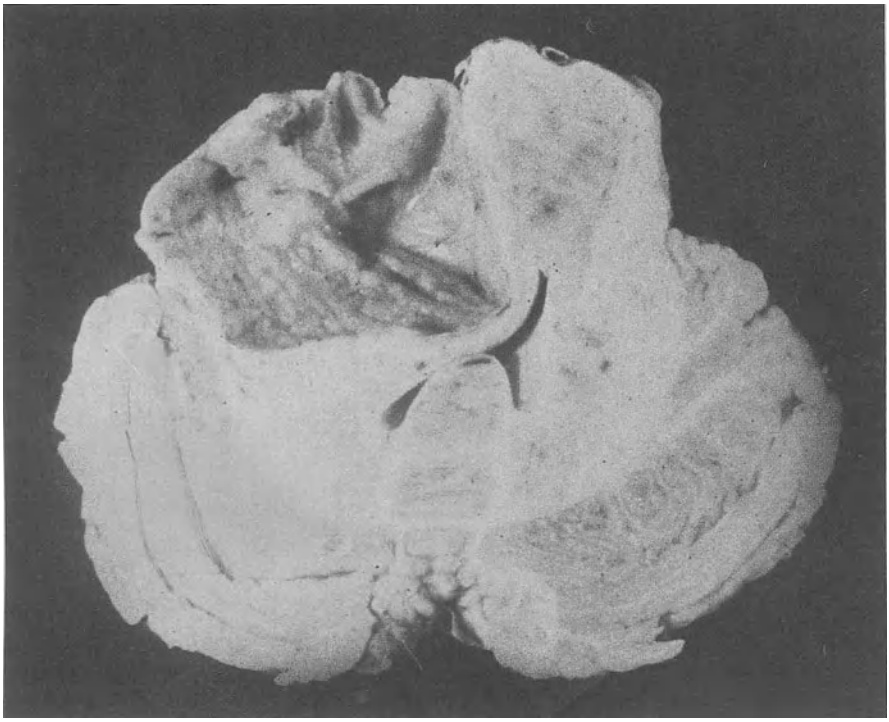


Fig.17.2. Neurinoma, tumor burrows in the pons and cerebellum

had been published before 1959 [1452]. A case in the labyrinth has been reported [1649].

Neurinomas of the twelfth nerve are even rarer [3046, 1927, 139], amounting to no more than 34 cases up to the end of 1989 [2062]. Neurinomas of the ninth, tenth and eleventh cranial nerves are very rare [1045], and up to the end of 1989, 100 cases had been reported, 23 of which were on the ninth nerve [2770]. Theoretically, the tumor may arise at any intracranial site, for example, cases of the fourth cranial nerve have been reported [242, 1148]. They may very rarely be found at sites distant from the cranial nerves, in the sella [949, 3045], in the frontal region, extracerebrally [2919, 1823A], or within the neural parenchyma [312, 2721, 528, 2420], as part of von Recklinghausen's disease. They may arise either from small nerves in the meninges or from ectopic Schwann cells.

The spinal tumors mostly arise from the sensory roots and are often situated dorsally or dorsolaterally to the cord. Sometimes, it is difficult to ascertain from which root they arise. There is no particular predilection for a given spinal level. The thoracic or lumbar roots are probably the ones most affected. The position of the tumor in relation to the dura assumes a particular importance in the spinal canal. The majority of neurinomas are intradural, but some are extradural or are both intra- and extradural. The latter are named "dumbbell" tumors because, after arising intradurally or at the transition between the intradural root and the extradural nerve, they cross the intervertebral fora-

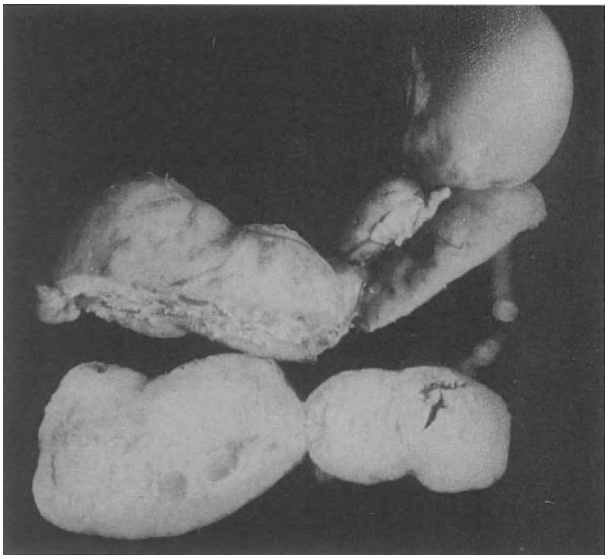


Fig.17.3. Neurinoma, tumor is lobulated and cystic

men and assume their particular shape. In a series of 163 cases [2277], 67% were intradural, 16.5% extradural and 16.5% both intra- and extradural. In another series of 266 cases [1404], 176 (66%) were intradural, 45 (17%) were extradural and 45 (17%) "dumbbell" tumors. Conversely, 48% of spinal "dumbbell" tumors (34/73) turned out to be neurinomas [2858]. The most frequent site of these tumors is cervical, followed by thoracic.

There are also very rare reports of intramedullary neurinomas [2170, 2277, 3070, 2323, 2267, 2576, 1018, 2131, 2892, 2368, 1118]. The hypothesis is that they originate from small nerve bundles penetrating the cord in association with a perforating blood vessel [2323]. Neurinomatous proliferations have been found in different diseases of the spinal cord, both degenerative and traumatic, even associated with reactive gliosis. It has been hypothesized that, even though these proliferations have neoplastic features, they may represent a reactive process [2208, 2388, 119, 2350] which can be found even in the normal spinal cord [2085, 2459]. For schwannosis in von Recklinghausen's disease, see Chap. 21. Neurinomas may affect the peripheral nerves at various locations.

17.1.3 Macroscopic Appearance

Neurinomas are usually solid, circumscribed, and encapsulated tumors, hard and elastic in consistency. Sometimes they are polylobulated, and the lobules may be cystic (Fig.17.3). Consistency is reduced in tumors with marked regressive phenomena. On the cut surface they may be grayish-pink or whitish-yellow and translucent, or reddish, depending on the presence of various regressive phenomena, for example, hemorrhage.

17.1.4 Microscopic Appearance

Histologically, two main forms are distinguishable, A and B according to Antoni [64] or 1st and 2nd according to Henschen [1107] and Jumentié [1329].

The A type is compact and fibrillary and is formed by elongated cells not easily distinguishable from each other. They are arranged in bundles with various orientations and in whorls (Fig.17.4a). The nuclei are elongated and cigar-shaped and tend to align themselves at the same level in the bundles, forming "palisades" (Fig.17.5). In transverse section, they appear roundish. Sometimes nuclei are large and abnormal with inclusions, but this is not necessarily indicative of malignancy (Fig.17.5b). Fine argentophilic fibers are arranged along the major axis of the cells (Fig.17.4b), corresponding to basal membranes, and reticulin and collagen fibers radiate from the blood vessels or from the capsule.

The vascularity is variable, and the vessels are often cavernous and lined only by endothelium (Fig.17.6a) or with thickened and hyalinized walls (Fig.17.6b). Large lacunae without even an endothelial lining are sometimes found. Exceptional cases have been described with intratumoral or subarachnoid hemorrhage, related to the abundant vascularity and to the weakness of the vessel walls [1594]. This appearance could be a feature of larger tumors [1357].

In type B, the tissue is loose, vacuolated, and often cystic. The cells acquire an astrocyte-like appearance (Fig.17.7a). Often fatty degeneration is found (Fig.17.7b), which gives the cells a honeycomb appearance. Frequently, accumulations of intra- and extracellular pigment occur (Fig.17.8). This can be due to hemosiderin or may be composed of lipopigments of ceroid type which could be produced by the Schwann cells themselves, recalling the capacity of these cells to produce myelin [1962]. The lipid constituents of neurinomas (phosphatides, cerebrosides, cholesterol, and cholesterol esters) are identical to those of the myelin sheath [1096, 1963]. The "fatty degeneration," therefore, might not be a true degeneration but the result of a thesaurismotic activity [466]. The pattern of associated esterase enzymatic activities is similar to that of the white matter oligodendrocytes [1918, 2497]. Ganglion cells from the ganglion of Scarpa are not uncommonly found within the tumor.

Under the electron microscope, the variations in shape of the different cell types appear as a modulation of the same cell type [2996, 406, 510]. The constant features include the presence of a basement membrane surrounding the tumor cells and the interdigitation of cytoplasmic processes, with 200-Å gaps (Fig.17.9). The fine argentophilic fibrils, much discussed during light microscopy study, correspond to the basement membrane seen with electron microscopy. The supporters of the neuroectodermal origin of the neoplasm emphasize that the presence of the basement membranes is a direct demonstration of the Schwann cell nature of the tumor cells. According to others [2960, 510], the perineural fibroblasts also have a basement membrane. However, the absence of a basement membrane could not exclude the derivation of the tumor from Schwann cells, because the primitive and immature lemmoblasts do not possess one.

The origin of the collagen in the tumor has been a matter of debate. According to some, it is the product of fibroblasts, but according to others its manufacture by Schwann cells cannot be excluded. Long-spaced collagen fibrils with 120–150 nm banding periodicity ("Luse bodies") [1716] are found in direct contact with the base-

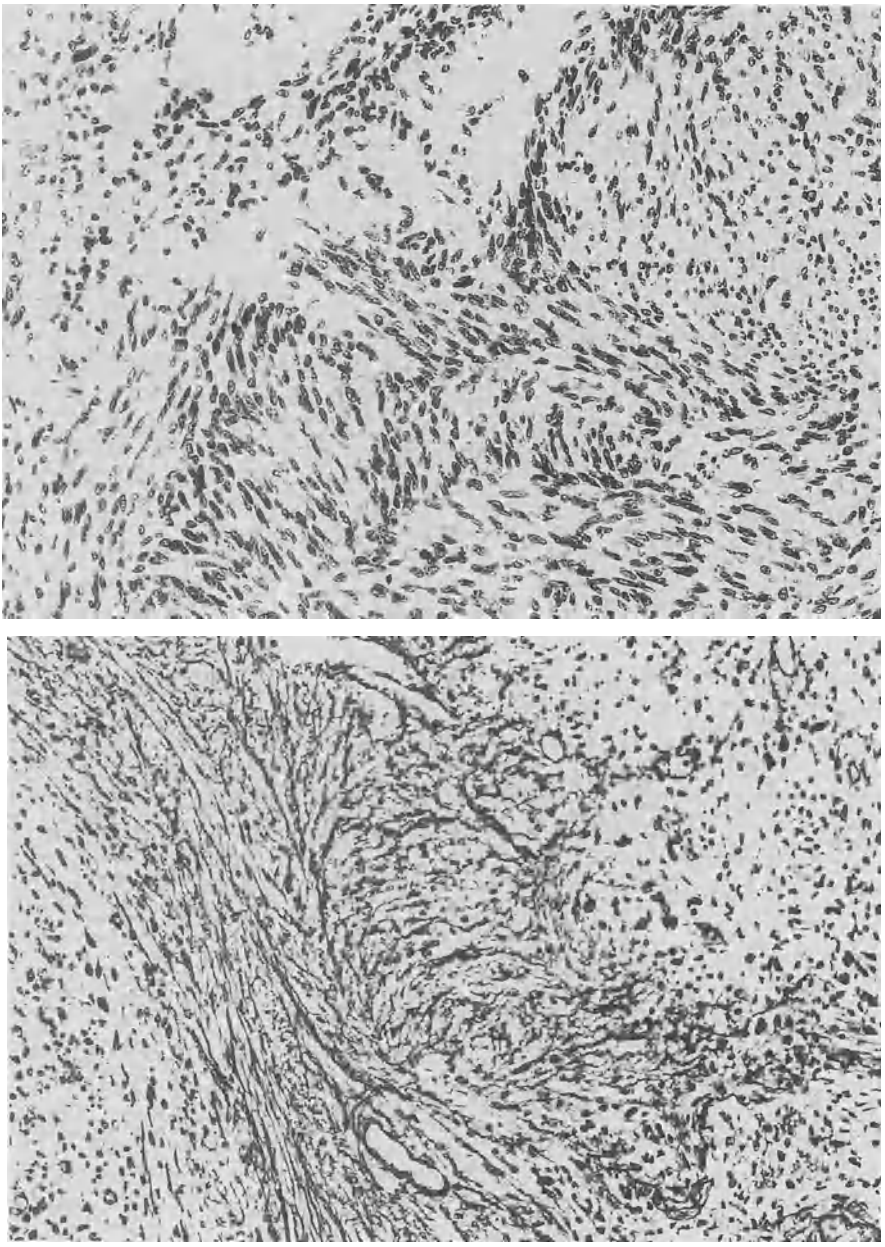


Fig.17.4a,b. Neurinoma: **a** cells are arranged in bundles, H&E, ×200; **b** densely packed reticulin fibers, Gomori, ×200

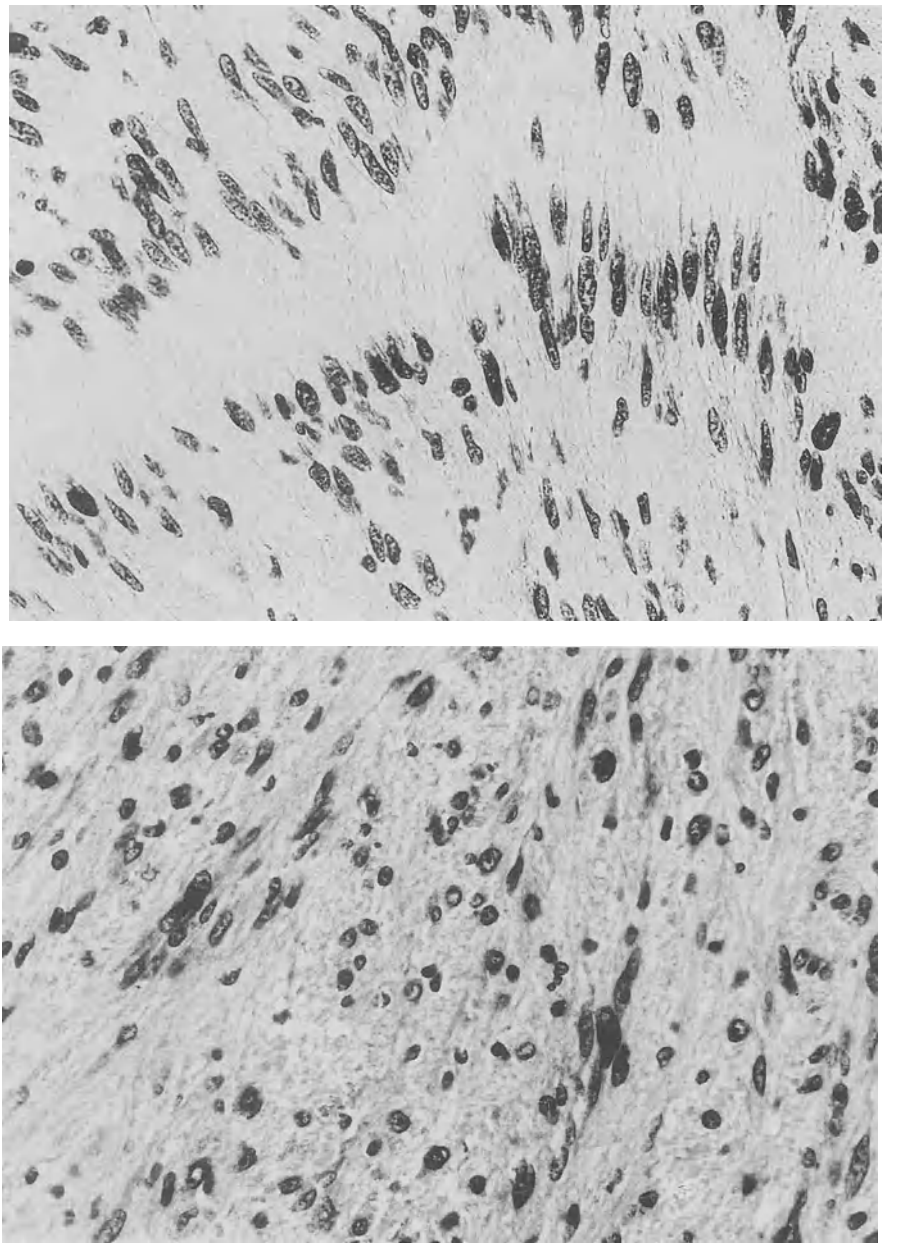


Fig.17.5a,b. Neurinoma: **a** typical palisades of nuclei, H&E, ×400; **b** polymorphic nuclei, H&E, ×400

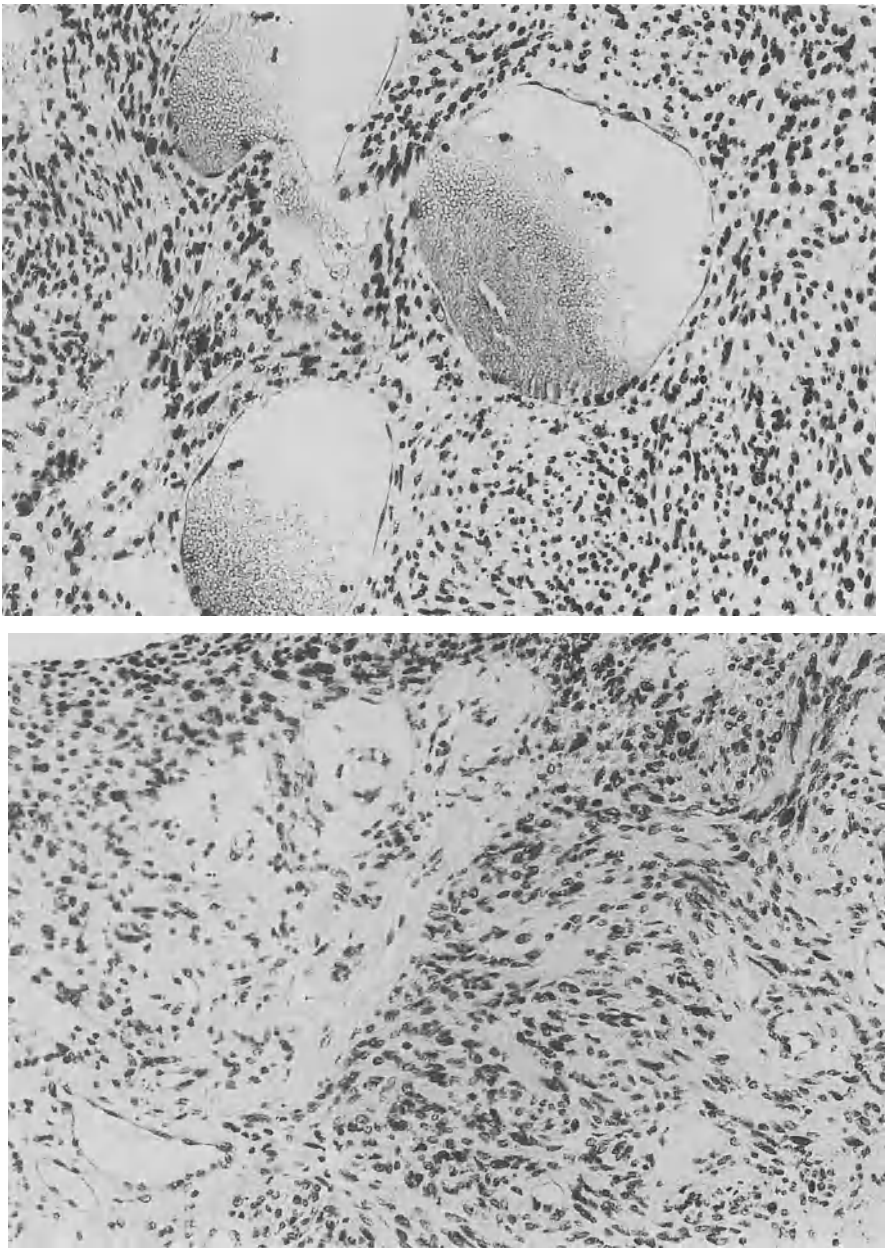


Fig.17.6a,b. Neurinoma: **a** vessels of cavernous type, H&E, ×200; **b** hyaline degeneration of vessels, H&E, ×200

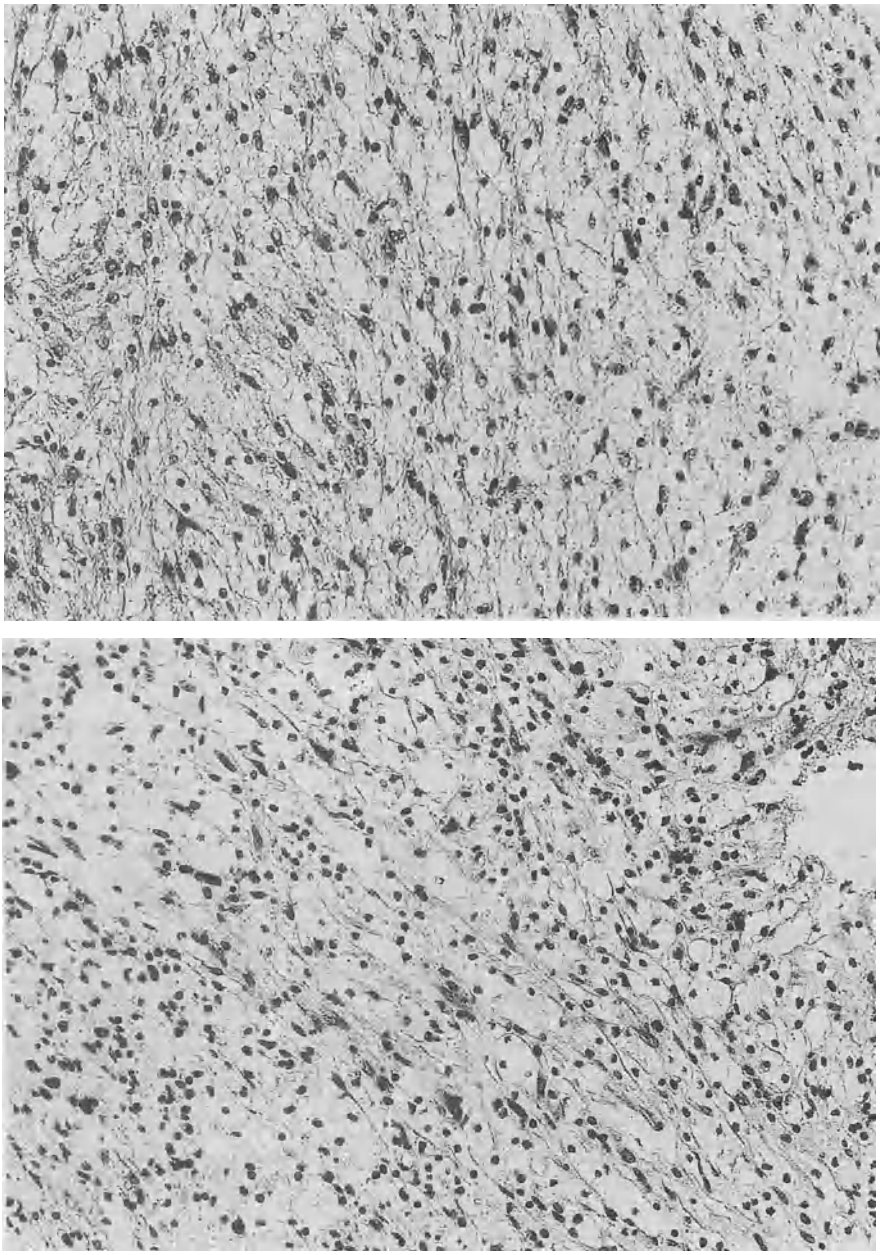


Fig.17.7a,b. Neurinoma: **a** B area with typical loose aspect, H&E, ×250; **b** fatty degeneration, H&E, ×200

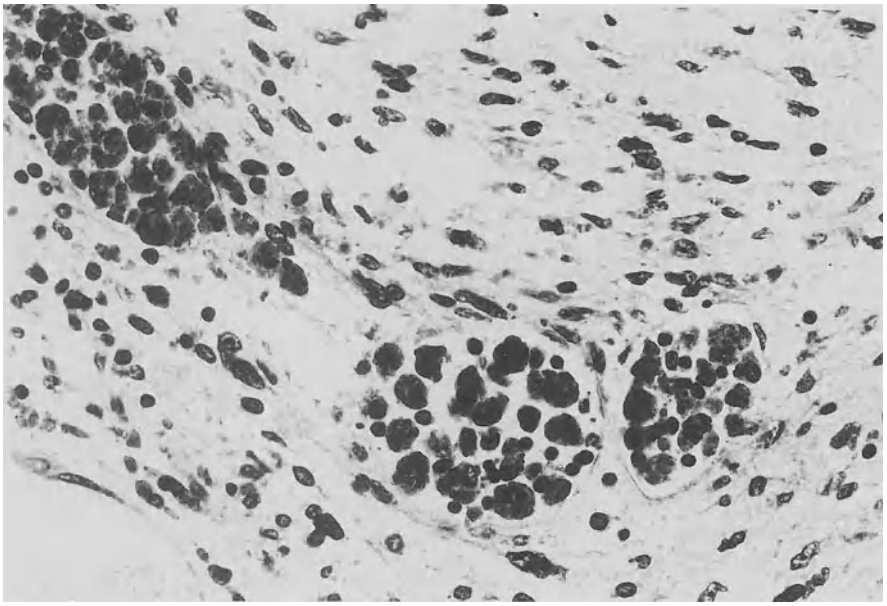


Fig.17.8. Accumulations of pigment, H&E, ×400

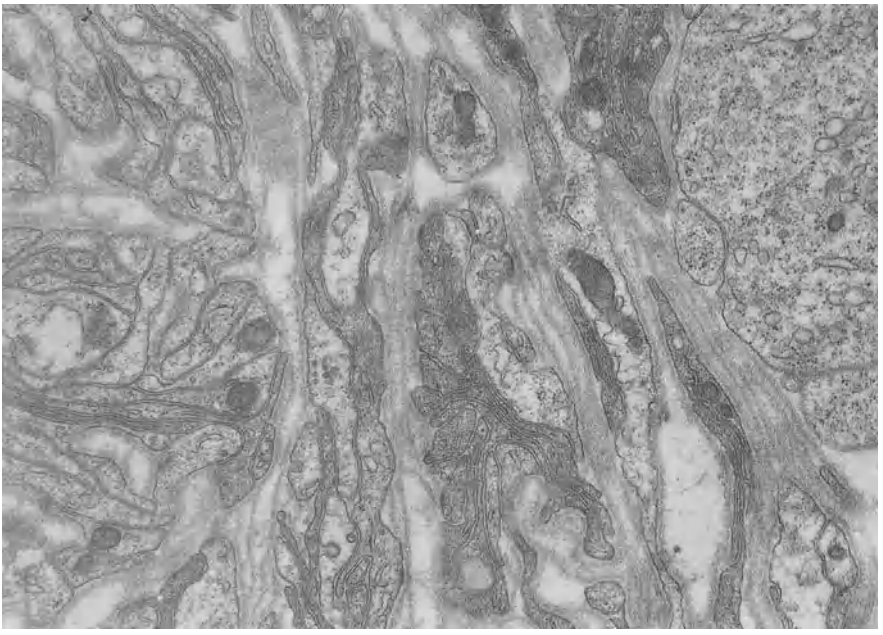


Fig.17.9. Neurinoma, interdigitating processes of tumor cells surrounded by basement membrane, ×18,000 [2486]

ment membranes [510]. Direct evidence of collagen production by Schwann cells is lacking, but it is thought that there is a process of organization of the collagen in which the GAGs of the basement membrane may play an important role [1912].

Immunohistochemically, two main antigens are in evidence, S-100 protein [3011] and Leu-7 (HNK-1) [2178], even though they cannot be considered as specific. Conversely, GFAP may be positive, both in the majority of neurinomas and in many neurofibromas [1865, 981, 2715, 1747]. This finding is, however, controversial: In some experiments in which a monoclonal antibody was employed, no staining was observed [2868]. It is possible that in the heterogenous group of GFAP polypeptides, those positive in Schwann cells are not identical to those positive in astrocytes [1312]. The laminin of the basement membrane is easily demonstrable immunohistochemically [1837].

17.1.5 In Vitro Culture

The cells growing in culture are identical to those found in Antoni A and B areas [1977, 1976, 1713]. The former are elongated and bipolar and arranged in a tandem fashion, while the latter have an ameboid appearance, with processes arranged in a characteristic way. According to some investigators [1409, 1713], they may transform into "Gitterzellen," demonstrating the capacity to phagocytose and to turn back into Schwann cells; however, this transformation has not been confirmed by others [512]. The origin of macrophages from Schwann cells has subsequently been observed [731]. The existence of a developed lysosomal apparatus in macrophages can be demonstrated by adding a fluorescent cationic dye to the medium. This may also be noted, to a lesser extent, also in elongated type A Schwann cells [801].

Neurinomas have also been maintained in organotypic culture, in which the production of an abundant basement membrane in the extracellular spaces and long spacing collagen [483] have been observed, as already reported [512].

17.1.6 Prognosis, Malignancy

Not infrequently, large, haphazardly distributed or clustered cells with large and hyperchromatic nuclei are found. Their significance is uncertain, but they are not related to malignancy.

Neurinomas in general do not become malignant and do not metastasize. A malignant variety has been described in peripheral nerves, mostly in von Recklinghausen's disease, and exceptionally in the cranial nerves, mostly in tumors arising from the Gasserian ganglion or from branches of the fifth nerve. With malignancy the cell density increases, and mitotic figures appear (Fig.17.10) while the organization into fiber bundles positive for reticulin staining is maintained (Fig.17.11). The tumor, which is encapsulated at first, acquires an infiltrative growth pattern and recurs after removal. Subsequently, necroses, pleomorphism, and epithelioid features appear. The tumor becomes anaplastic, and the origin from Schwann cells may only be recognized by NSE detection [1810] or at the electron microscopic level by demonstrating basement membranes [1119]. Bony, adipose, cartilaginous, and muscle metaplasia may appear, and a rhabdomyoblastic component may be of importance [558, 670, 1479]. The final picture is what was called "neurogenic sarcoma" or "neurofibrosarcoma" in the earlier literature. Neurinomas usually have a good prognosis, and satisfactory results are essentially related to total surgical removal. The operative mortality is low and is usually due to pontine infarction.

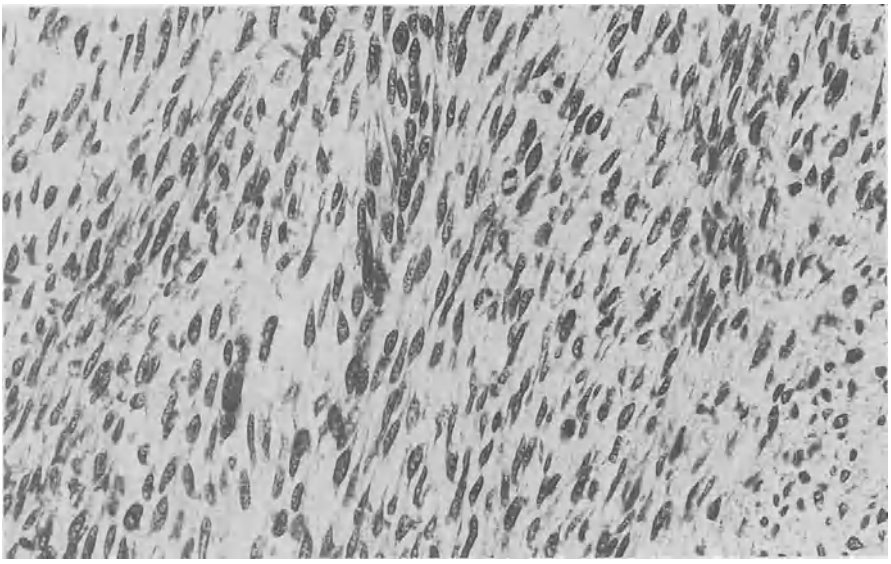


Fig.17.10. Malignant neurinoma, mitotic figures, higher power magnification of Fig.17.11a, H&E, ×400

17.2 Neurofibroma

This is a rare lesion in the spinal canal where, even if solitary, it may be indicative of von Recklinghausen's disease. It is more frequently found on the peripheral nerves.

The cutaneous neurofibroma arises from small nerves in the dermis and presents as a small pedunculated mass, well delimited from the epidermis. Histologically, it is formed by elongated, twisted, and eel-shaped cells, admixed with a varying number of collagen fibers. The collagen matrix imparts a fibroblastic appearance. Under the electron microscope Schwann cells are recognized because of their basement membrane [1582]. This tumor is usually part of von Recklinghausen's disease.

17.2.1 Plexiform Neurofibroma

Intraneural neurofibroma, also called "plexiform," arises from large nerves anywhere but particularly in the cervical, brachial, and lumbosacral plexuses. Macroscopically, it presents as a variably enlarged stretch of nerve or as a moniliform swelling along the nerve. It has a hard, elastic consistency and appears whitish and translucent upon cutting. Microscopically, proliferating Schwann cells are thin and elongated and are dispersed in a GAG and collagen matrix, traversed by axons. These are usually clustered centrally. Peculiar structures, reminiscent of Meissner's corpuscles, may be found.

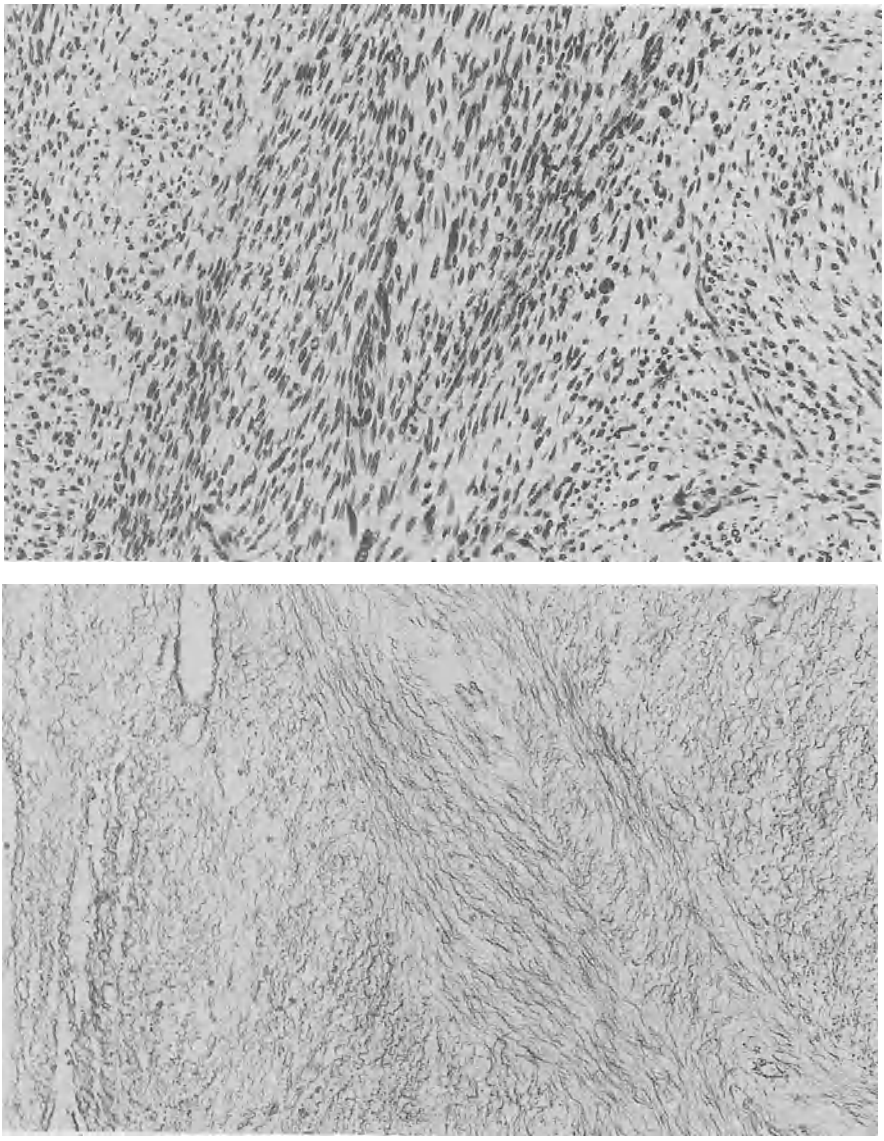


Fig.17.11a,b. Malignant neurinoma: **a** bundles of elongated cells with many mitoses, H&E, ×200; **b** preservation of reticulin fibers, Gomori, ×200

Under the electron microscope, Schwann cells predominate, and long-spacing collagen is found in the interstitial spaces [2960, 2212, 3006], while fibroblasts seem to play a secondary role. However, recently, the importance of the perineurial cells has been emphasized [726], and intermediate characteristics between the two cellular types have been found [1143], favoring the unitary hypothesis of Schwann cells and perineurial cells [483]. Melanotic neurofibromas have been described.

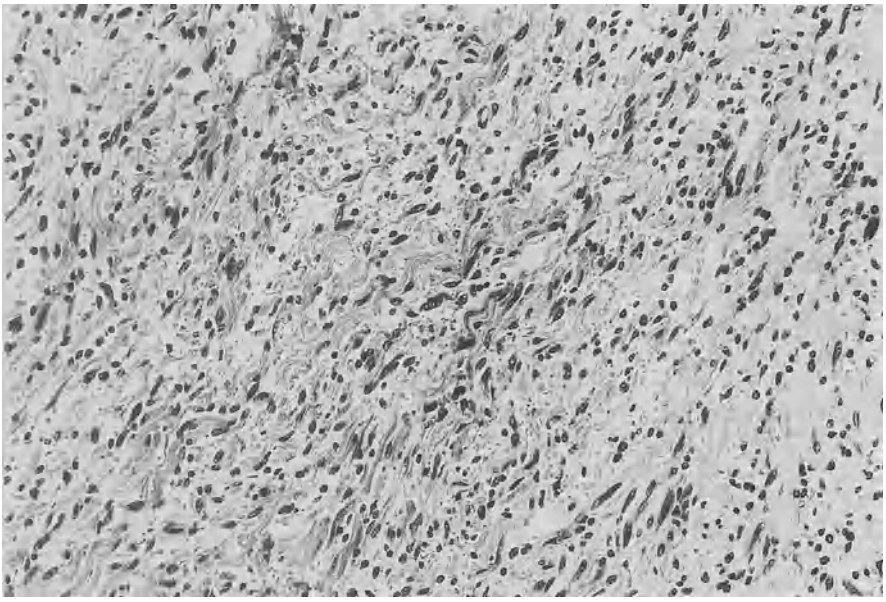


Fig.17.12. Neurofibroma, elongated, twisted, and eel-shaped cells, H&E, ×400

17.2.2 Malignant Variant

Malignant variants can be primary or arise from transformation in a plexiform neurofibroma. The most common sites are the neck, the extremities and the retroperitoneum. In general, they are part of von Recklinghausen's disease, but there are reports of such tumors in the absence of neurofibromatosis. The tumor has no capsule and shows an infiltrative growth. Histologically, it is formed of elongated and closely packed cells, with mitotic figures. Multinucleated cells may appear. The pleomorphism may reach extreme degrees, to the point of "neurogenic " sarcoma and "neurofibrosarcoma." An epithelioid or whorled appearance may be present. Recently, reports of postirradiation neurofibrosarcomas have appeared [669].

18 Tumors of the Meninges

18.1 Meningiomas

18.1.1 General Considerations and Nomenclature

The first accounts of meningeal tumors were those of Louis [1695] and Cruveilhier [528], while the first distinction of "psammomas" from fibromas and dural sarcomas was made by Virchow [2943]. However, it was with Bailey [107] and Cushing [538, 541] that the nosography of meningiomas was outlined, as for many other tumors of the CNS. It is evident that both the terminology and the various classifications proposed reflected all the uncertainties regarding the tissue of origin of meningiomas [2469]. For many years, for example, the opinion that these tumors originated from endothelial "dural" cells prevailed, so that they were called "dural endotheliomas." Cleland [457] commented on their possible origin from arachnoid cells which had remained included in the dura, an idea which was reaffirmed and sustained by Schmidt [2538] and by Cushing and Weed [545]. Though the origin of endotheliomatous meningioma from arachnoid residues in the zones of development of pacchionian granulations is today generally accepted, uncertainties still exist for the fibroblastic type [3068]. Many have attempted to clarify the last point. Mallory [1745] and Penfield [2171], on the basis of Ribbert's concept [2310], tried to demonstrate that the fibroblast is the typical cell composing a meningioma. They proposed the term "fibroblastoma." On the other hand, other authors [2058, 2381, 2379], and in general the French school, sustained the neuroectodermal origin of the leptomeninges and of the neoplastic derivatives. Faced with these contrasting opinions, grounded mainly on embryogenetic criteria, classifications based on morphological and biological criteria became increasingly important.

The use of embryogenetic criteria appeared, however, to be very complicated [941]. The possible origin of the tumors from embryonal remains, which were responsible for their growth, became the basis for interpreting the presence of various cellular forms within the confines of the ontogenetic differentiation, such as fibroblasts, angioblasts, osteoblasts, etc. It was somewhat more difficult to ascertain whether all the structural elements of the tumor, such as the blood vessels and fibers, derived from the meningothelial cells of the arachnoid. However, in the light of phylogenetic and ontogenetic considerations, it seemed reasonable to concede that one or more components of the various layers of the meninges (and therefore of the diverse structures of meningeal tumors) could originate from embryonal residues and then differentiate. The frequent presence of remnants of poorly differentiated meningeal tissue in some cerebral malformations supported this interpretation.

The term meningioma was coined by Cushing [538] who adopted it to avoid futile discussions on histogenesis. According to the concept of Cushing and Eisenhardt [544], in meningiomas there is a basic cell which could appear sometimes in a pure form and sometimes in a variously modified form thereby justifying the variants.

Because of uncertainties regarding the classification and nomenclature (fibroblastoma or endothelioma), which reflected the histological composition of the meninges, i.e., meningothelial cells and fibroblasts, the introduction of the term meningioma was expedient to end the debate. Moreover, it corresponded to the anatomical situation.

The dura mater is formed by connective tissue with parallel and interwoven fibers, fibroblasts, and large cells within the interstices. The arachnoid is formed by fibrils interwoven with fibroblasts, lymphocytes, and histiocytes. It has an external thin layer containing epithelial-like cells with a covering function called meningothelial cells. Under the electron microscope, the meningothelial cells show an extreme interdigitation of the cell membranes [1383] which cannot be recognized by light microscopy and the cell membranes appear so fuzzy as to give rise to the syncytial appearance. Meningothelial cells are not only in direct contact with the inner dural layer formed by the so-called cells of the dural border without any real interposed space, but the two layers even merge, also forming serrate junctions with desmosomes [2462]. A thin basal lamina then separates the external arachnoid layer from the inner one [1389]. It has to be taken into account that in culture, meningothelial cells form whorls [1410] and that in normal arachnoid villi, these undergo calcification. There is, in general, agreement that meningiomas arise from the arachnoid, in particular from its external layer, but other cellular components of the arachnoid, for example fibroblasts, which are found in the inner layer, may contribute to their composition: This could explain the frequent biphasic, meningothelial and fibroblastic, appearance [1389].

An unresolved problem which has influenced the classification of meningiomas is that of the embryology of the meninges. Even if there is general agreement that the primitive meninx derives from the condensation of the mesenchymal layer situated around the neural tube, between this and the ectoderm, discussions regarding the participation of the neural crest in its formation are still going on. One should not forget that all the variants of meningioma (chondro-, fibro-, angioblastic, etc.) follow the lines of mesenchymal differentiation, while there is no aspect categorically supporting derivation from the neural crest: There are no doubts that meningioma must be considered a mesodermic tumor [2391, 1389].

If an all-embracing classification, including clinical and neuro-imaging characteristics, must be adopted, the 1979 WHO classification is not completely satisfying. Such a need does exist [1299], so the suggestion to renounce the desperate search for the cells of origin and to follow that of identifying specific cell differentiations [2471] seems most promising.

In this book the classification scheme recently proposed by the WHO is adopted.

18.1.2 Frequency

In the series of 2023 primitive intracranial tumors of Cushing [542], meningiomas represent 13.4%. In various North American neurosurgical series they vary from 13% to 19% [1389]. In pathological series, they represent 17%–18% [3134, 2486, 3138]. In our present pathological and surgical collection of 8549 cases, they represent 18%.

It is to be noted that in neurosurgical series, meningiomas found casually at autopsy are not considered. On the other hand, asymptomatic meningiomas may be found ca-

sually by CT scan; they do not necessarily grow further [779]. Therefore, the average incidence of some series can be calculated to be about 20%.

The geographic distribution is fairly uniform throughout the world, with the exception of Africa, where meningiomas seem to be more frequent. This, however, may be a relative factor, more expressive of a lower incidence of gliomas [837].

Regarding populations, the Rochester studies give an incidence of 6/100,000 in a clinical and postmortem series [1539], while another clinical series gives 2.3/100,000 [2348], similar to that in the reports before CT came into use.

18.1.3 Age

Meningiomas are single or multiple tumors clearly more common in adults. In large series, the average age found varies from 46 [542] to 45 years [3134]. In a personal series, there is a clear-cut preponderance in the 6th decade of life, with an average age of 51 years. It has to be underlined that the frequencies according to age differ between surgical and autopsy series: Of 300 asymptomatic tumors found at autopsy, 100 were meningiomas, and these occurred more frequently in the seventh and eighth decades. By contrast, symptomatic cases were concentrated in the fifth decade [3075].

Meningiomas are rare in infancy: The percentage varies from 1.1% to 4% [2810, 544, 534, 525, 1123, 2447, 571, 660]. To date, 197 cases have been reported in the literature [769]. In the personal series of pediatric intracranial tumors, they represent 1.4%. In 15%–20% of cases, the tumors are intraventricular [658]. There are rare reports of congenital meningiomas [1868, 325].

Some observations indicate a more malignant character of meningiomas in childhood [525], probably because of the prevalence of the hemangiopericytic and papillary variants [2419], a higher incidence of intraventricular [2055] and spinal epidural meningiomas [366], and a male rather than a female preponderance [1953]. Exceptional cases of giant tumors situated in the parieto-occipital region [1803] and in the foramen magnum [2653] have been reported.

Meningiomas tend to occur more frequently in patients over the age of 60 years: 35% in the series of Cooney and Solitare [487]. With advanced age, the higher percentage may be expressive of the high frequency of "incidental" meningiomas, i.e., which do not cause death and are occasional autopsy findings.

18.1.4 Sex

The prevalence for the female sex is unanimously acknowledged [3134, 1389, 2420]. In the personal series, the female to male ratio is 1.8:1. It has to be noted that the difference between the sexes disappears, as has in part been said, above and below a certain age [1389]. The preponderance of the female sex in middle age is due to estrogen stimulation, generally recognized as a growth factor for tumors. The same explanation is given for the rapid growth of meningiomas in pregnancy, especially those close to the sella turcica. Whether it is real growth or a reversible increase in volume caused by electrolytic imbalance has yet to be established with certainty [1881]. Another factor sug-

gesting the importance of female hormones in the growth of meningiomas is given by the more than casual association between these tumors and breast carcinoma [2552]. This is one of the arguments for considering meningioma as a hormone-dependent tumor. In fact, estrogen and progesterone receptors have been found in a certain number of cases, both biochemically and histologically [651, 2213, 2544, 2847, 3107, 1131, 1789].

The evidence for the association between meningioma and breast carcinoma rests on 36 reported cases in the literature [1462]. In 6 women, not only was the breast carcinoma associated with meningioma of the sphenoid ridge, but a genital tumor was also present [1269]. It has been proposed that a disturbance of the regulation of the oncogenes, similar for the two tumors, is the basis of this association. The possibility that in a breast cancer bearer neurological symptoms may be related to a meningioma and not to metastases has been emphasized [1462]. It is surprising that the large series of meningiomas reported by Cushing and Eisenhardt in 1938 and Zülch in 1956 have not included such observations.

18.1.5 Familial Tendency

Meningiomas in members of the same family are found in von Recklinghausen's disease and also in the absence of this genetic affliction [864, 2962, 1326, 1012, 2581].

18.1.6 Association with Other Tumors

Even excluding von Recklinghausen's disease, an association with other tumors is frequent, mostly with gliomas, in particular glioblastomas. Several cases have been reported [1760, 2486, 1389, 807]. It may be a fortuitous association, given the frequency of these tumors, but there may also be a relationship dependent upon the effect of the stimulus of one tumor on the other [1986], especially if the meningioma is malignant. An association with pituitary adenomas, intestinal carcinoids, parathyroid adenomas, and choroid plexus melanoma has also been reported [1389]. Among nontumoral lesions, aneurysms are those most frequently associated with meningiomas [807]. In exceptional instances, carcinomatous metastases in a meningioma have been described [766, 189]. In this context, it should be remembered that carcinomatous metastases to the meninges are not rare [176, 310, 566, 1765, 2714].

18.1.7 Site

Intracranial meningiomas are more frequent than spinal ones, with a 16:1 ratio [542]. Four main sites are usually considered: intracranial, spinal, ventricular, and extracranial. At these sites meningiomas demonstrate elective locations which are statistically and embryologically significant.

In the intracranial region, the following elective sites are distinguished in order of frequency: parasagittal, convexity, sphenoid, Sylvian, olfactory groove, tuberculum

sellae, parasellar, tentorium, Meckel's cave, falx, pontocerebellar angle, ventricles, clivus [541, 3134].

Parasagittal meningiomas are usually situated, in order of frequency, in the middle third of the sagittal sinus, the posterior third, and then the anterior third [2078, 1164, 3134]. The high incidence of meningiomas at these sites has been related to the frequent presence of pacchionian granulations, the importance of which has already been mentioned. Meningiomas often occupy the angle between the dura and the sinus, to which they are strongly adherent. Their development is mostly extracerebral, but sometimes they partially or totally penetrate the parenchyma, compressing and shifting it.

Convexity meningiomas are mostly located anteriorly; they do not show any relationship with the sinus but adhere to the dura mater, sometimes so tenaciously that it is impossible to dissect them away from it. This is the most common site for multiple meningiomas, which take on the appearance of multiple nodules of various sizes in the dura mater.

Sphenoidal meningiomas and those of the Sylvian region very often show similar modes of development. They are variable in shape, size, and direction of growth, and they may reach and occupy the middle or anterior fossa, or both. Sphenoid meningiomas have been further subdivided into those of the clinoid and those of the middle part of the sphenoidal angle. The global ones, involving the pterion, often have an "en plaque" appearance. A more recent categorization, more expressive of surgical considerations, is the petroclival category, which may involve the cavernous sinus and extend to the anterior clinoid process. Blood vessels and nerves of the base of the skull may become enveloped in the neoplastic mass which also sends tumor prongs into the neural parenchyma.

In the olfactory groove, the frontobasal structures, particularly the olfactory bulb, the optic nerve and the anterior cerebral arteries are affected. The tumor extends mostly towards the chiasm and the frontal lobes, often on both sides of the falx. Tumors arising from the optic nerve sheath have occasionally been reported [456].

As above, meningiomas of the tuberculum sellae and of the parasellar region (Fig.18.1) particularly involve the chiasm, but also the optic and sometimes the olfactory nerves. They are usually small tumors which find their growth space in the frontobasal regions.

Tentorial meningiomas which arise from and adhere to this structure may develop in both the supra- and infratentorial regions. In the latter case, they take on the known dumbbell shape.

In Meckel's cave, they originate from the dural covering of the cavum itself and always develop in relation to the temporal lobe. Also, in this location they may present as "en plaque" growths or extend neoplastic prongs into the surrounding neural tissue. They are not common: Overall, 46 cases have been described up to and including 1983, plus two personal ones [349].

Meningiomas of the falx are to be distinguished from parasagittal meningiomas because, unlike the latter, they do not show a direct relationship with the superior sagittal sinus. Rather, they are adherent to the falx itself. They almost always develop towards the cerebral tissue, sometimes on both sides of the falx.

In the pontocerebellar angle, they follow, in general, the same modes of growth and involvement of the local structures of this region as other neoplasias.

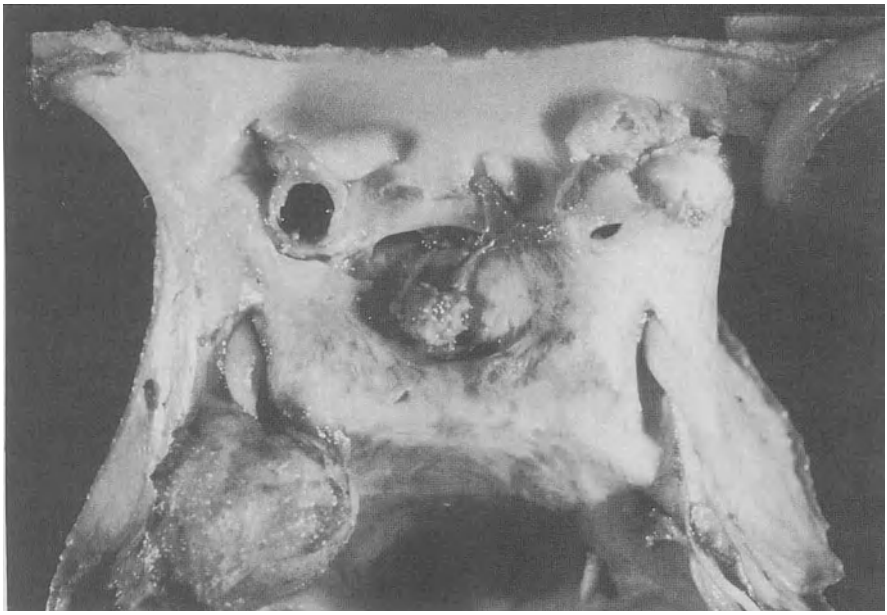


Fig.18.1. Multiple parasellar meningioma

The lateral ventricles are not infrequently involved [85, 888]. These tumors adhere to the choroid plexuses, sometimes reaching sizable proportions, especially on the left (Fig.18.2). Of 407 meningiomas reported in a series from 1958 [2876], 8 were intraventricular. Seven of these were of the fibroblastic variety. The fourth ventricle is certainly one of the rarest sites: up to 1950, only 2 cases had been described [2946] and 8 up to 1963 [408]. To date, 10 cases have been reported, plus a recent one of the osteoblastic type [1318]. They may originate from the choroid plexus, most probably from the inferior tela choroidea [2466].

The clivus is one of the less frequent localizations. Because the tumors often develop in the direction of the foramen magnum and can reach the spinal canal, they are called craniospinal meningiomas. Many authors distinguish these tumors from those arising from below, which are called spinocranial meningiomas [2727].

Tumors may rarely originate from the intracranial part of the jugular foramen and extend extracranially or may, even more rarely, arise from the foramen itself [1250].

In general, meningiomas of the posterior fossa are not common. They represent 9% of 1854 cases collected from the literature [5]; the percentage varies in different series: 13.4% [544], 8.4% [392], 4.2% in the present series, in respect to intracranial meningiomas.

In relation to dural attachment, meningiomas are divided into those of the cerebellar convexity, tentorium, posterior surface of the temporal bone, clivus, and foramen magnum. Meningiomas formed 12.6% of 455 operated tumors of the posterior fossa [1593]. This percentage is not very far from that of meningiomas in general, with respect to the total of intracranial tumors.

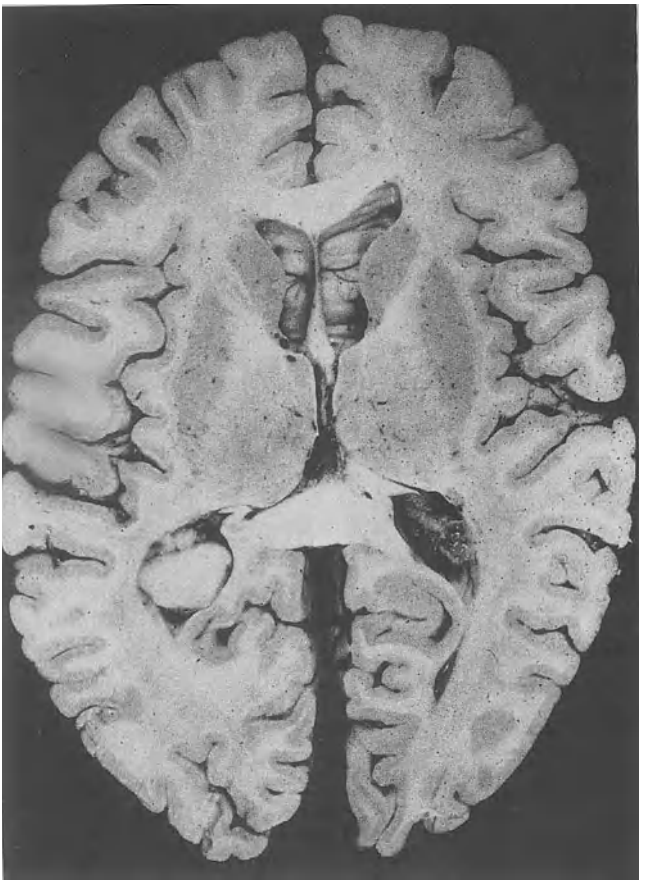


Fig.18.2. Meningioma of the lateral ventricle

Spinal meningiomas are far less frequent than intracranial ones: the ratio has been calculated to be 1:16 [542], but the relative percentage is quite variable, from 12.7% [2691] to 8.4% (personal series). The thoracic location is the most frequent. The relative frequency of meningiomas among primary spinal tumors, evaluated in many series, varies from 5.5% to 37.5% [2116].

Unusual extracranial and extraspinal sites are also found. This may be due to meningiomas extending from the cranial cavity, losing their site of origin. They may also be truly ectopic tumors, originating from arachnoid remnants, from arachnoid cells covering the craniospinal nerves at their point of exit, or they may even arise through metaplasia. Some have even hypothesized that they may arise without relationship to structures in the cranial and spinal cavities [1214].

The real frequency of extracranial meningiomas is not exactly known. Up to now, 504 cases have been reported with the same distribution for age and sex of intracranial tumors [2632]. The most common sites are the orbit, nasal cavities, paranasal sinuses,

scalp, calvarium, orbit, and the region of the basal foramina. The tumors of the orbit represent the majority. They arise mostly from the meningeal sheath of the intraorbital portion of the optic nerve [3078]. Those of the calvarium may be intraosseous, calvarial, extracalvarial, or subgaleal [218, 2071]. Other sites include the oral cavity, parotid gland, ear, neck, mediastinum, and skin. Those in the skin have been distinguished in tumors of the scalp and paravertebral areas (mostly benign and found in infancy), tumors of the skin around the sensory organs (eye and ear), and tumors which grow in the skin but originate in the craniospinal cavity [1690]. Histologically, extracranial meningiomas are similar to the intracranial ones; very few are malignant. Their origin is a matter of debate. It seems possible that they derive from meningocytic cellular rests or from Schwann cells [2632].

18.1.8 Multiple Meningiomas

Multiple meningiomas frequently occur in von Recklinghausen's disease, but also independently of this condition. This entity has poorly defined nosographic limits with regard to meningiomatosis: If the meningiomas are numerous, the distinction from meningiomatosis is very difficult [2117, 2747, 249]. Meningiomas are not only multiple concurrently but also at different sites, and this must not be confused with recurrence. The incidence of multiple meningiomas varies from 1% to 2%–4% [1992, 1389, 704, 2132]. If, however, not only histological but also CT data are considered, the percentage rises to 4.4% [1680], 5.4% or even 10.5% [1719, 1992, 752, 350]. In autopsy series, the frequency may reach 16% [3075], because asymptomatic tumors and elderly patients are included. Critical, comparative, clinical evaluation seems to indicate a proportion of 0.58% before and 4.5% after the introduction of CT scanning [649]. The occurrence of multiple meningiomas in the spinal canal is a rare event, but both supratentorial and spinal cases have been reported [497, 3118, 2028, 15, 1348].

18.1.9 Macroscopic Appearance

In general, from the surgical point of view, meningiomas are distinguished into three types: the "iceberg" tumor (Fig.18.3), so called because it is attached to the dura but embedded in the neural parenchyma; the "en plaque" type, which grows within the meninges and is most frequently situated on the sphenoid wing; and the type accompanied by bony hyperplasia, which is often located in the parasagittal region.

The tumor is usually well encapsulated and shiny with a smooth surface, reddish in colour, and has a hard-elastic consistency. On the cut surface, it appears mostly compact and fibrous. Many variations on these appearances, in part dependent on the histological type but often conditioned by regressive events, may be seen. For example, when fatty degeneration is present, the appearance of part or all of the tumor may be granular, yellowish, and of a soft, friable consistency. Calcification, which is rather frequent, may modify the color and especially the consistency of the tumor in the opposite way and may be felt on cutting. When meningiomas are multiple, especially over the convexity, they present as nodules more or less tenaciously adherent to the dura. Some-

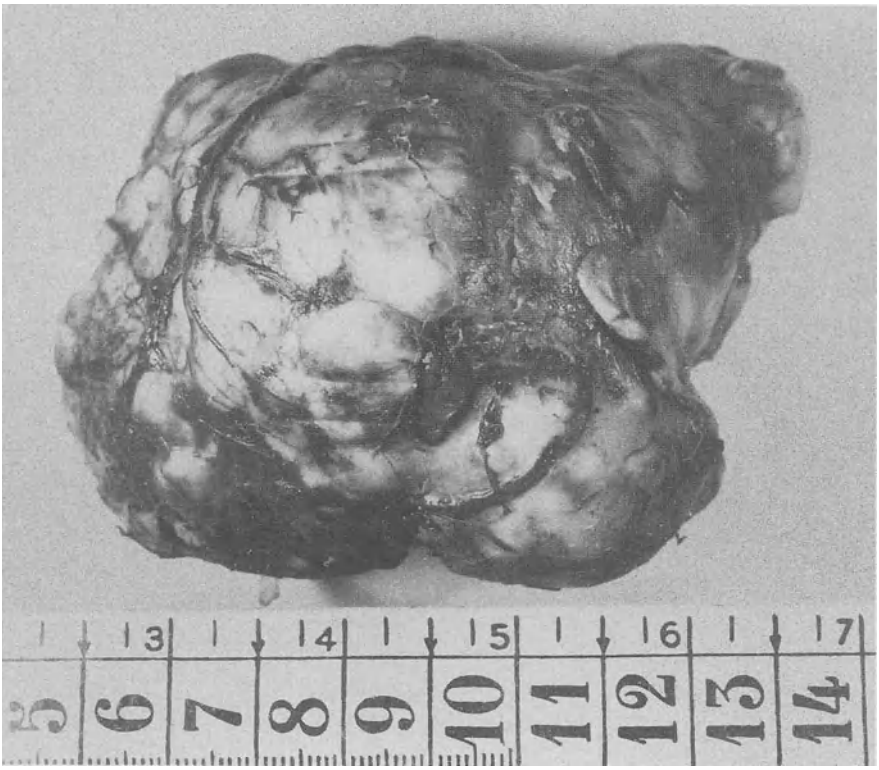


Fig.18.3. Meningioma, hard and polylobulated mass

times, the neoplastic masses, dura, eroded and/or hyperplastic cranium are so compacted that they need to be removed en masse. When they are single, meningiomas have very variable dimensions, from the size of a pea to that of a large orange, or bigger. The weight of the fresh tumor varies from a few to several grams. In two cases reported by Zülch (1956) [3134], it was 835 g and 1300 g, including the infiltrated bone in the latter. The largest specimen of the personal series reached 550 g. The shape also shows marked variations, especially in relation to the location of the tumor. It may be roundish, elongated, "en plaque," or dumbbell, etc.

In the majority of cases, meningiomas create a space by compressing the surrounding neural tissue, forming niches in the neural parenchyma or growing in preexisting spaces such as the ventricles and the subarachnoid cisterns. The growth tends to follow pathways of lesser resistance. The tumors demonstrate an altogether different behavior with respect to mesodermal structures, such as the falx, tentorium, dura, and bone. In fact, these are infiltrated by the neoplastic proliferation, even if they are certainly benign, both histologically and biologically.

Meningiomas of the base of the skull, those of the sphenoid, and of the Sylvian fissure take on an "en plaque" appearance more frequently than others, engulfing and constricting nearby vascular and neural structures because of the way they grow along the

meningeal planes. Both erosive and hyperplastic bony changes are often associated with meningiomas, especially in the parasagittal, convexity, and sphenoidal locations. Sphenoid tumors cause changes in the sella, such as decalcification and erosion, more frequently than those of the sellar region. Spinal meningiomas, as the intracranial ones, adhere densely to the dura. They are mostly situated in the subdural space, in a lateral position and in direct relationship with the spinal roots, and may take on different shapes and sizes but are generally rounded or elongated. Even at this site, they may present as multiple tumor nodules. The presence of intratumoral cysts is fairly rare.

18.1.10 Microscopic Appearance

Meningiomas usually show a high cell density and are composed of polygonal, rather large, epithelial-like cells arranged in lobules, trellises, or islands, with a syncytial appearance (Fig.18.4a). Parenchymal cells in the common histological preparations demonstrate ill-defined borders (Fig.18.4b). The discretely eosinophilic cytoplasm usually appears homogeneous and is sometimes finely granular. The nuclei, of average size, rounded or slightly elongated, have a discrete quantity of mostly uniformly stippled chromatin, sometimes clustered on the nuclear membrane, and show the presence of 1–2 nucleoli. In some areas of the tumor, with marked variations from one case to the other, the nuclei feature vacuolization (Fig.18.5a) with central vacuoles which appear either to be optically empty or to contain eosinophilic inclusions. Mitoses are scarce or absent. In some cases, there are circumscribed areas with a higher cell density, showing the appearance of growth centers, sometimes with mitoses (Fig.18.5b).

An interstitial collagenous stroma of variable density subdivides the neoplastic mass into the cell territories mentioned. Such stroma shows marked variability, not only from one tumor to the other, but also from one region to the next of the same tumor. It may be abundant, but especially in florid tumor areas, it is mostly sparse and limited. It contains thin blood vessels and a delicate framework of connective tissue. Reticular fibers are clearly confined to the stroma. Contrary to Mallory [1745] and Bailey [107], Klose [1457] never found free elastic fibers in the parenchyma, but only in relation with blood vessels.

Like nonneoplastic arachnoid cells, meningothelial cells can arrange themselves in a spiral fashion and form whorls (Fig.18.6a). These may be occasional and isolated or occupy the entire neoplasm. Whorls are formed around the meningothelial cells, blood vessels, or other structures; collagenous fibers, which may stain for reticulin and collagen, may be deposited. They may undergo hyalinization and other phenomena connected with calcification, becoming psammoma bodies. These tumors have been called endotheliomatous, meningotheliomatous, or syncytial meningiomas.

A different histological appearance, characterized by fusiform and elongated cells, arranged in interwoven bundles, morphologically similar to fibrocytes, may be present in some tumors (Fig.18.6b). Whorls, although less common and less structured than in the previous type, are often formed, but they sometimes have a clearly perivascular arrangement. Psammoma bodies are observed less frequently and are, on the whole, less numerous. The nuclei, usually ovoid or elongated along the major cell axis, are similar to those of the previous type. Their occasional alignment should not be confused with

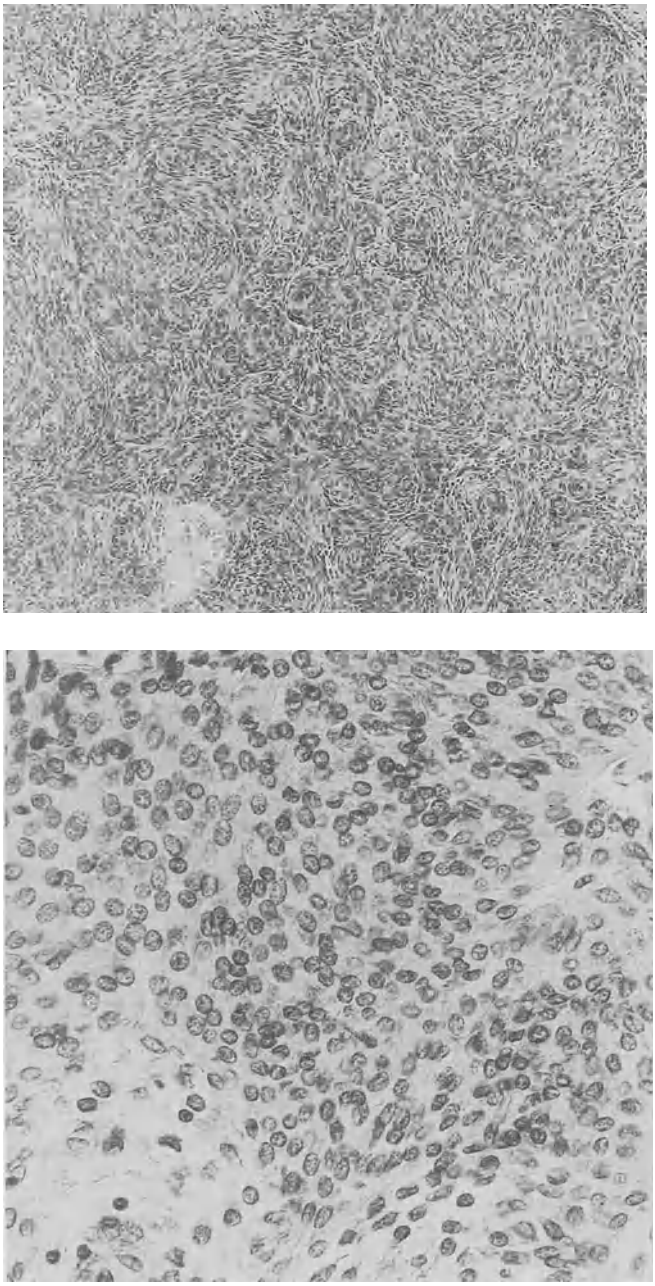


Fig.18.4a,b. Meningioma: **a** general aspect with many lobules, H&E, ×150; **b** syncytial meningioma, ill-defined cell borders, H&E, ×300

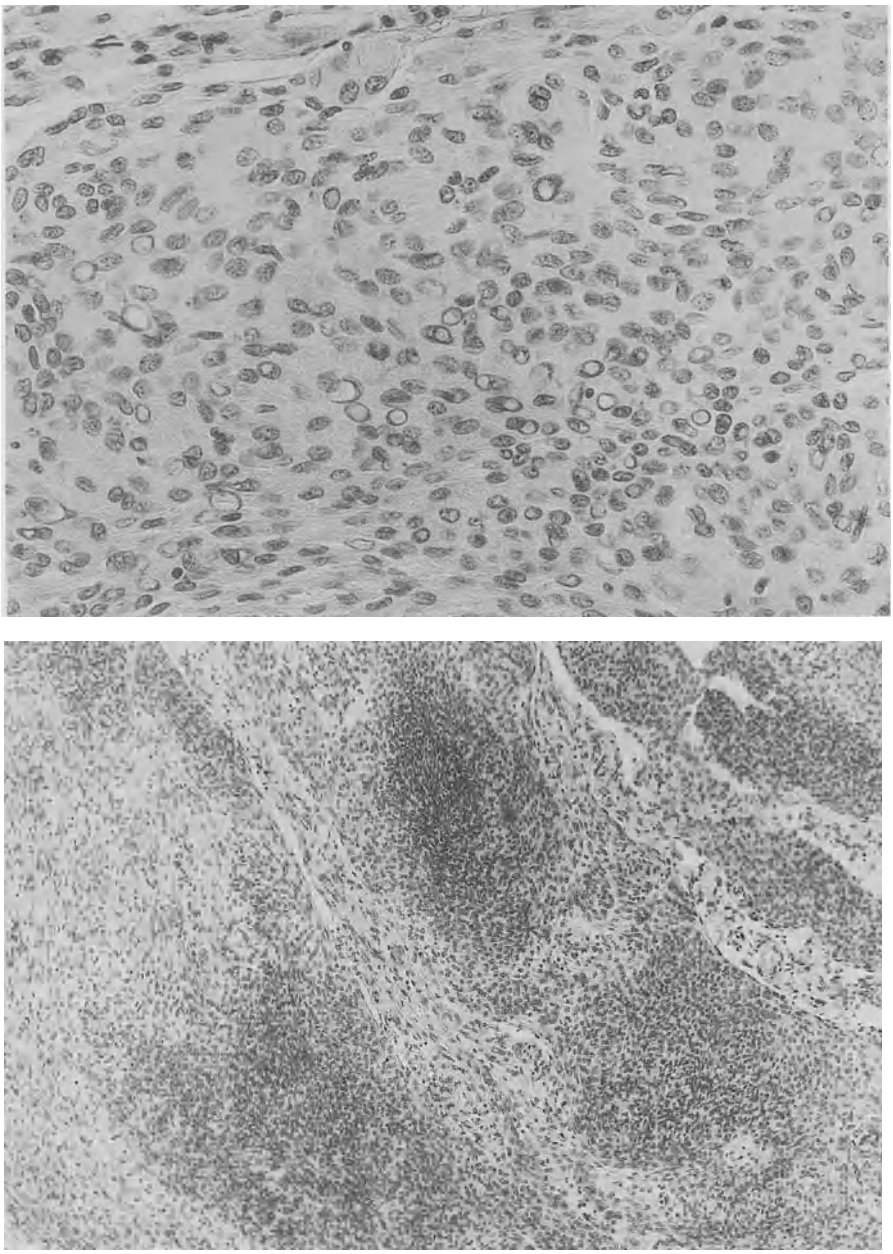


Fig.18.5a,b. Syncytial meningioma: **a** vacuolated nuclei, H&E, ×300; **b** areas with high cell density, H&E, ×200

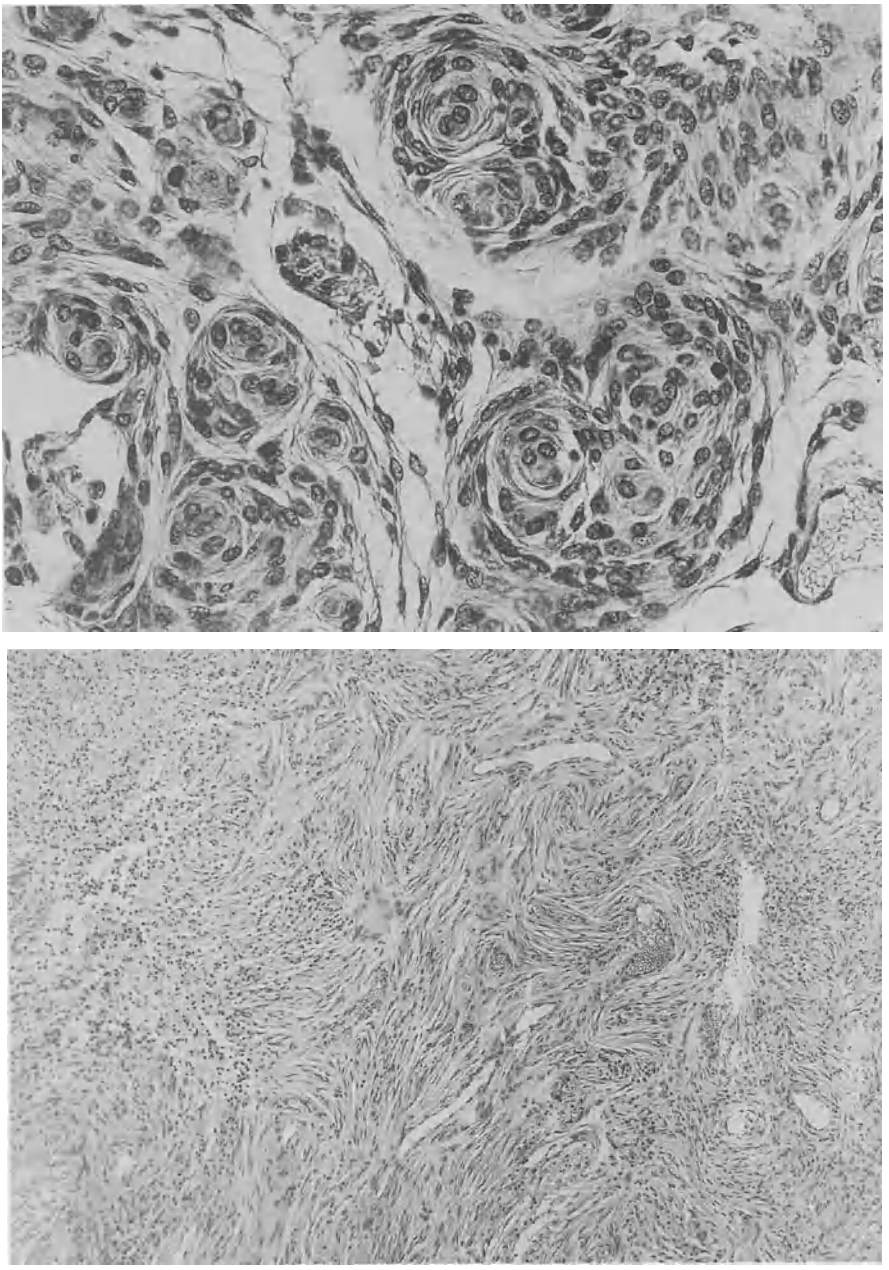


Fig.18.6a,b. Meningioma: **a** formation of whorls, H&E, ×400; **b** fibroblastic meningioma, H&E, ×200

the palisades of neurinoma. An important differential characteristic of these meningiomas is represented by the richness in collagenous and reticulin fibers. The latter are particularly well developed and form a fine intercellular network; however, they remain confined to the septa and blood vessels and do not belong to the parenchyma, even if they may appear between the tumor cells. Tumors of this type are called fibroblastic meningiomas, even if extravascular reticulin usually does not appear. When the fibroblastic and syncytial appearances coexist, one may speak of transitional meningiomas. In both these tumor types, the expression of laminin and intercellular type IV collagen is controversial: Both positive [1837, 2065] and negative [162] results have been reported.

In general, meningiomas have a clear-cut boundary with the neural tissue (Fig.18.7a) and may be considered encapsulated tumors, although this capsule is variable in thickness and may even be altogether lacking. It is formed by an arachnoid membrane, the pia, and the tumor stroma. The limit between tumor and healthy tissue has been classified as "smooth," "fingerlike expansion," "lobular", and "invasive". In the last type, the demarcation is poor, and invasion occurs along the Virchow–Robin spaces [2003].

18.1.10.1 Angiomatous Meningioma

These are less frequent. Their main histological characteristic is represented by a spongy appearance, caused by a large number of blood vessel lacunae (Fig.18.7b). The latter appear delimited by endothelial cells arranged in a single layer. In some cases, as in the angioblastic areas of the previous types, the angiomatous structure is very similar to that of hemangioblastomas from which these meningiomas must be distinguished on the basis of light and electron microscopy findings. In hemangioblastomas, the blood vessel lacunae are mostly of irregular dimension and shape, from small capillary-type dilatations formed by one or two parietal cells to large, cavernous, irregular, and sinusoidal cavities. In angiomatous meningiomas, the rich vascularization, especially capillary, is not in strict relationship with the neoplastic elements. Endothelial cells frequently appear swollen, so as to occlude partially or totally the lumen of the blood vessel. The nuclei are generally more irregular than in the previous types, both in shape and in chromatin content. The presence of vacuoles is common to hemangioblastomas. Mitoses are occasionally observed.

The connective tissue stroma is formed by polygonal cellular elements, morphologically similar to the endothelium of the lacunae, and by an abundance of collagenous and reticulin fibers, which form a well compacted network with a mesh often corresponding to the blood vessel lacunae. In general, with respect to the previous tumor types, there is a greater tendency to cellular atypia and architectural disorganization. It should, however, be emphasized that in cases in which such characteristics are more evident, the biological behavior does not differ from that of other tumors of the same group which remain benign. It seems reasonable to interpret these morphological features as the consequence of regressive events rather than anaplastic ones.

Angiomatous meningiomas are common meningothelial meningiomas, rich in blood vessels. Some tumors, however, have a different appearance: Small blood vessels

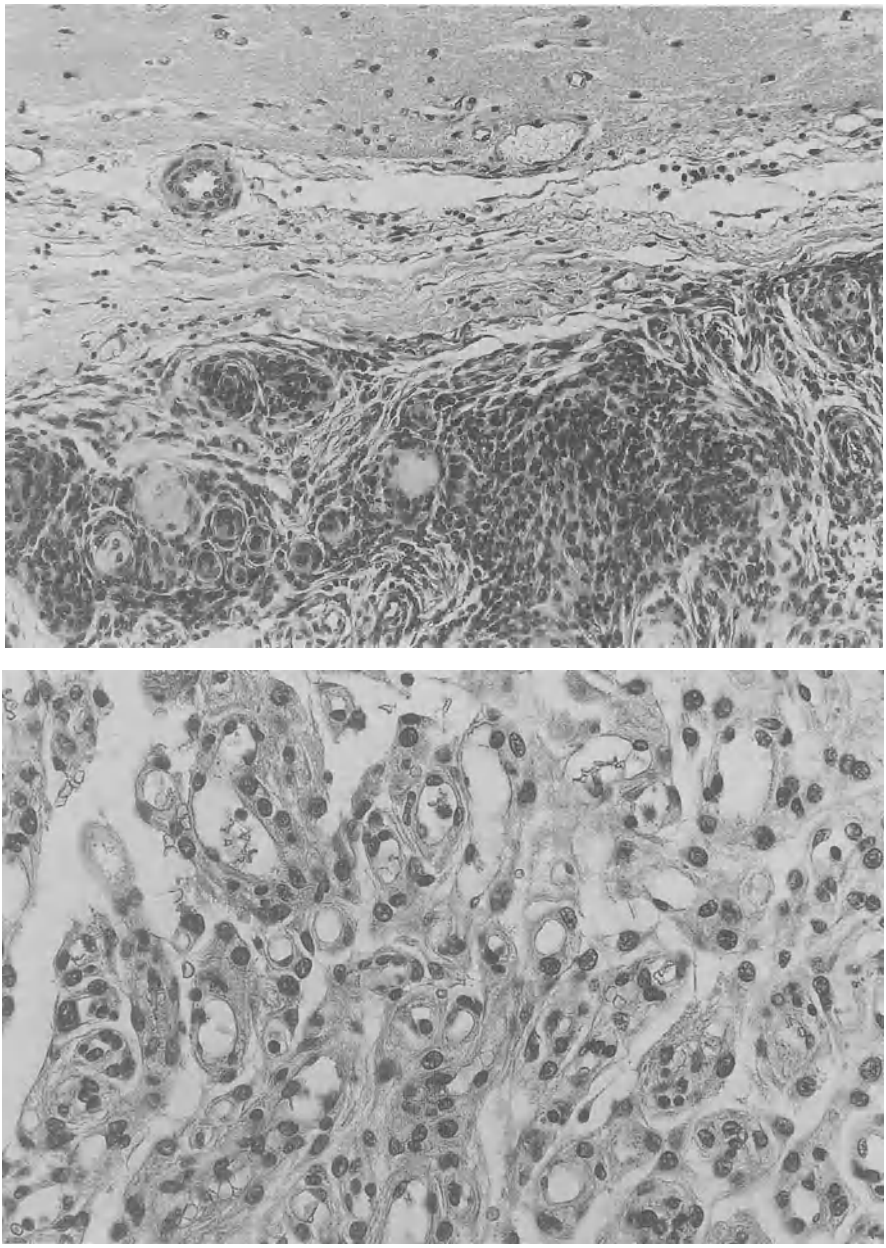


Fig.18.7a,b. Meningioma: **a** definite borders toward normal nervous tissue, H&E, ×200; **b** angiomatous meningioma, H&E, ×400

are totally enveloped by tumor cells, and foamy cells are especially noticeable between the blood vessels, so that they resemble cerebellar hemangioblastoma. Whether this tumor is a hemangioblastoma or a hemangioblastic meningioma is still a matter open to discussion. It has been underlined that cells wrapped around capillaries are not characteristic of hemangioblastoma, but of meningioma. These tumors should not be considered as a hemangioblastic variety of meningioma, but rather as pure angiomatous meningiomas [1389]. There are tumors which have a structure typical of cerebellar hemangioblastoma, hemangioblastomas of von Hippel–Lindau disease [1389]. According to others, transitional forms between hemangioblastoma and angiomatous meningioma occur [2420].

18.1.10.2 Malignant Meningioma

All types of meningiomas may be malignant. A high number of (atypical) mitoses [743], circumscribed necroses, infiltration of neural tissue [520], and high cell density [2659] are useful criteria of malignancy (Fig.18.8). All of these signs have an undoubted prognostic value, even if they have to be evaluated with caution [1301].

The definition of tumor infiltration of the nervous tissue is not easy. While for some the "fingerlike expansion" of the interface between tumor and healthy tissue (Fig.18.9a) is an expression of invasiveness [520], for others [2003] this is a sheer peculiarity of tumors without a definite border which infiltrate along the Virchow–Robin spaces. There may be real infiltrative growth (Fig.18.9b).

The definition of malignant meningioma is easy when all the signs of anaplasia are present at the same time. The WHO has established six parameters, on the basis of which a diagnosis of malignant meningioma may be made, but there may be more [2348]. However, it is difficult to identify the malignant variant when it has to be decided on a quantitative basis or when only some signs are present. There are, in fact, contradictory observations when histological features are compared with survival data. Automatic image analyses have demonstrated that neither the nuclear nor the cell density are prognostic elements. The histological type is also not predictive, while recurrences are more frequent in young subjects, in males, and in parasagittal sites. Circumscribed necroses and bony infiltration are more frequent in recurrent meningiomas, while cortical invasion is not significant [446]. According to others, anaplasia with typical and atypical mitoses would be more indicative than necroses and invasion of healthy neural tissue [2834]. The topic will be taken up again in the discussion on prognosis. It is, however, useful to recall that, using the six histological above-mentioned parameters of the WHO, meningiomas have been classified into four grades with increasing malignancy: benign, atypical, anaplastic, and sarcomatous. This classification has been found to correlate well with the tumor doubling time [1266] and also with radiological features. In particular, it has been observed that the recurrence was 3% for benign, 38% for atypical, and 78% for anaplastic tumors, with recurrence times of 7.5, 2.4, and 3.5 years, respectively [1267]. Another suggestion is to identify malignant meningioma on the basis of high cell density and nuclear polymorphism, associated with one of the other negative prognostic signs such as mitoses, necroses, invasion of neural tissue, papillary features, and hemangiopericytic variant [422].

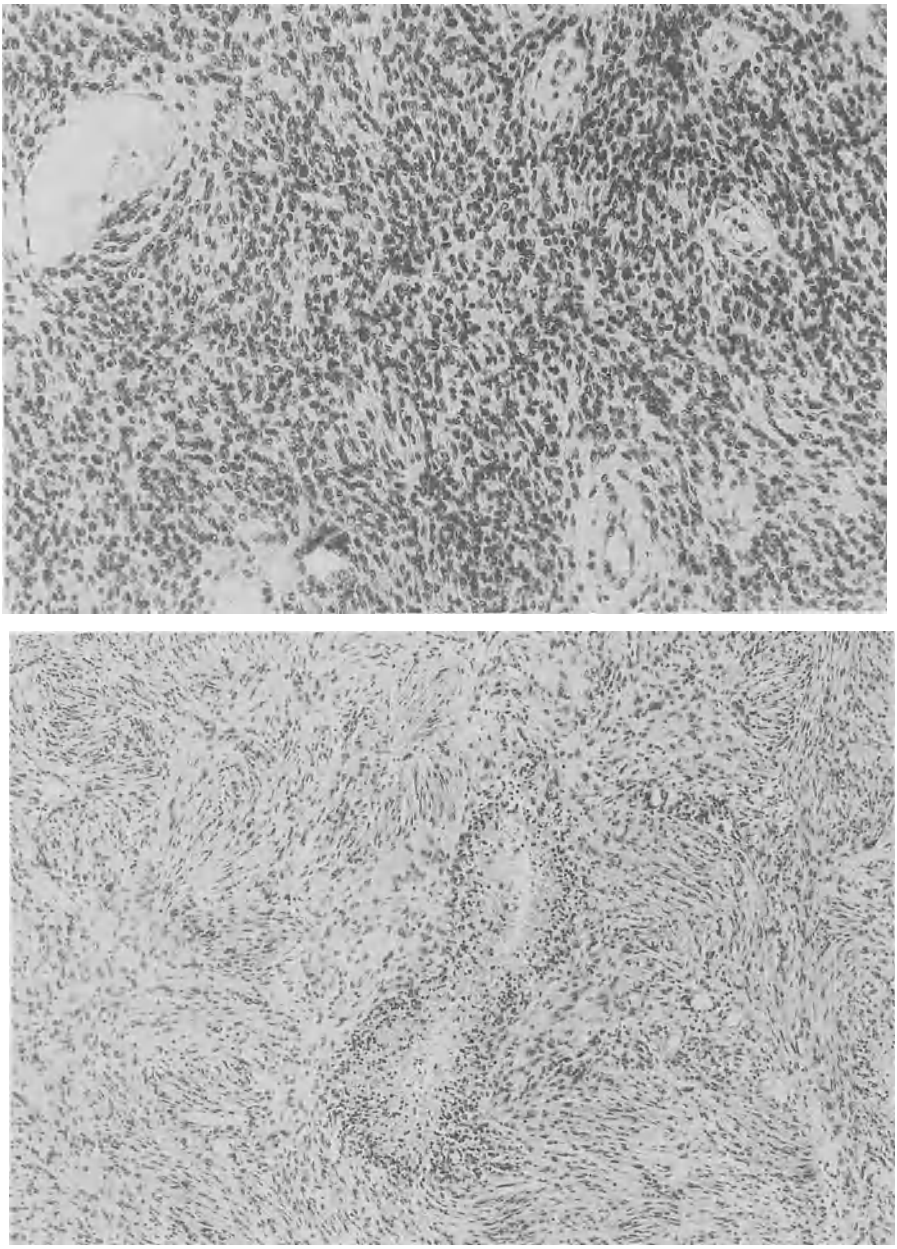


Fig.18.8a,b. Malignant meningioma: **a** very high cell density and many mitoses, H&E, ×200; **b** circumscribed necrosis, H&E, ×200

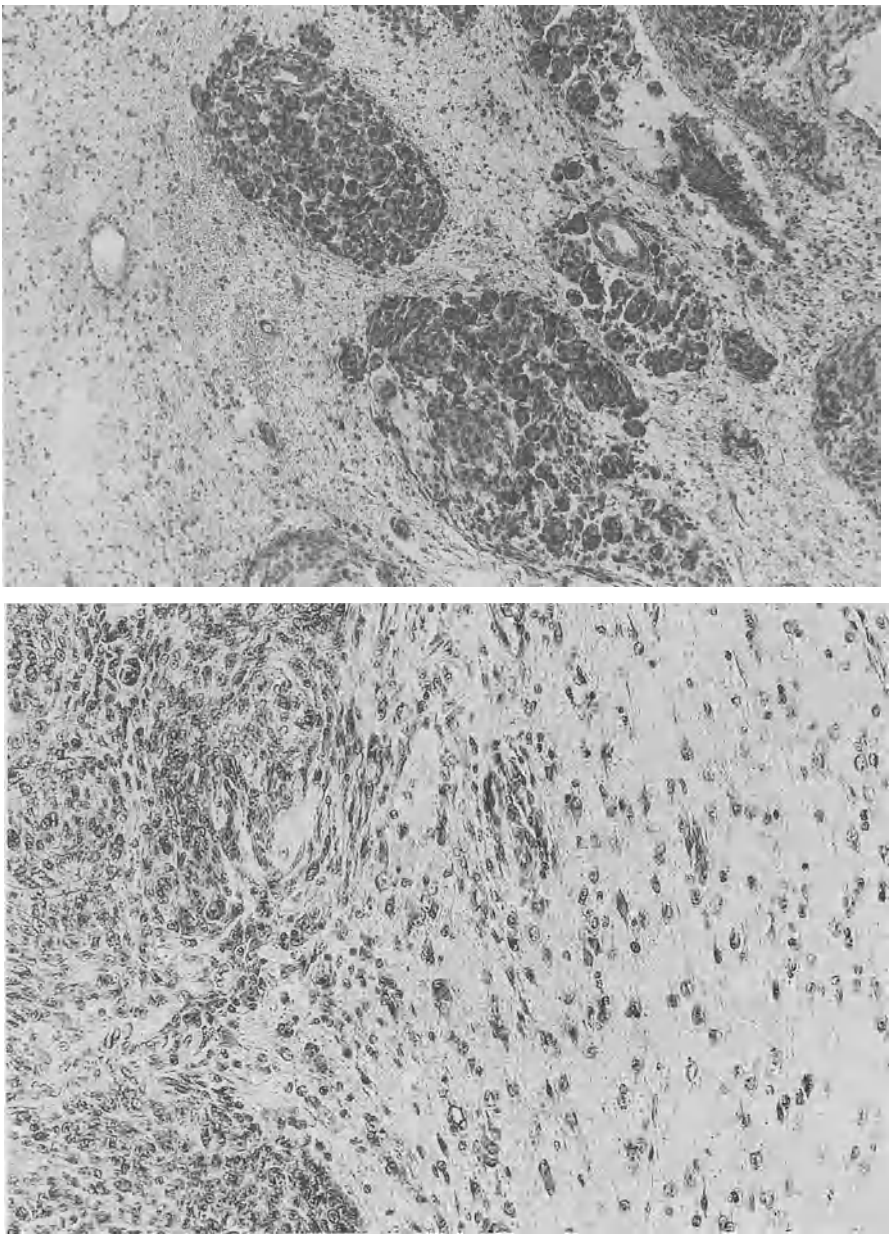


Fig.18.9a,b. Meningioma: **a** fingerlike expansion, H&E, ×200; **b** infiltration of tumor cells in the normal nervous tissue, H&E, ×200

Malignant transformation may also occur during the biological life of a meningioma, as may be found with repeated operations [1612]. This probability of transformation has been estimated to be 14% [1267].

The papillary variant has to be considered with the malignant variant, because the former is usually found in tumors which show an unfavorable biological behavior [285, 2139], tend to recur, and produce distant metastases [1707]. For others, instead, it is a secondary phenomenon, without clinical and biological significance [2719]. The papillary appearance is due to the arrangement of the cells in relation to blood vessels and to the relaxation of the intervascular tissue. It may appear in any type of meningioma, although it is more common in the hemangiopericytic variant and at younger ages [2420]. This variant gives serious problems in the differential diagnosis with regard to other tumors, either neuroectodermal, mesodermal, or secondary. Immunohistochemistry testing is, without a doubt, of great help.

18.1.11 Metaplasia in Meningiomas

An event occurring with variable frequency is lipoblastic metaplasia. Fat droplets accumulate in the cytoplasm and, by confluence, transform the cytoplasm into a single droplet of fat with a peripherally situated nucleus, as in adipocytes (Fig.18.10a). It should not be mistaken for fatty degeneration. Various authors disagree on the real existence and on the frequency of this variety, which seems rather unusual and is not considered in some series [1579]. Single cases have been reported [1618, 2440].

In xanthomatous metaplasia one observes foamy cells with a central nucleus and cytoplasm filled with fine vacuoles, in transition from normal tumor cells (Fig.18.10b). These cells have to be distinguished from phagocytic or perihemorrhagic and perinecrotic cells.

Myxoid and chondroid transformation are not rare and are often associated (Fig.18.11a). The former gives to the tumor a diffusely mucinous appearance, which recalls the "primitive mesenchyma". There is diffuse positivity for GAG [1067]. This variant is very close to the microcystic one, characterized by the presence of many vacuoles and microcysts filled with proteinaceous fluid.

A chondro-osteoblastic transformation is also considered. The presence of cartilage in meningiomas is a very rare occurrence, so it would be unjustified to describe a separate category of chondroblastic meningiomas [3135]. Even though the formation of bone is a rare finding, an osteoblastic variant has been described [110, 544, 820, 1109, 583] and accepted by some, but denied by others [941]. Although bone formation is possible in all types of meningioma, sometimes in relation to calcified psammomatous bodies, the justification for a distinct variety of osteoblastic meningioma is rather doubtful [2420]. The formation of bony structures in meningeal tumors has at least two pathogenetic possibilities [740]: through a process of metaplasia of the tumor, arachnoid cells, or the stromal connective tissue or through ossification secondary to a process of calcification. There is general agreement as to the first pathogenetic modality, because the arachnoid tumor cells are relatively undifferentiated elements capable of producing, under suitable circumstances, fibroblasts, osteoblasts, and osteoclasts. Phenomena of metaplastic ossification from collagen are observed in various extraneural sites and in

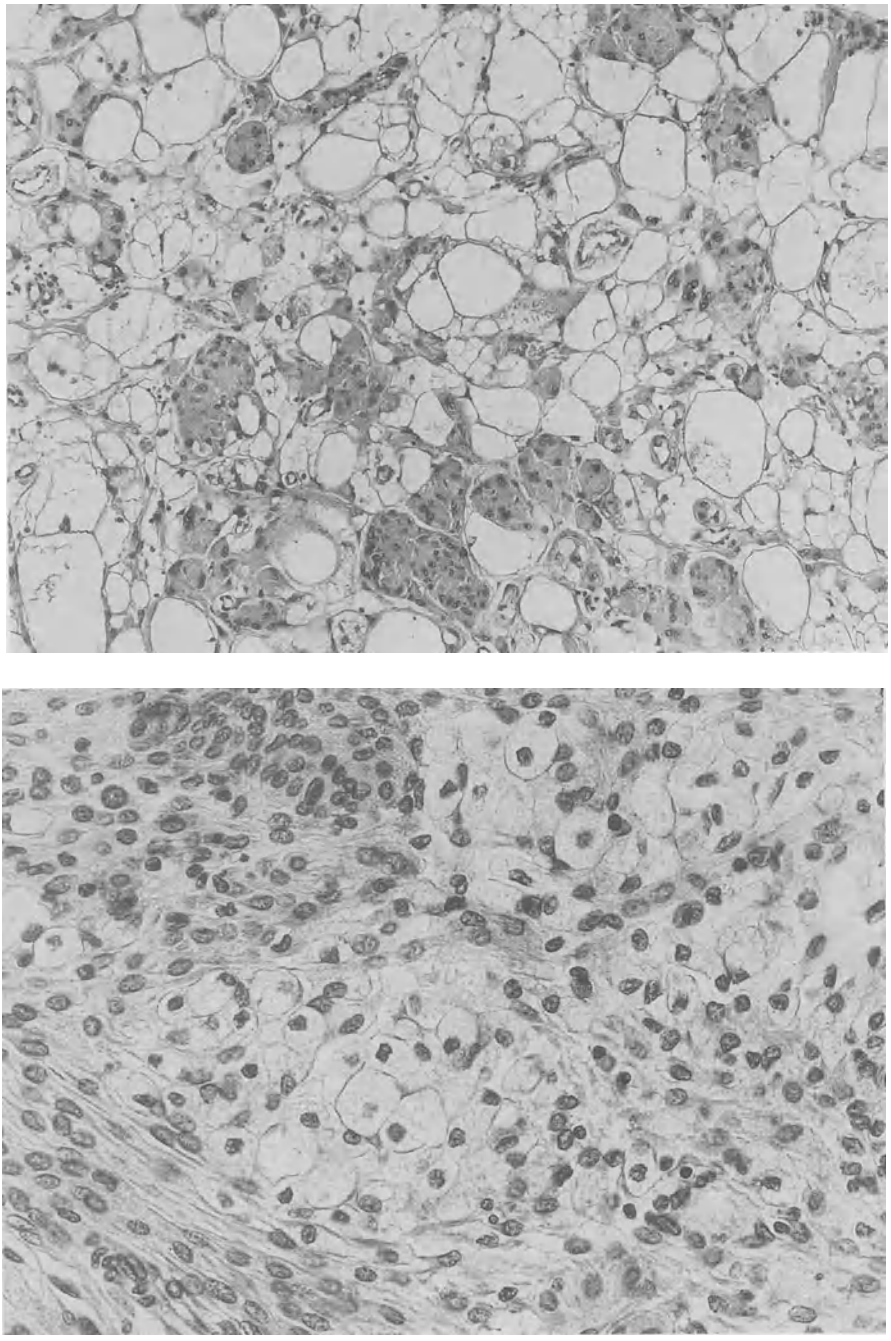


Fig.18.10. a Lipoblastic meningioma, H&E, ×300; **b** xantomathous meningioma, H&E, ×300

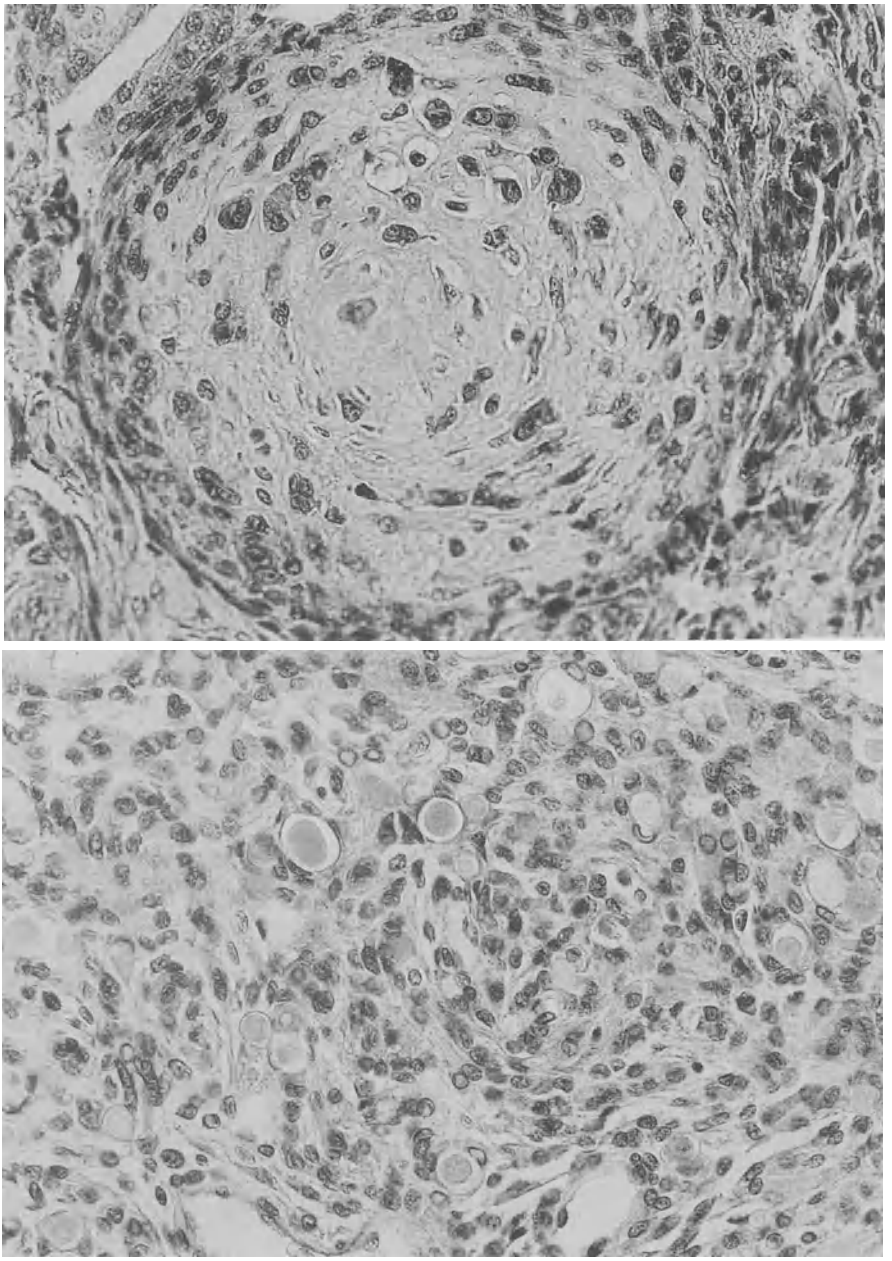


Fig.18.11a,b. Meningioma: **a** myxochondroid metaplasia, H&E, ×400; **b** pseudopsammoma bodies, H&E, ×400

various pathological conditions. The formation of bone could represent the final stage of the process of calcification. Pseudocalcium and hydroxyapatite production up to the formation of bone are, in fact, related to the processes of "kalzifizierende Organization" [232] and "knöcherne Organization" [1510].

Sometimes, strongly eosinophilic PAS-positive inclusion bodies, called "pseudopsammoma bodies" (Fig.18.11b), are found in the parenchyma of meningotheliomatous meningiomas [1384]. They have been described in a limited number of cases [979] and found to be similar to hyaline globules of other tumors. They have been interpreted as evidence of a possible secretory differentiation of meningiomas [1386]. From the immunohistochemical point of view, they have been observed to be positive for the human secretory components IgA and IgM [320], cytokeratin, vimentin, EMA, and CEA in the surrounding cells [2829, 1859, 979].

Melanin-containing tumors of the leptomeninges deserve to be mentioned. The finding is not infrequent and usually occurs in tumors of the posterior fossa or the spinal canal (Fig.18.12a). The problem is complicated by the fact that in some cases they could be melanocytomas rather than meningiomas, arising from nevus cells of the leptomeninges [1652, 3060]. However, there appears to be no doubt concerning the existence of classical meningiomas containing melanin [2877, 1389].

In meningiomas, it is not rare to find lymphocytic and plasmacytic infiltrates, both diffuse and perivascular. The lymphocytes are of the T subset, an expression of immunological defense mechanisms, and are found with greater frequency in the anaplastic variant than in meningotheliomatous and fibroblastic meningiomas [156]. Independent of these observations, there is a group of meningiomas which is characterized by a large number of lymphocytes and plasma cells (Fig.18.12b) obscuring the meningiomatous component [1193, 2713, 1389, 1904, 2420]. Raised levels of IgG have been found in the serum of these patients. In one, there was a high blood level of IgG and IgA, which dropped after surgical removal of the tumor [912]. Tumor infiltrates are activated B lymphocytes and plasma cells (of inflammatory and not of tumor origin), whose polyclonality has been demonstrated immunohistochemically [2713, 1904]. The nature of the association is not clear [2420]. The possibility may be excluded that it is a plasma cell granuloma with included meningeal elements [3020], because of the extent of the meningothelial areas [1389]. Lymphoplasmacytic infiltrates have recently been found in meningiomas, with a chordoid appearance in children and adolescents [1401].

18.1.12 Regressive Changes

Regressive changes in meningiomas are so frequent as to constitute one of the main features of this oncotype. This frequency, together with the multiplicity of processes, has been the main reason for the description of many varieties and subgroups. Also, the cellular polymorphism, sometimes simulating the anaplastic features of malignant tumors, is often due to regressive changes which typically present with features of great variability from tumor to tumor and from area to area of the same tumor. The changes are degenerative in nature, corresponding to the various processes of metamorphosis of general pathology (vacuolar, albuminoid, adipose, and mucosal) and to the typical vascular necroses. They may also be due to various storage processes.

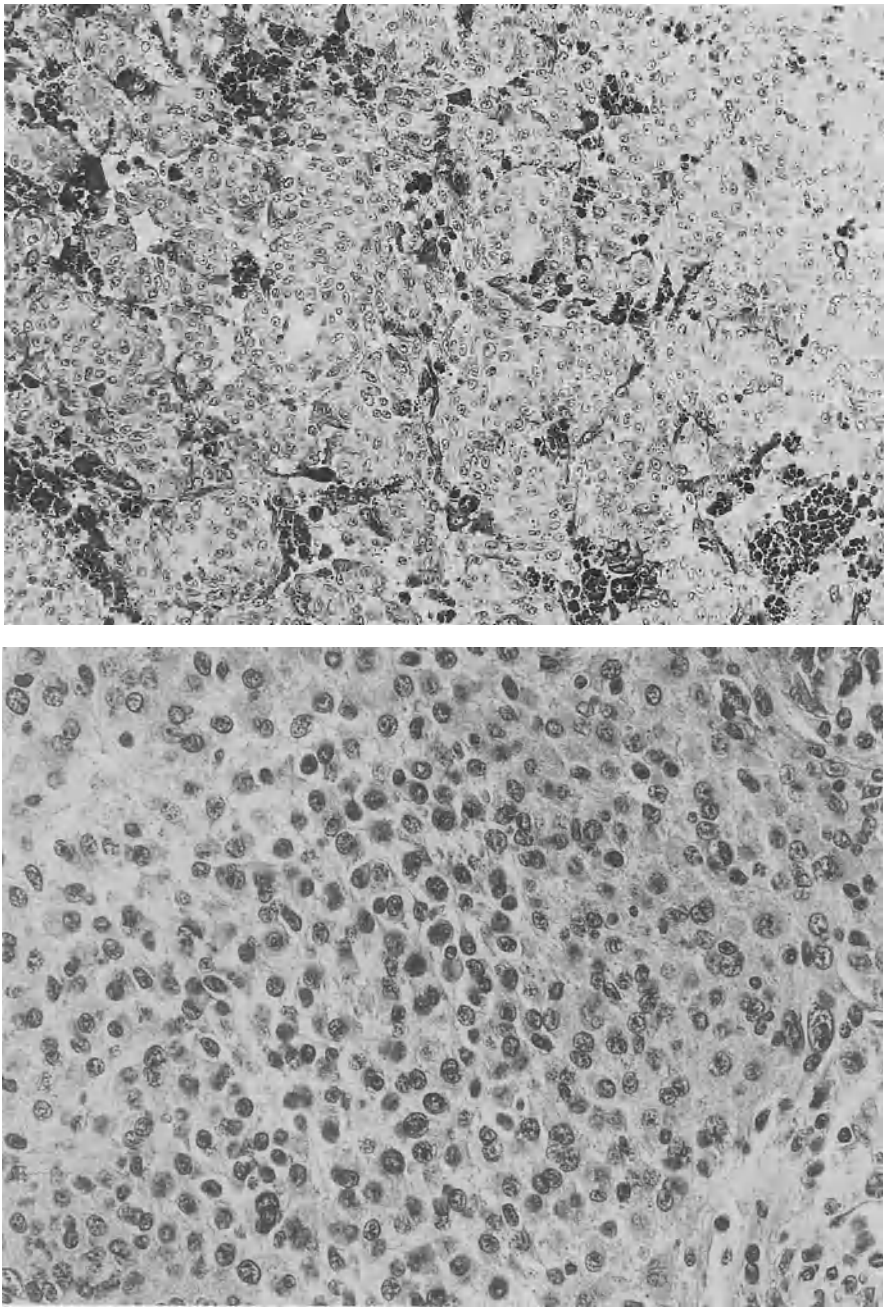


Fig.18.12. a Melanin-containing meningioma, H&E, ×200. **b** Lymphoplasmacellular infiltration, H&E, ×300

Ischemic necrosis here does not differ in its appearance from that seen in other tissues. In general, it presents with the picture of granular degeneration of the cytoplasm, less frequently with that of tumor liquefaction. In parallel, the nuclei demonstrate regressive changes with pyknosis, karyorrhexis or karyolysis. In some meningiomas, particularly the syncytial type, necrosis is found at the center of a lobule, decreasing centrifugally (Fig.18.13a).

In all the basic types described, but especially in syncytial meningioma, vacuolar degeneration may particularly involve the nucleus, where it presents as one or two large central or eccentric vacuoles. In the cytoplasm, instead, it shows a granular pattern. Sometimes, fluid accumulation goes beyond cellular swelling, causing hydropic swelling of the tissue, with cyst formation. In these cases, the process of tissue liquefaction is likely to be the result of a true accumulation of fluids (Fig.18.13b), as occurs in some forms of edema in other tissues. The phenomenon may be extended to the whole tumor, giving a variety of microcystic meningioma, the so-called "méningiome humide" of Masson [1794, 444, 1920, 1447, 1879, 2422]. This, however, does not seem to be of particular biological significance [2420].

Hyaline degeneration certainly represents one of the most common and most typical occurrences in meningiomas. It can involve all the structures of the tumor, from the parenchyma (Fig.18.14) to the stromal connective tissue, to blood vessels (Fig.18.15), etc., but, in its most frequent form, it starts in the whorls and proceeds centripetally.

Fatty degeneration is a fairly frequent event and when it results from other regressive cellular events, appears as colliquative foci rich in lipidized phagocytes in various stages of degeneration. In the phagocytic cells, the cytoplasmic borders disappear, and the nuclei undergo regressive changes. The phagocytosed lipids are formed by isotropic and sudanophilic material with the histochemical features of neutral fats and fatty acids.

Pseudoglandular structures, resembling adenocarcinoma, may form [1398], as the result of the degeneration of the center of the cell nests.

18.1.13 Calcifications

Calcification is one of the most frequent regressive events. It leads to the formation of psammoma bodies, a term coined by Virchow in 1900. From the earliest observations, a clear tendency of all meningioma variants to develop these structures has been noted. In some tumors, it is so marked as to justify the recognition of a "psammomatous" type. As first commented upon by Bailey and Bucy in 1931, it has the same origin as the endotheliomatous type with which it was then grouped. In the past, the possible origin of psammoma bodies from blood vessels or parenchyme was debated. According to some [941], they were formed by vascular buds with a blind end. Others [737] recognized six pathogenetic possibilities, in each of which the fundamental process was represented by a mostly hyaline regressive alteration of the parenchyma and of the stroma. Still others [1579] considered the majority of psammoma bodies to originate from the transformation of a whorl.

Electron microscopy and in vitro cultures demonstrated that the fundamental process in the genesis of psammoma bodies consists of two main factors: the tendency of the meningothelial cells to form whorls and the production by the same cells of a proteinlike material [1383] which tends to impregnate whorls, blood vessels, and collagenous stromal fibers. Histochemically, it has been identified as a protein-GAG complex.

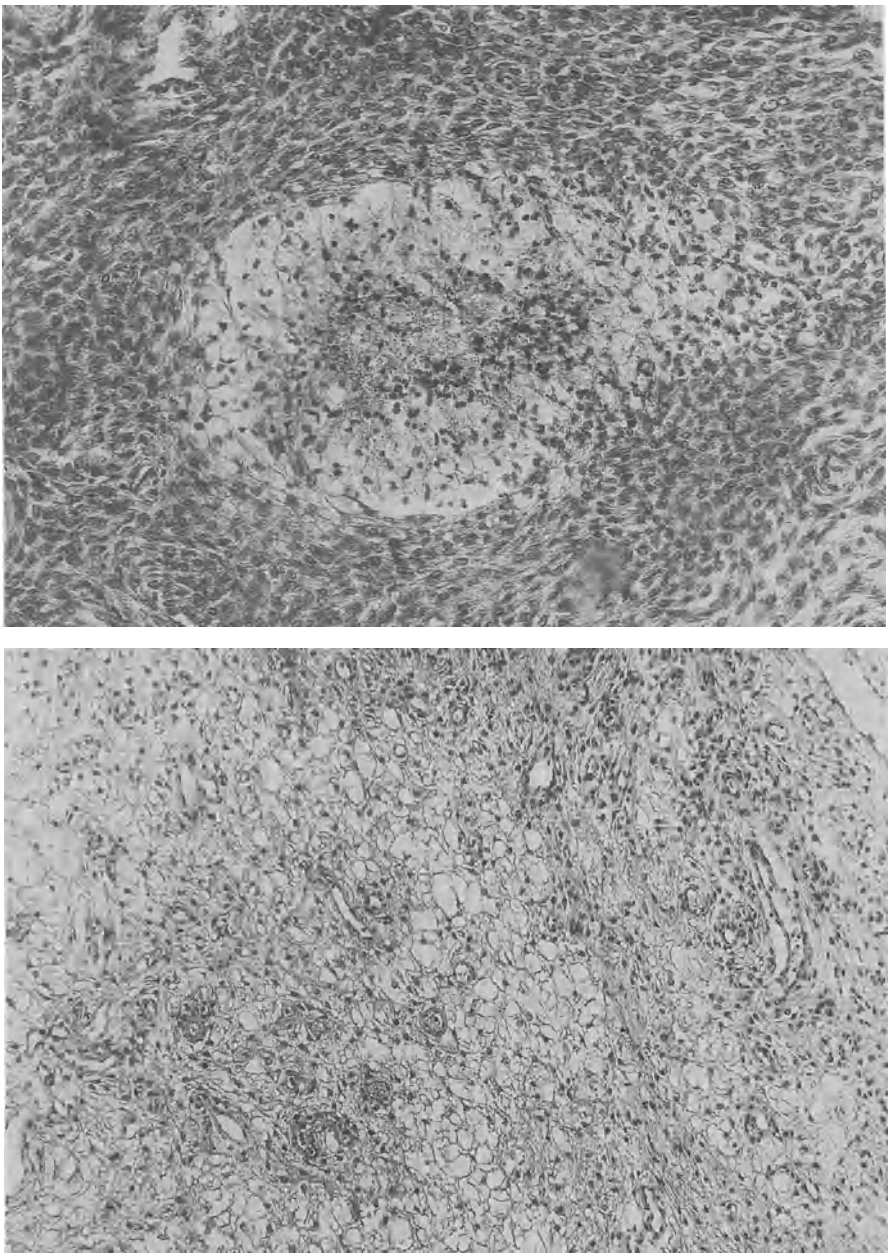


Fig.18.13a,b. Meningioma: **a** ischemic necrosis at the centre of a lobule, H&E, ×200; **b** fluidification of the tissue, H&E, ×200

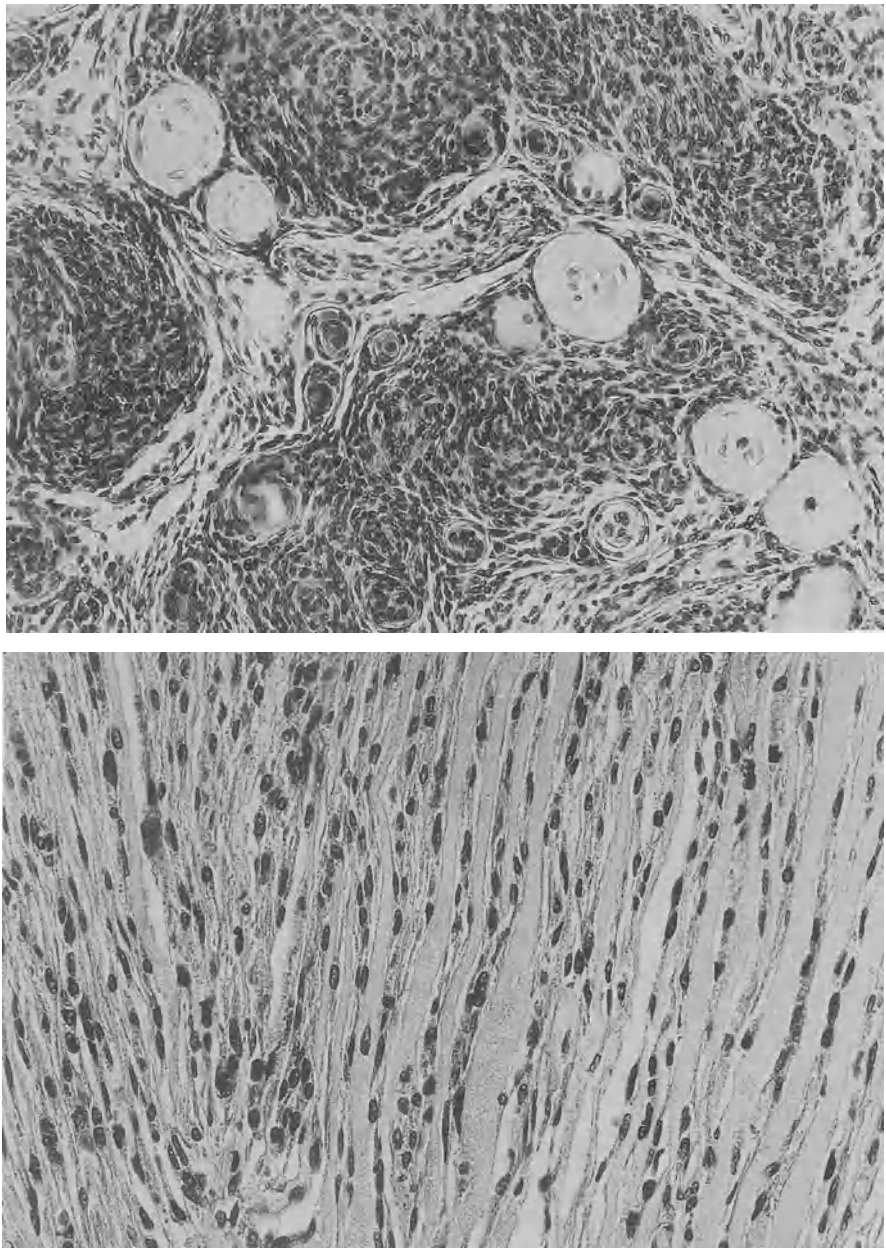


Fig.18.14a,b. Meningioma: **a** hyaline degeneration of whorls, H&E, ×200; **b** hyaline degeneration in fibroblastic meningioma, H&E, ×400

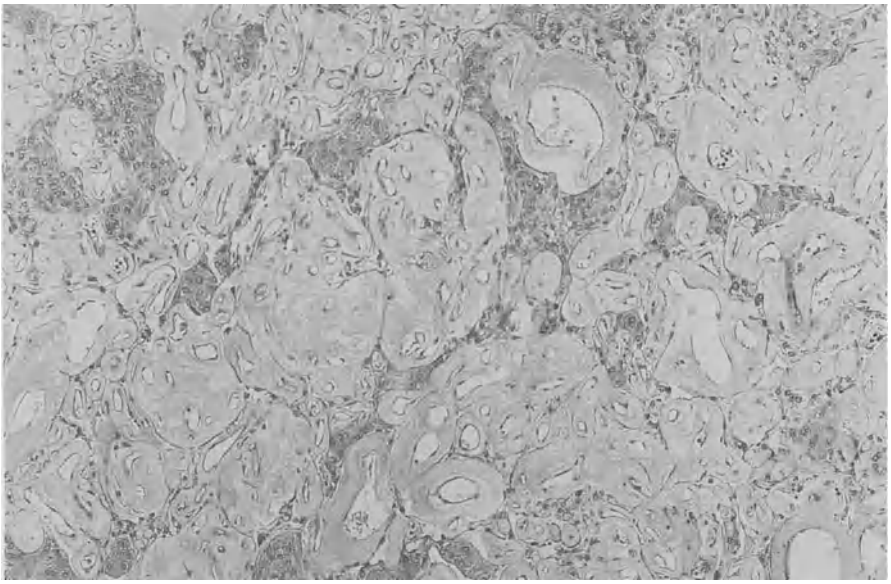


Fig.18.15. Meningioma, hyaline degeneration of vessels, H&E, ×200

Some cellular whorls neither hyalinize nor calcify; others are impregnated with a hyalinelike substance and organize into classical psammoma bodies [1384], on which mostly calcium salts precipitate. The production and deposition of the hyaline substance may be found in intra- and extracellular accumulations on which, in the absence of concentric cellular structures, the so-called pseudo-psammomatous bodies organize. Although the majority of psammoma bodies show a parenchymal genesis, there certainly are structures of the same appearance which form and organize in the stroma, in particular around blood vessels [1457]. This possibility has also been raised on the basis of electron microscopic observations but is less frequent than the origin of the psammoma bodies from cell whorls [971].

The appearance of calcifications in meningioma is a frequent event radiologically, and even more so histologically. In surgical and autopsy series, the histological frequency of calcifications is very high: According to Martin and Lemmen [1784] it reaches 18%, Schiffer et al.[2490] found 50%, and Huh [1223], 37.7%. The greater incidence obviously occurs in meningiomas of psammomatous type. For spinal locations, the frequency is higher.

Calcifications may occur as single concrements or foci of concrements which sometimes tend to become confluent in larger, more or less regularly polycyclic and stratified formations [1548, 737]. The size of these conglomerates sometimes reaches enormous dimensions [1721]. In one personal case, the masses of calcified and conglomerated material formed the main part of the meningioma, which was larger than a fist. In this case, calcification developed primarily in the whorls and the fibrous connective tissue [741].

The morphology and site of the calcifications are variable and consist of four fundamental precipitation patterns (Fig.18.16):

1. In the necrotic and prenecrotic zones as fine, dustlike, hematoxyphilic material, whose distribution is independent of the preexisting parenchymal structures
2. In the blood vessel walls, a rare eventuality which more frequently occurs in the media and/or adventitia of arteries
3. In the whorls, particularly in meningiomas of the endotheliomatous type
4. In the fibrous bundles of fibroblastic meningiomas

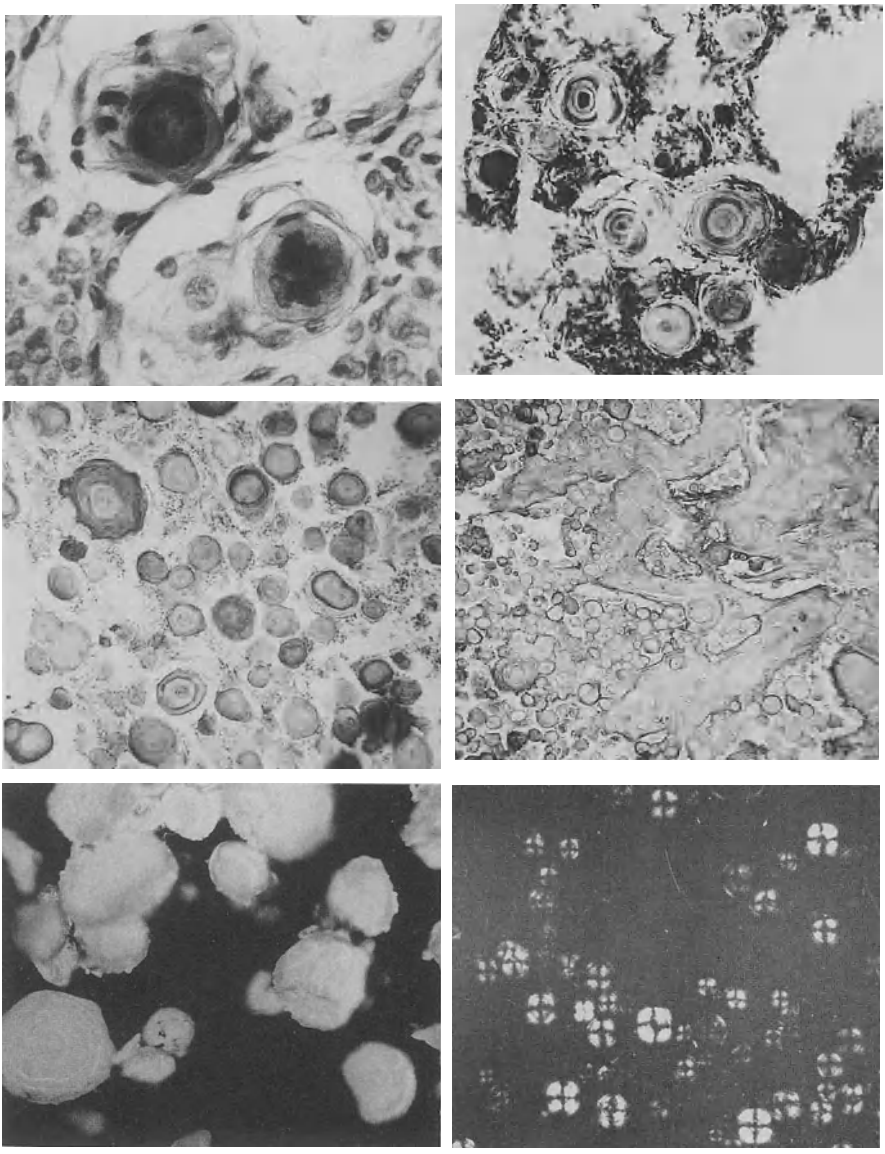


Fig.18.16a–f. Calcification in meningioma: **a** basophil pCa-Ca deposition in whorls, H&E, ×400; **b** pCA-Ca deposition in the whorls; further evolution of the process, cresyl violet, ×200; **c** psammomatous bodies with variable basophilia, toluidine blue, ×200; **d** calcified and confluent whorls, toluidine blue, ×400; **e** microincineration of psammoma bodies at 550°C, ×400; **f** Maltese cross of polarization in calcified whorls, polarized light, ×200 [2486]

In the whorls, the dynamics of the calcification process follow two possibilities (see also Chap. 5). A dilamination of the whorl separates its external layers, which acquire a fibroannular appearance. The internal concentric layers are reduced to some cell elements with pyknotic nuclei and irregular cytoplasm. Subsequently, small droplets of pseudocalcium appear which tend to become confluent in irregular, intensely basophilic, PAS-positive masses. In this phase, calcium salts are already present. The mass becomes progressively rounded and, whilst its external part reacts more intensely with the methods mentioned above, the internal one shows a concentric stratification because of the alternation of clear and dark rings. The pseudocalcium ends up occupying the whole of the central part of the whorl by adhering to the fibroannular part. At this stage, calcium salts predominate and the concentric stratification is very evident. As mineralization progresses, there is a progressive impoverishment of the organic matrix, as revealed by the reduction in the basophilia. In the terminal stages, the concretion appears vitreous and may become fragmented [2490].

The second mechanism of calcification of the whorls is the appearance of hyaline degeneration, followed by the precipitation of pseudocalcium. The subsequent evolution of the process repeats the stages already described. The concretion is surrounded by a hyaline ring during the whole process.

In general, the process of calcification in meningiomas does not demonstrate substantial differences in respect to that of other calcifying events in the CNS [2492, 2494, 1648]. Calcium phosphate is deposited in a complex form as hydroxyapatite [2481]. It is possible that the GAG matrix is provided by mast cells, which are important in many spontaneous and experimental calcifying conditions, such as processes of calcergia and calciphylaxis [2593]. In the meninges, mast cells are very common [1406]. They have frequently been observed in meningiomas and related to the mucoid degeneration [3134]. They may be scarce or abundant, often distributed at the periphery of the tumor, along the interlobular septa, along blood vessels, or even deep in the parenchyma, irrespective of the structures of the tumor, or in the center of a whorl. In this particular site, they may show a dispersion of the metachromatic granules and form the substrate for the precipitation of calcium salts, being rich in sulfated GAGs [2498].

Under the electron microscope, there are corresponding observations. In the whorls, extracellular spaces between the central and peripheral cells contain amorphous material, collagen fibers, microfibrils, elastic fibers and reticular material resembling proteoglycans. In this material there are calcified areas (Fig.18.17), foci or aggregates of apatite crystals oriented along the collagen fibers. At the periphery of the psammoma bodies there are spherical bodies similar to the vesicles of the matrix, typical of calcifying tissues with rare apatite crystals [54]. Such vesicles seem to originate from cell processes of the central cell in the whorl. The accumulation of these structures gives rise to the psammoma bodies [1513, 1514, 1515]. The same process occurs for psammoma bodies forming around blood vessels in which vesicles form from degenerated cells in perivascular spaces [1516, 1518].

On plain X-rays, calcifications show an amorphous, cloudy aspect. They are less frequent than in pathological series, > 10% [2816, 667]. On CT study, calcifications appear as nodular foci and are more frequent in the posterior fossa [2022] and less common in malignant meningiomas [1267]. On MRI scans, calcifications are seen as black areas [275].

18.1.14 Electron Microscopy Study

Numerous contributions from electron microscopy studies have been made in the past 30 years [1716, 1383 , 1028, 2258, 971, 2004, 2338, 391, 405, 2806, 1386, 2335, 493, 409]. The most important finding is the extreme interdigitation of the cell membranes, similar to that of the normal arachnoid cells, which explains the syncyitial appearance (Fig.18.18). Among the cells, desmosomes or other junctions and cisternlike spaces occur. This explains why the cell borders are not easily recognizable with the light microscope. The whorls are easily identified, sometimes with a capillary in the center. Tono-

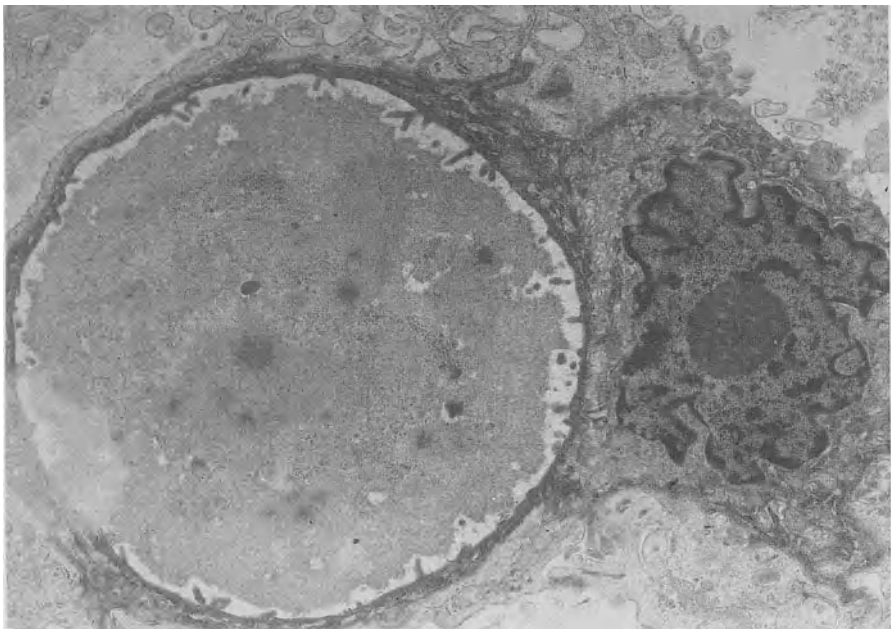


Fig.18.17. Calcification focus in a whorl, ×8000

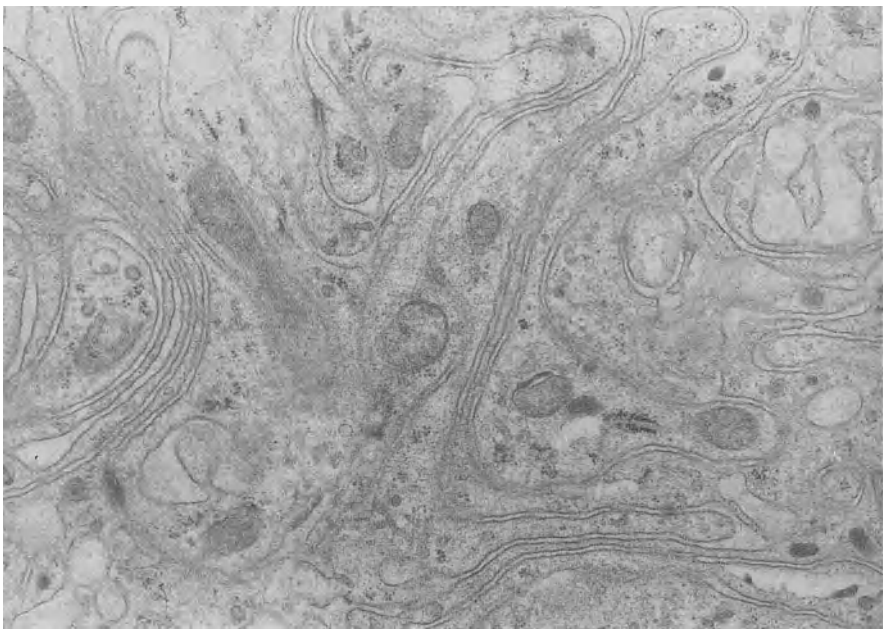


Fig.18.18. Syncytial meningioma, interdigitating processes and small desmosomes, ×24,000

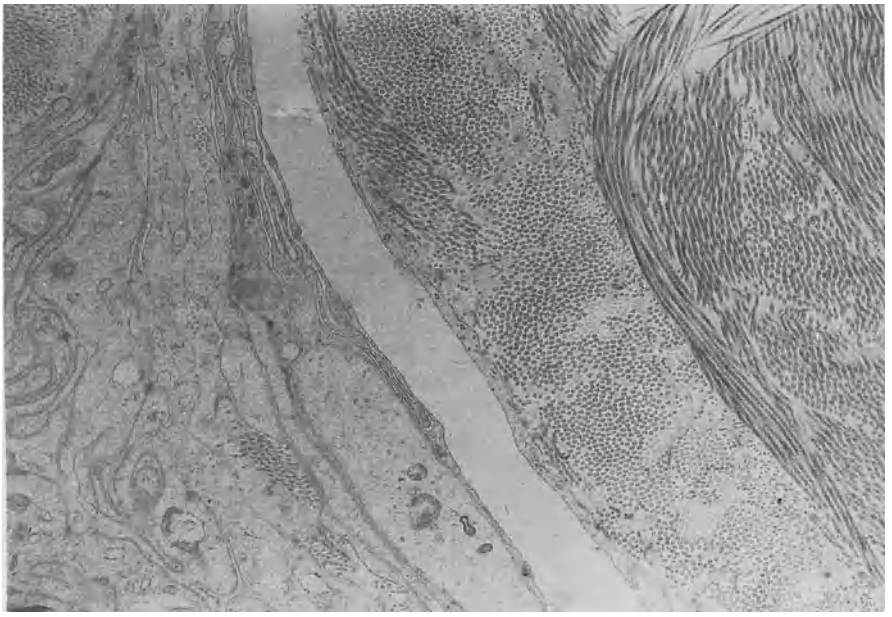


Fig.18.19. Atrophic endothelium and abundant collagen fibers in a vessel wall, ×8000

filaments, often arranged in a spiral, are present in the cytoplasm. Cilia may be found, even if not protruding but contained in the cytoplasm. It may happen that the cells are not adherent to each other, and granular and osmiophilic material interposes itself between the cell membranes. Often, it is in continuity with filamentous material corresponding to protocollagen and mature collagen fibers [1383].

The hyaline material, which is often found under the light microscope in the center of the whorls, appears to be formed by residues of degenerated endoplasmic reticulum, lysosomal components, and mitochondria. In it, hydroxyapatite crystals appear [1663]. In the vessel walls, an abundant production of collagen fibers can be found (Fig.18.19).

Nuclear inclusions are formed by invaginated and sequestered cytoplasm. There are also other types of inclusions, such as dense and osmiophilic nuclear ones [2338] or floccular material without membranes. Filamentous spheroid structures may be found [405]. Eosinophilic inclusion bodies correspond to granular material, situated in an intracellular cavity similar to a duct, delimited by microvilli which contain the same type of material [1383].

18.1.15 Receptors for Steroid Hormones

Meningiomas are more common in females and increase in incidence in pregnancy and during the luteal phase, but not in the proliferative phase of the menstrual cycle [1619]. Furthermore, as already mentioned, they have been reported in association with breast carcinoma, although this has not been fully established [2552].

Estrogen receptors have been identified in meningioma [651], but more obvious is the presence of progesterone receptors, because they are numerous and present in a larger number of patients [2213, 2847]. These data have been confirmed by numerous authors. Some have even found androgen receptors [1620]. Notable uncertainties, however, still remain as to the correlation between receptors of one or the other steroid type with age, sex, and histological type [1257] and as to whether the receptors are really functional [1131, 844]. That receptors intervene in the tumor growth has been demonstrated in vitro [2082], even if our knowledge needs, at this point, further data [1775].

Using high-affinity progesterone-specific antibodies, it has recently been demonstrated immunohistochemically that the receptors truly exist and are not simple progesterone-binding proteins [2570]. This could render the meningioma amenable to manipulation with hormones [1776, 2957]. The presence especially of progesterone receptors and to a minor degree of estrogen receptors has been ascertained by using many methods at the same time, among them the nuclear binding assay [2702] and some of these are functional [1051]. A recent investigation demonstrated, however, that there is no correlation between the presence of progesterone, estrogen and somatostatin receptors and age, sex, histology, and behavior on CT [1223A].

18.1.16 In Vitro Culture

In the first attempt to culture meningioma in vitro, it was observed that cells grew easily and that typical primary structures, for example whorls, were lacking [222]. Subsequent studies, however, demonstrated that such structures may be produced "ex novo" [2219, 498, 1410, 1711]. It has been found that while meningiomas in a standard culture of plasma show a scarce or no capacity to form whorls, their potential ability to form them may easily be revealed with simple changes of culture conditions, e.g., employing trypsinized suspensions of arachnoid tumor cells [1410]. According to these authors, concentric structures were the result of a primary deformation of a single cell, forming the regulatory center of the whole process, which occurs because of successive adaptation of the adjacent cells.

The growth in culture never shows the characteristic morphological differences observed among the main types described by histology, so that the histological terminology cannot be directly applied. The explant usually manifests its maximal proliferative activity during the first week. In this phase, at the periphery, elongated cells similar to fibroblasts of normal leptomeninges prevail, but sometimes they show more than two prolongations and arrange themselves in moniliform chains or in concentric formations. This tendency to concentric arrangements is more marked in the center of the explant where rudimentary whorls or syncytial structures may be found. Intra- and extracellular fibrils are observed, particularly where the growth is syncytial. They show features of precollagen reticular fibers [498, 499].

The recognition of various cell types is difficult. They may be small, bipolar, elongated cells with hyperchromatic nuclei; cells of medium size with large, oval nuclei, often in mitosis and tending to grow as a syncyitium; or larger cells with extended cytoplasm containing one or more nuclei [1947]. In the last instance, mitoses are never observed, whilst amitotic divisions are frequent. The cells of the second type are, in gen-

eral, the real tumor cells and represent the main part of the explants. In 19 cases, neither whorl formation nor differences between endotheliomatous and fibroblastic meningiomas were observed. With the utilization of microcinematography recordings, the formation of small rudimentary whorls was observed, sometimes presenting hyalinization and calcification up to the formation of psammoma bodies [2220]. Initially, these structures show complex rotatory movements of "peristaltic" type. With the same technique, it was also possible to observe that some of the neoformed whorls were undergoing disaggregation. The growth in culture permits one to distinguish between disorganization and reorganization of the architecture [2099].

The in vitro culture of meningiomas has improved the differential diagnosis, for example, between certain neurinomas and fibroblastic meningiomas [1410] or between angiomatous meningiomas and angioblastomas [1961].

Polyamines, such as aminoguanidine, spermidine, and putrescein, induce variations in the growth velocity in relation to concentration, in particular morphological changes, usually represented by atypical cell features and multinucleated cells [679]. The formation of giant cells may increase following repeated subculturing and, therefore, has a degenerative significance [1365].

18.1.17 Growth Modality

Meningiomas are usually benign tumors, and their tendency to metastasize is considered to be an exceptional event. On the other hand, recurrences are fairly frequent, even though they can often be related to incomplete surgical removal or to a multicentric tumor growth pattern [1954]. In the great majority of cases, the tumors are capsulated and delimited from the surrounding tissue. The tendency to infiltrate is usually limited to tissues of mesenchymal origin, such as the dura, venous sinuses, periosteum, bone and even pericranial muscle, but it is always a local phenomenon (Fig.18.20).

Bone abnormalities are frequently encountered in meningiomas, but they are difficult to appreciate. The most common occurrence is hyperostosis or endostosis, followed by bone destruction. Hyperostosing "en plaque" meningiomas are characterized by invasion of the haversian canals by meningioma cells, which stimulate the hyperostotic response. This condition is typical of women, and of the sphenoid bone. It implies surgical problems in removal. Calvarial hyperostosing "en plaque" meningiomas follow in frequency. Apart from these conditions, there may be bone destruction, more frequent at the base of the skull, hyperostosis by the invasion of a subjacent tumor, and endostosis. Also, intradiploic meningiomas have been reported [622].

The problem of malignant meningioma has already been dealt with. Some considerations regarding the cell kinetics, independent of malignancy, should be added. By the in vivo administration of BUdR it has been shown that the LI reaches not inconsiderable levels, and that in malignant recurrent meningiomas, it is much higher compared with classical recurrent meningiomas [1206, 854]. The LI allows evaluation of the doubling time of the tumor and is correlated with the growth of the tumor as seen on CT scan [430]. Using the monoclonal antibody Ki-67 it has been observed that in recurrences and in anaplastic tumors the LI reaches 20%, while in classical meningiomas it is 1%. [2346]. Using flow cytometry, the biologically malignant behavior has been

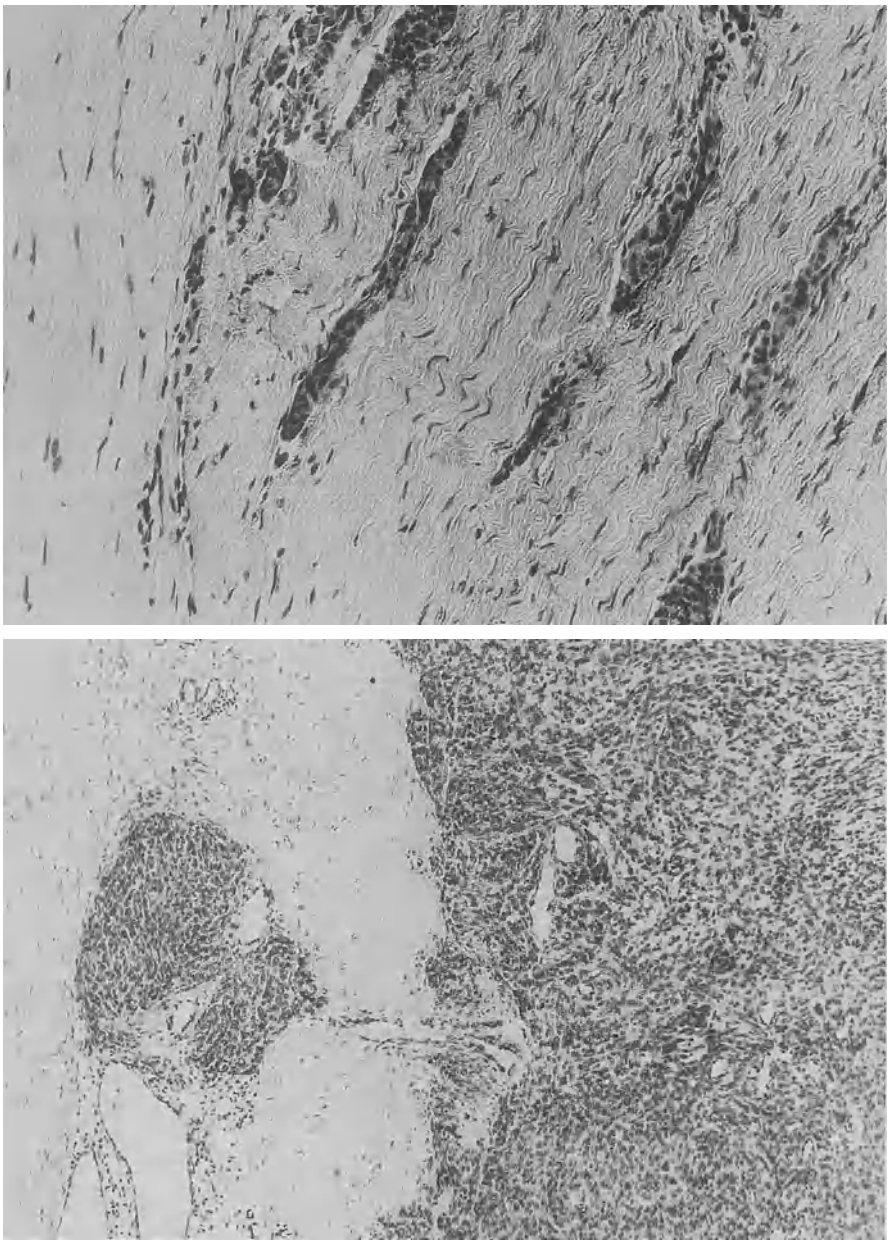


Fig.18.20a,b. Meningioma: **a** tumor growth along fibers in the dura, H&E, ×300; **b** dural satellite growth, H&E, ×200

found to correlate with aneuploidy [1258] and with a high proliferative index obtained from the percentage of cells in S and G_2/M phase [1828]. These studies tend to demonstrate the predictability of the malignant behavior and of recurrence, not obtainable with the observation of the common histological signs indicating malignancy, including mitoses, which may be absent. The mitotic index has gross limitations [707], being of value only if positive: In many tumors, which later recurred, with a high proliferative index by flow cytometry mitoses were absent [1828]. Regional variations do not appear to play a role in these evaluations [1258].

18.1.18 Metastasis

Metastases via the CSF are extremely rare, considering the frequency of meningiomas: In a review of the literature, 12 cases have been found [1389], nine of which showed histological signs of malignancy. In some rare cases, it was a benign, nonoperated tumor [2420]. Sporadic cases have been reported [1453, 1264]. A case of malignant intraventricular meningioma with metastasis via the CSF to the spinal cord has also been reported [1346].

Extraneural metastases are also rare, no more than 85 cases having been described up to 1982 [1389]; however, another 13 cases were found, and perhaps many have not even been reported [2420]. In a recent review, about 113 were listed, mainly in association with local recurrence [2436]. They are mostly tumors in adults, without any sex predilection, with some features of malignancy and predominantly of hemangiopericytic, papillary, or sarcomatous type. In many cases, they are histologically classical meningiomas [2331, 1512, 1891], and distant metastases are not synonymous with malignancy. The most affected organs are the lungs, followed by the liver, lymph nodes, bone, pleura, kidney, and pancreas [1389]. In general, these metastases occur in patients with recurrent reoperated tumors, sometimes even with characteristics of malignant transformation [1612].

18.1.19 Imaging of Meningiomas

The first thing to be stressed is that, like other tumors of the CNS, meningiomas induce peritumoral edema. This happens in 46%–92% of tumors [274, 946]. Among the many possible factors responsible, four have been identified: disruption of the BBB, mechanical compression, vascular compression, secretion of edemogenic factors or a combination of these [1658].

On CT scan, meningiomas appear isodense to slightly hyperdense, homogeneous, and well demarcated. Calcifications may confer a punctate appearance or present as large foci. After contrast enhancement, the tumor has an intensity which is due to the passage of contrast from capillaries into the interstitial spaces. Focal necroses may appear as low-density areas, and if the tumor is completely necrotized, it may appear as an enhanced ring [1583]. Prior to the use of gadolinium, CT was superior to MRI in detecting meningiomas, because of the poor distinction between the tumor and cortex, but

now gadolinium MRI is the best diagnostic study for intracranial [3126] and spinal canal meningiomas [90].

Angiography is of great help in characterizing meningiomas. The interpretation of the pictures is based on the assumption that the tumor is supplied by the normal meningeal arteries to the meninges of the tumor site and on the vascular blush in the late arterial phase [1270].

PET studies using F-2-fluorodeoxyglucose give useful information [589].

18.1.20 Prognosis, Treatment

Meningiomas are usually treated by complete surgical removal, which leads to total recovery. However, recurrences are common. Cushing [541] performed 522 operations on 282 patients. In the experience of Olivecrona [2078], recurrence appeared in 10% of parasagittal tumors, and according to Simpson [2647] in 21% of 332 meningiomas.

In general, the frequency of recurrences varies between 2.3% and 30% [1286, 1861, 2799]. These are meningiomas which at the first operation demonstrated benign histological features. In these cases, there may be at least two possible causes. On the one hand, it may be an incomplete surgical removal. In this case, the tumors presumably recur after a short interval, on average within 1–2 years [2224]; recurrences after a long time are, however, possible [763], given the slow growth of the tumor. There are numerous tumors, especially parasagittal, whose recurrences appear more likely to be related to arachnoid residues included in the dura or in the bone, and independent of the previous tumor proliferation. In these cases, the interval has been calculated to be 5 years [2647]. These latter occurrences, therefore, seem related to the same cause which determines the frequent appearance of multiple meningiomas.

The histological examination of strips of dura taken from the base of attachment of meningiomas has demonstrated that they contain nodules or nests of clustered meningotheliomatous cells, which are not found in strips of dura taken from other pathological cases. These clusters may explain a number of recurrences [265]. It remains to be clarified why these aggregates start to proliferate at a certain moment.

Histologically malignant tumors often recur; however, we still do not know which histological features are indicative of a poor prognosis. A partial answer to this question has already been given. As has been said, the frequency of recurrences seems to be closely correlated with an atypical or malignant histological appearance [1266, 1267].

Apart from studies finding more frequent recurrences of syncytial meningioma in comparison with the fibroblastic one, the histological features of poor prognostic value include mitoses, focal necroses, infiltration of neural tissue [520], and greater cell density [2659]. Malignant meningioma, identified on the minimal basis of high cell density and polymorphism, recurs in 44% of cases, as compared with 6% in classic meningioma [422]. Salcman [2436] demonstrated that benign tumors recur in 3%–38% of cases and malignant tumors in 41.6%–78%. The length of follow-up is very important in this evaluation [2194]. Today, special attention must be given to tumor necroses, because they could be the result of therapeutic preoperative embolization [1751, 2342].

Meningiomas usually grow slowly. In incidental meningiomas, discovered by CT, the annual growth rate has been calculated by repeated CT or MRI scans, and it was low [779].

A useful method for calculating the recurrence time may be that proposed by Cho et al. [430]: After administering BUdR to patients, the LI is compared with the doubling time as calculated on CT scans. The two parameters correlate, so the BUdR LI may be useful in predicting the tumor growth rate. In a recurrent tumor, with malignant transformation, the BUdR LI was found to be 9%, very high in comparison with 1% for classic meningiomas [1264].

Another prognostic factor identified in recurrences of intracranial meningiomas is the angioblastic variant [1301 , 446 , 12]. Moreover, recurrences are uncommon in very old patients, in spinal sites, and in fibroblastic tumors [115].

Radiotherapy of meningiomas is carried out occasionally for tumors in a special location or with a malignant histology or for repeated recurrences. It has been observed that the recurrence rate after radiotherapy diminishes from 74% to 29% [2981], and favorable results are sporadically reported in single cases or groups of cases [3094, 382]. Controlled observations do not seem to attribute positive effects to radiotherapy [1267]. Interstitial brachitherapy with radioactive iodine has also been efficaciously used in cases in which the surgical removal was difficult because of the location [1529].

18.2 Other Mesenchymal Tumors of the Meninges

18.2.1 Hemangiopericytoma

This tumor, rich in blood vessels, was at first included by Cushing and Eisenhardt [544] among the angioblastic meningiomas. Since the first observations, an aggressive behavior of the tumor was recognized, and it was included with the hemangiopericytomas described in various parts of the body [159], being called meningeal hemangiopericytoma. The fundamental problem regarding this neoplasm is nosographic, i.e., whether it is a hemangiopericytoma developing in the meninges but similar to those in other parts of the body [159, 2223, 2175, 444, 1301] or a variety of angioblastic meningioma [2391, 1192]. Apart from the purely speculative interest of this debate [1389], some [2420] seem to be prone to consider it a variant of angioblastic meningioma, whereas others consider it to be a separate entity, not originating from arachnoidal cap cells [1304].

Different reasons have been given to keep this tumor separate from the meningioma group. Among the those put forward [343], the most important is that the tumor does not show any meningothelial characteristics. Transitional forms between hemangiopericytoma and meningioma exist [1389]. Though we have cases in our series, in our opinion this is not sufficient to deny it the dignity of a separate entity.

The frequency of hemangiopericytoma is not known with certainty: It varies from 2.4% [1030] to 4% [1301] and 7% of all meningeal tumors [1304].

All ages may be affected, with a predilection for the fourth, fifth, and sixth decades, with no prevalence for sex, as in meningiomas. The locations of the tumor are those of meningiomas, with more frequent tentorial and subtentorial ones [1304].

The macroscopic aspect is that of a mass adherent to the dura, soft or consistent, with a smooth surface, and not capsulated. Usually, the tumor is highly vascularized.

Microscopically, the tumor is highly cellular. The cells are round or oval or irregular with a variable number of mitoses. There are many capillaries and small vessels with a slitlike lumen, lined by single endothelial cells (Fig.18.21). The endothelium is separated by a basement membrane from masses of tumor cells which often abut on the lumen as a "cushion." Cells may also crowd into clusters. Tumor cells, supposed to be pericytes, are immersed in an abundant quantity of reticulin (Fig.18.22). This is in continuity with the adventitia of blood vessels and forms a chaotic network. An interesting three-dimensional reconstruction study has been performed on vessels. Arteries abrubtly divide into a large number of capillaries, and sinusoids show remarkable variations in caliber and bizarre indentations. The vascular structure can explain some angiographic characteristics of the tumor, such as the accumulation of contrast media and the prolonged circulation time [2949A].

Under the electron microscope, the tumor cells show neither interdigitating processes nor the typical desmosomes of meningioma, whereas there is an abundant extracellular, basal lamina-like material [561]. These features are important in differentiating this tumor from meningiomas. Attempts at whorl formation and intracytoplasmic filamentous condensations forming dense bodies similar to those of smooth muscle cells were seen [2175]. Both meningothelial cells and pericytes may be present [409, 1902].

Immunohistochemical observations are rather inconsistent. On the one hand, there is evidence that vimentin and keratin are present in the arachnoid granulations, and in both meningiomas and meningeal hemangiopericytomas, contrary to the hemangiopericytomas of other parts of the body [1173]. This would confirm the meningiomatous nature of hemangiopericytoma. On the other hand, others have shown that both meningiomas and hemangiopericytomas are positive for vimentin and negative for EMA [1263, 3054].

Hemangiopericytoma has an aggressive behavior relative to the total group of meningiomas: Mean survival is 84 months in the former as compared with 100 in the latter [413]. Survival at 5 and 10 years was 67% and 40% [1030] vs. 83% and 77% [1901] respectively. It has high recurrence and metastasizing rates [2659], even years after operation. Local recurrences and metastases were 29 of 44 and 10 of 44, respectively [1030].

Radiotherapy has been repeatedly carried out in this tumor, but the results are difficult to evaluate because of the poor definition of the tumor and the inadequate number of cases. In a large series [1030], the free interval was overall better, changing from a mean value of 34 to 75 months. Doses higher than 45 Gy seem to be more effective, without producing radionecrosis, which is rare after the irradiation of meningiomas [853, 3094].

18.2.2 Fibrosarcoma

Fibrosarcoma is the most common malignant meningeal tumor. Initially located in the craniospinal dura, it may subsequently extend into the dura itself, bone, leptomeninges, and neural parenchyma. In the 30 cases of Zülch (1956) [3134], there was no preferential location or predilection for age or sex. In another series of 25 cases [448], the average age was 29.5 years with 9 cases in patients younger than 20 years.

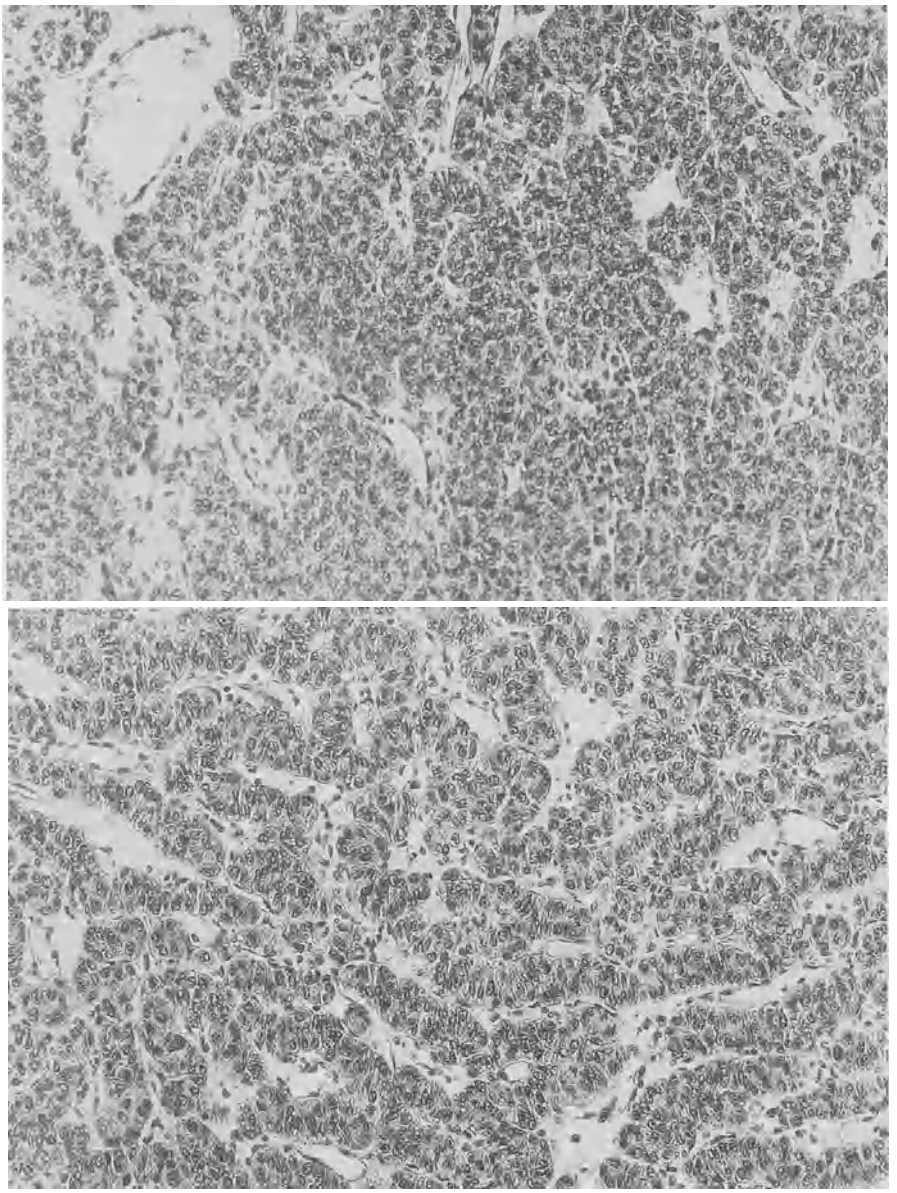


Fig.18.21a,b. Hemangiopericytoma: **a** slit-like vessel lumina, H&E, ×200; **b** cordonal aspect, H&E, ×200

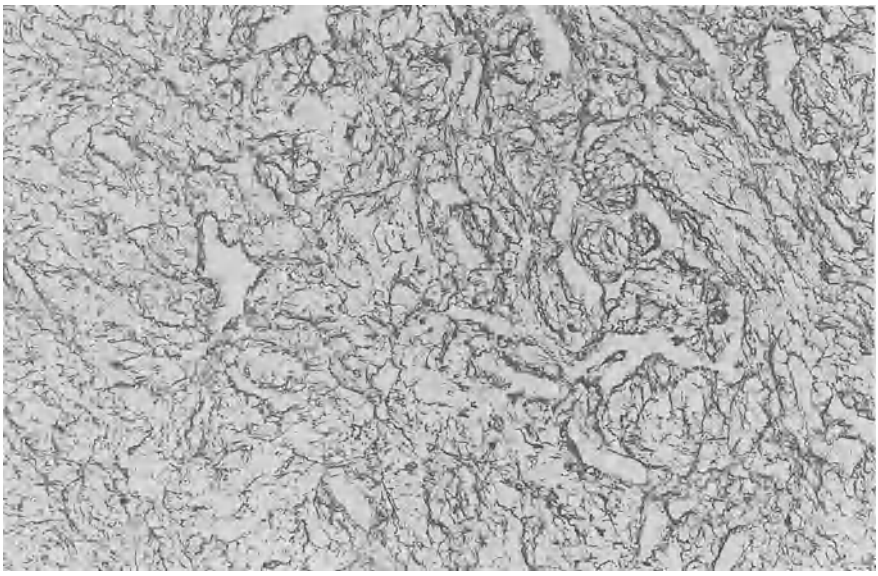


Fig.18.22. Hemangiopericytoma, typical reticulin network, Gomori, ×200

Histologically, it is characterized by elongated cells, arranged in bundles in varying directions and forming reticulin and collagen. The tumor must be differentiated from reactive, or even neoplastic, changes of the meninges secondary to invasion from malignant gliomas. Mitoses may be present in large numbers (Fig.18.23). Transitions have been shown between this tumor and malignant fibrous histiocytoma, with which it is often confused [1304].

Fibrosarcomas may also arise in the neural parenchyma, originating from the mesenchyme of the blood vessels, from perithelial cells, or from the meninges themselves. Histologically, they demonstrate the usual fibrosarcomatous features, including a tendency to nuclear polymorphism, numerous mitoses, and such differentiation phenomena as the formation of bone and cartilage. The differential diagnosis has to be made with gliosarcoma and gigantocellular fibrosarcoma. Very important is the report of cases arising after radiotherapy [2044, 2979, 2561, 494, 2072].

18.2.3 Primitive Melanoblastosis of the Leptomeninges

This is a rare condition, with fewer than 250 cases reported [2205, 323, 120]. In about 30% of cases, it is associated with hairy nevi of the skin. It is included in the group of neurocutaneous malformations [2897], and has no well defined clinical picture, and the prognosis is dismal. It can be identified in vivo only by cytological examination of the CSF.

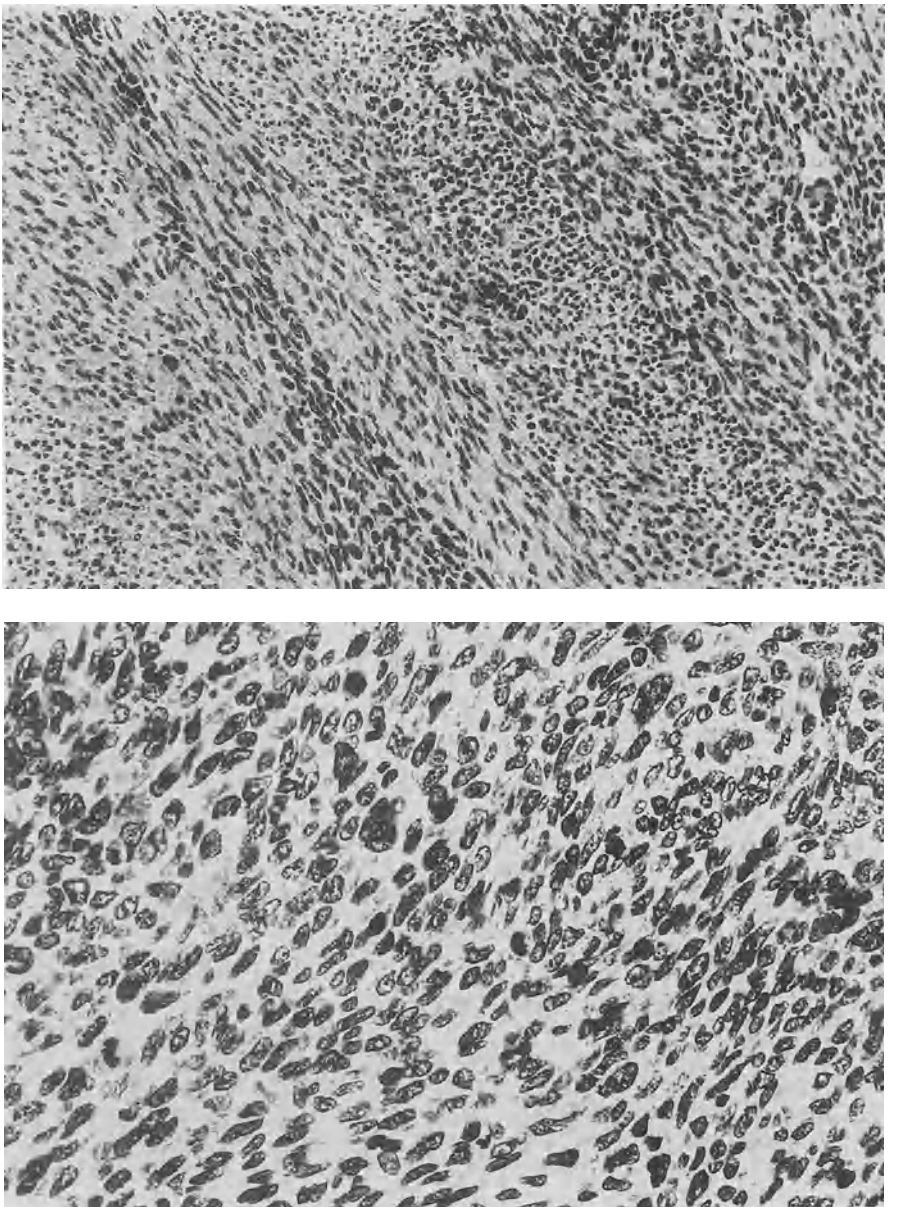


Fig.18.23a,b. Dural fibrosarcoma: **a** bundles of elongated cells, H&E, ×200; **b** nuclear polymorphism and mitoses, H&E, ×400

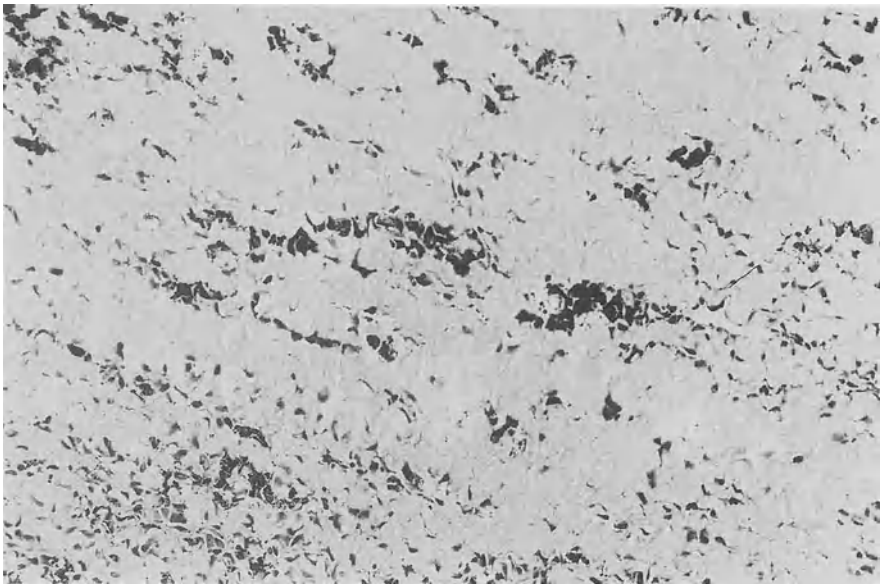


Fig.18.24. Meningeal melanoblastosis, H&E, ×200

The macroscopic appearance is characterized by cells containing pigment covering the meninges and filling the cisterns. This aspect is, however, variable, going from the discrete presence of pigmented cells to very aggressive tumors which may form tumoral masses.

Microscopically, the cells have a round, polygonal, or elongated shape, and most contain melanin (Fig.18.24). The nuclei may be polymorphous, but mitoses are not seen. Virchow–Robin cortical spaces may also be filled.

The pathogenesis of melanoblastosis has to be related to the hypothetical origin of the leptomeninges from the neural crest, to the definite origin of the pigmented cells from it,and to the presence of a certain number of melanocytes in the normal pia mater. The disease, therefore, belongs to the neuro-crestopathies, like von Recklinghausen's disease, Sturge–Weber disease, tuberous sclerosis, etc. It may present as melanosis or melanoblastosis, associated or not with growth centers and hairy nevi. In 63% of cases, it is represented by diffuse or multifocal melanoblastosis, in 37% by solitary pigmented tumors, and in 26% by melanosis or neurocutaneous melanoblastosis [120].

Disseminated melanomatosis principally concerns the meninges but may involve the cortex. The main problem in this disease is establishing whether it is a primary or a secondary form in which the primary tumor is not known. There are, in fact, cases in which the diffusion is such as to lead to the suspicion of a metastatic phenomenon, but the primary tumor cannot be demonstrated [1237]. It should not be forgotten that, after the lungs and liver, the brain is the preferential site for metastatic melanoma [2142]. In some cases focal melanotic masses may be found in the meninges or in the brain, with a preference for locations such as Meckel's cave. Their nature (primary or metastatic from a malignant melanoma) is very difficult to establish [3060].

The diagnosis of the disease is made by cytological examination of the CSF and is based on the demonstration of melanin, because the clinical symptoms are only poorly indicative or may generically indicate a carcinomatous meningitis [2842].

Radio- and chemotherapy are ineffective.

18.2.4 Malignant Fibrous Histiocytoma

These tumors appear as dural masses, either circumscribed or infiltrating adjacent structures. Histologically, it is a tumor of histiocytic origin with fibroblastic expression and showing a storiform pattern. The number of histiocytes and fibroblasts may vary, and often giant monstrous cells are present. A series of 20 cases has been reported [181].

The ultrastructural appearance is characterized by the two components [1065]; the histiocytic elements can be highlighted immunohistochemically with lysozyme and α_1-antichymotrypsin [1425], even though the latter marker does not seem to be specific and monohistiocytic markers are negative or give questionable results [2151, 2347].

The histological appearance is mostly that of elongated cells organized in bundles, pleomorphic, at times inflammatory, myxoid and angiomatoid [3010] or with giant cells [1304]. The tumor is GFAP-negative, apart from some reactive astrocytes (Fig.18.25).

The few cases of intracranial localization described thus far [975, 1388, 1557, 1343] appeared connected to the meninges. Some intraparenchymal cases have also been reported [2648, 2641,2352], one of which arose after irradiation [975]. A particular case in which the tumor arose 2.5 years after the removal of a mixed oligoastrocytic tumor has been noted [2151]; it is probable that the causal event was the surgical trauma. The prognosis is very poor, with local recurrence and distant metastases [2641, 2155].

18.2.5 Meningiomatosis or Meningoangiomatosis

This is a rare, benign condition with meningiomatous and angiomatous hallmarks. Since it was first described [3077], no more than 17 cases have been reported; some others, after review, have then been reclassified differently. Recently, another case has been published [1655]. The condition may present clinically in two ways, either with epileptic fits and hemicrania in children or young subjects, or asymptomatic and found at autopsy in carriers of von Recklinghausen's disease. Intracranial calcifications visible on CT scan or abnormal blood vessels demonstrated at angiography are characteristic. Macroscopically, the meninges appear thickened and opaque, sometimes with the sulci filled by a granular material, especially in the temporal region.

Histologically, the thickened meninges show meningothelial proliferation, both diffuse and whorl-forming, admixed with lymphocytes and macrophages. In the meninges, there are calcifications and sometimes fibrocartilage or bone. In the underlying cortex, there is a proliferation of small blood vessels surrounded by fibroblastic elements. The neurons are decreased in number. Sometimes there is gliosis, and Alzheimer's neurofibrillary tangles have been found.

In a recently described case [2152], there were "free fibroblasts" clustered in groups in the cortex, especially around blood vessels, immersed in protocollagen III and colla-

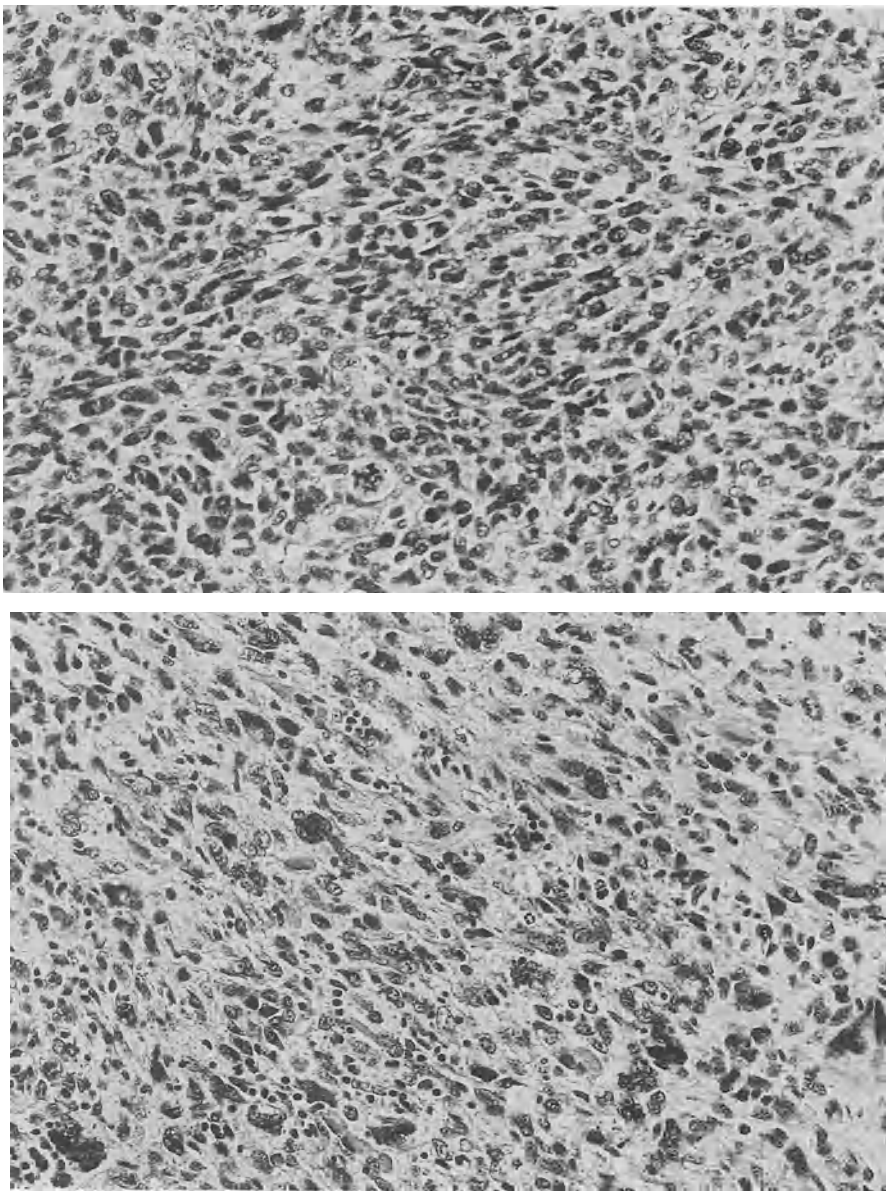


Fig.18.25a,b. Malignant fibrous histiocytoma: **a** fibroblastic and histiocytic aspects, H&E, ×300; **b** polymorphic aspect, H&E, ×300

gen IV and VI deposits, unlike perivascular cells which instead expressed protocollagen I.

It is distinguished from diffuse meningeal sarcomatosis because of the malignant character of the latter, the presence of cortical blood vessel proliferations, and the meningiomatosis.

Three pathogenetic theories have been put forward [1356]: an error in development; a cortical response to meningiomatous invasion; a vascular malformation followed by meningothelial proliferation. According to some authors [2152], the "free fibroblasts" are of meningothelial origin. It is probable that the proliferative perivascular response in the cortex can be attributed to these elements. In the study of a recent case it was proposed that the lesion is a vascular malformation and that fibroblasts derive from vessel walls [946A].

A difficult problem is the presence of neurofibrillary degeneration. It has been supposed that the hydroxyapatite deposits responsible for the calcifications develop in neurons, thus interfering with the axonal transport of neurofilaments [1050]. This association has not been satisfactorily explained.

18.2.6 Primary Meningeal Sarcomatosis

This is a diffuse sarcomatous infiltration of the meninges without a tumor mass, which occurs mostly in children [2831]. The lesion may spread around the spinal cord and may involve the brain. Histologically, it is composed of small, round or fusiform cells. The differential diagnosis includes extraneural sarcoma and lymphoma.

18.2.7 Miscellaneous

Other malignant mesenchymal tumors of the meninges are chondro-, lipo-, osteosarcomas, and mesenchymal chondrosarcoma.

19 Mesenchymal Tumors

19.1 Chordoma

19.1.1 General Considerations

The first description of these tumors was provided by Virchow [2941], who called them "ecchordosis physaliphora." However, the chordal origin was suggested by Müller [1960], and the main hypothesis that the tumor arises from normal or aberrant residua of notochord [2312] was confirmed later [107] and is still widely accepted. The notochord, containing vesiculous embryonal tissue, appears at the fourth week of i.u. life and progressively disappears in the seventh week. Its cephalic extremity is in close contact with the inner surface of the sphenoidal bone, in the region of the dorsum sellae, and extends along the midline over the pharyngeal surface of the developing occipital bone.

In the skull, nests of notochordal cells remain in the pharyngeal vault, the odontoid process, the spheno-occipital synchondrosis, and on the surface of clivus. In the vertebral column, these nests are found in the nuclei pulposi of the intervertebral discs, whereas in the sacrococcygeal region they are located laterally, ventrally, and dorsally. Chordomas may develop in all these sites.

Generally, a distinction is made between ecchordosis physaliphora, representing ectopic notochordal tissue, and true chordomas. The former is represented by small, asymptomatic nodules incidentally found at autopsy [3080, 2712] on the clivus, in the sacrococcygeal region, and, rarely, in the nasopharyngeal submucosal tissue or in the vertebral body [2886].

Chordomas can be classified topographically [1109], as tumors of the dens, clivus (spheno-occipital), hypophysis (sellar), occipit, sacrococcygeal, and vertebral regions. In relation to the developmental stage, they can be chondroblastic, chordoblastic in evolution, mature, and sarcomatoid. Mature forms are characterized by physaliferous and vacuolated cells and abundant intercellular mucoid substance, whereas sarcomatoid forms are characterized by anaplastic, giant, and monstrous cells. Immature, intermediate, and mature forms have also been distinguished [870].

The frequency of chordomas is very low: 2% at autopsy [107] and 0.2% in pathological [3136] series. Until 1965 and up to 1979, 300 [870] and 600 [2765] cases respectively had been published. It is likely, however, that many tumors escape detection.

The sites are those already indicated for notochordal nests. Half the cases are located in the sacrococcygeal region, 35% in the clivus and 15% vertebral [803, 152, 996].

All ages are affected: Cranial chordomas prevail in young people, and the sacrococcygeal tumors in the 5th and 6th decades. The difference, however, might be due to the earlier discovery of intracranial tumors. There is a male prevalence, especially for sa-

crococcygeal locations. It seems that trauma plays a pathological role, especially in sacrococcygeal locations, since the association is more frequent than sheer coincidence would indicate [2717]: Notochordal cells may be displaced from their cartilaginous covering.

19.1.2 Macroscopic Appearance

Ecchordosis physaliphora appears as small, circumscribed, gelatinous masses.

Chordomas are usually rounded, smooth or lobulated, whitish or yellowish, and gelatinous. The size may reach that of a nut. From the skull base, tumors may invade the interpeduncular cistern, sphenoidal cavity, and nasopharyngeal spaces. Those of the clivus (Fig.19.1) may reach the foramen magnum and posterior clinoids. All the cranial fossae may be invaded by the tumor, which may erode the sphenoid, ethmoid, and petrous bones with the orbit. Nervous structures are usually compressed but not invaded.

Vertebral tumors destroy vertebral bodies and also laminae and transverse and spinous apophyses. Sometimes the tumor may grow in the adjacent soft tissues, such as the laterocervical region, mediastinum, and pelvis. The spinal cord may be compressed.

Sacrococcygeal tumors may be divided into pre-, retro-, and central-sacral ones. There is always accompanying bone destruction.

19.1.3 Microscopic Appearance

Ecchordosis physaliphora is composed of vacuolated cells with a peripheral nucleus, often containing inclusions. The vacuoles may be empty or filled with metachromatic, PAS-positive, and alcian-philic material. The electron microscope reveals many affinities with chordomas [1151].

In chordomas, the aspect is that of notochordal tissue. The cells are disposed in bands or islands, with a mosaiclike or a honeycomb pattern, often around vessels [2591] or in a glandlike pattern [870].

Round or elongated cells with eosinophilic cytoplasm and a hyperchromatic nucleus correspond to the chordoblasts of cytogenesis (Fig.19.2a). Physaliphorous cells have a vacuolated or foamy cytoplasm with an eccentric nucleus which is poor in chromatin (Fig.19.2b). Still other cells are globular, with a small nucleus and an extremely vacuolated cytoplasm. These cells represent the most mature elements of the chordal series. The cell types are variably present in all the tumors, but according to the prevalence of a specific cell type, three forms of chordoma may be distinguished: immature forms, composed mainly of chordoblasts and rare, vacuolated, physaliphorous cells; evolutive forms, composed of cells in maturation and a mucoid, intercellular substance; mature forms which contain physaliphorous cells and large quantities of mucoid substance [2857]. Anaplastic forms are called sarcomatoid and contain atypical cells and rare mitoses [870]. The intercellular substance is basophilic, metachromatic, and rich in glycogen.

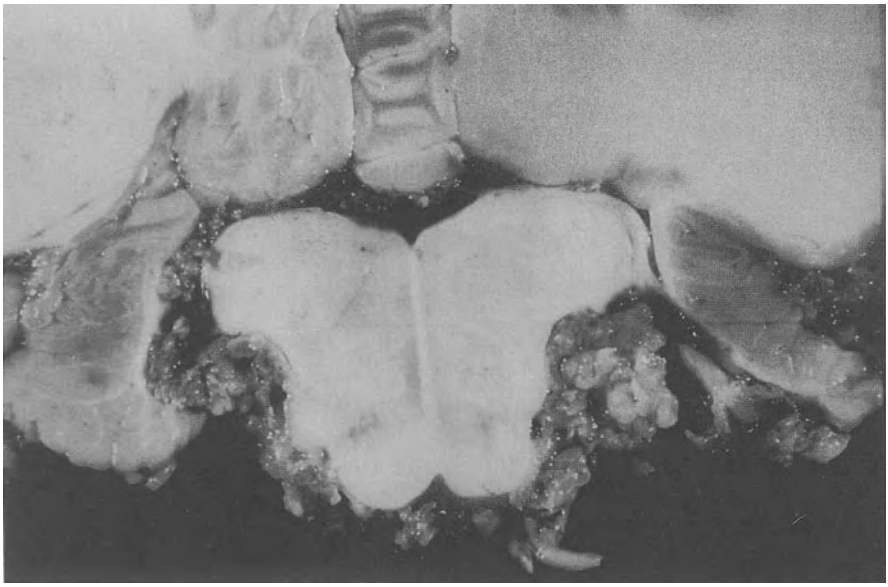


Fig.19.1. Chordoma of the clivus

The stroma is composed of reticular fibers dispersed among the tumor cells. Collagen bundles, sometime hyalinized, may be formed. Perivascular lymphocytic infiltrates may be present.

19.1.4 Electron Microscopy

Under the electron microscope [833A, 373], both elongated and physaliferous cells are provided with long, ramified, and indented processes. The large vacuoles one sees are extracellular spaces delimited by the cell processes. In the cytoplasm of all cell types there are 75 Å thick fibers forming dense interlacing bundles. Smooth and granular ER may be abundant, and sometimes vacuolated. In the vacuoles there is a granular material similar to that of the extracellular "vacuoles." Golgi apparatus are well represented, and mitochondria are abundant in areas without fibrils.

Intermediate filaments of 7–9 nm occur, of suspected tropocollagen nature, from which collagen is formed [2775]. They stain positively for keratin [13, 1883], which would suggest an epithelial nature, as suspected for the notochord itself [1378]. This hypothesis is confirmed by the occurrence of desmosome junctions in both chordomas and ecchordosis physaliphora [1151]. There are also linear subplasmalemmal densities, possible markers of a mesodermal mesenchymal nature [1903, 1151]. The double epithelial and mesodermal nature has already been attributed to the notochord itself [1053].

The study of the notochord in the rat demonstrated that the main difference from chordoma is the poorness of the extracellular spaces and the presence of mucoid mate-

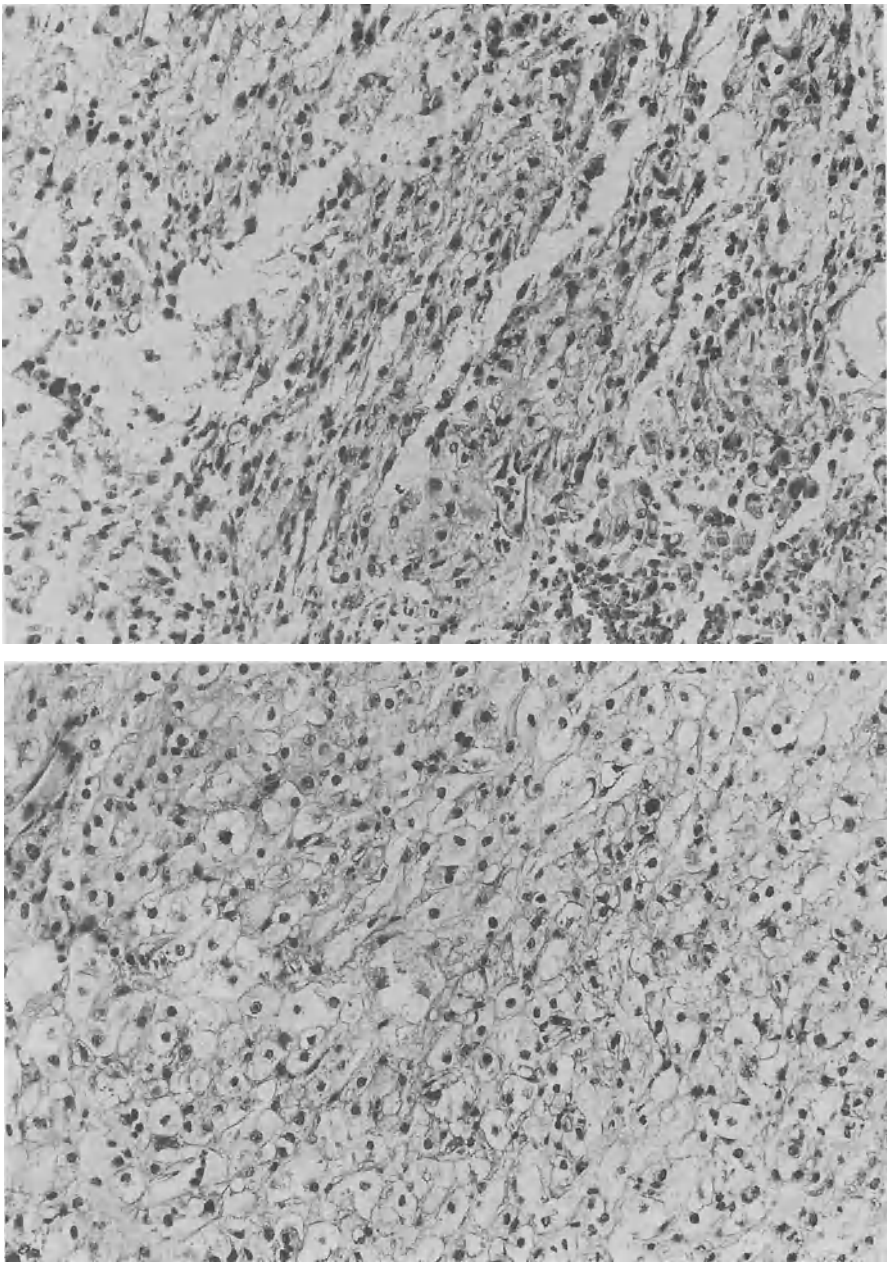


Fig.19.2a,b. Chordoma: **a** elongated cells—chordoblasts, H&E, ×300; **b** typical physaliphorous cells, H&E, ×300

rial. The production of granular material, which corresponds to the mucoid substance, takes place in the distended ER [373, 727, 905].

19.1.5 Differential Diagnosis

The differential diagnosis has to include the newly introduced variant of "chondroid chordoma" [1094] and chondrosarcoma, because of their varied clinical courses. Chordomas are positive for cytokeratin [2260], EMA, CEA, and also for tissue polypeptide antigen (TPA), which is a marker of tumors derived from the epithelial lining of body cavities [339]. The testing of four epithelial markers on chordoma and chondromas demonstrated that the former are positive and the latter negative; chondroid chordomas behave like cartilaginous tumors. This means that either chondroid chordomas do not exist or they are "low grade chondrosarcoma" [300].

19.1.6 Prognosis

There is no general agreement regarding the occurrence of distant metastases, which has been reported to vary from 5% to 43% [2765] and is more frequent for vertebral than for clivus tumors [1175, 2745]. Local recurrences are frequent, especially for sacrococcygeal tumors. They are due to incomplete removal rather than to malignancy, because only rarely can chordomas be totally resected. There does not appear to be any correlation between the histological appearance and clinical course [2765], even though immature forms are believed to have a malignant behavior. Chordomas, however, must be considered malignant, with invasive growth and local recurrence.

Radiotherapy is of limited value. Postsurgical, fractionated proton irradiation for skull base chordomas, however, repeatedly gave an 82% survival rate at 5 years [94]. Radiosurgical treatment is now being proposed [1478A].

19.2 Chondroma

Under this term are included all the tumors composed of differentiated cartilaginous tissue. Classically, those of the convexity and cranial base are kept separate from the spinal ones. Until 1961, there were in the literature no more than 42 operated or autopsied intracranial chondromas reported [2268]. However, by 1962 there were 50 [78] or 60 [906]. In Zülch's published series, there are 20 chondromas, corresponding to 0.3% of all brain tumors.

In agreement with the dysontogenetic interpretation, tumors are mostly located at the skull base, where bone is formed upon the cartilage. The bones of the convexity, where these tumors are rarer, are formed, on the contrary, through a direct ossification of connective tissue. Two different pathogenetic theories are available for the two tumor locations: Convexity tumors could originate by metaplasia and be akin to menin-

giomas [544], while tumors of the skull base are more likely of dysembryogenetic origin and more akin to tumors at the same location, such as osteomas, lipomas, and fibromas, to which they may be related [906].

Chondromas may be solitary tumors or belong to multiple chondromatosis (or Ollier's disease) or to Maffucci's syndrome, in which there is an association with subacutaneous hemangiomas [2861].

Chondromas of the skull base, initially located outside the dura and small in size, subsequently penetrate the cranial cavity. They are more common in females. An interesting case in a retrosellar location was reported [2932]. Convexity chondromas are more common in the frontoparietal and parasagittal areas. They frequently originate from the convexity meninges, but sometimes from the falx, may reach a large size, and unlike those from the skull base, are more common in men.

Macroscopically, the tumors are whitish, smooth or lobulated, and hard-elastic in consistency.

Microscopically, they are composed of typical mature cartilage tissue, hyaline, fibrous, or elastic. In comparison with normal cartilage, they show slight morphological and structural anomalies: an uneven distribution of chondrocytes, morphological changes of isogenous groups, abnormal staining of the ground substance (Fig.19.3a), etc. Frequently, regressive phenomena such as vacuolar and mucous degeneration, hemorrhages, calcification, and ossification occur.

Chondromas are benign tumors, even though they are often difficult to treat surgically, especially those of the skull base. In rare cases, a malignant transformation has been reported.

19.3 Chondrosarcoma

Today, chondrosarcomas are accepted as a tumor entity and usually described as "central" and "peripheral" [1646], or "primitive" and "secondary" [904], depending on whether they originate from normal cartilage or from a chondroma. In two rare cases, there was an association between a secondary spinal chondrosarcoma and an hereditary multiple exostosis [526].

Chondrosarcomas represent 7% of the primitive malignant tumors of bone [557], but they are very rare among craniospinal tumors. A location at the skull base [1109, 78] is more frequent than that in the vertebral column [2748, 526]. Patients in the third and fourth decades are most often affected, even though "primitive" tumors seem more frequent in young subjects [476, 1646]. There is no difference between the sexes.

Macroscopically, they resemble chondromas with more pronounced cystic or hemorrhagic aspects.

Microscopically, all the stages of cartilage development may be observed, from that of embryonal mesenchyma to adult cartilage. Tumor cells are disposed in bands or trellises and form irregular, isogenic groups. There is nuclear pleomorphism with giant cells (Fig.19.3b); mitoses are frequent and often atypical. There are intermingled fibrous, mucoid, and hyaline areas. The ground substance shows staining anomalies and is usually strongly basophilic and metachromatic.

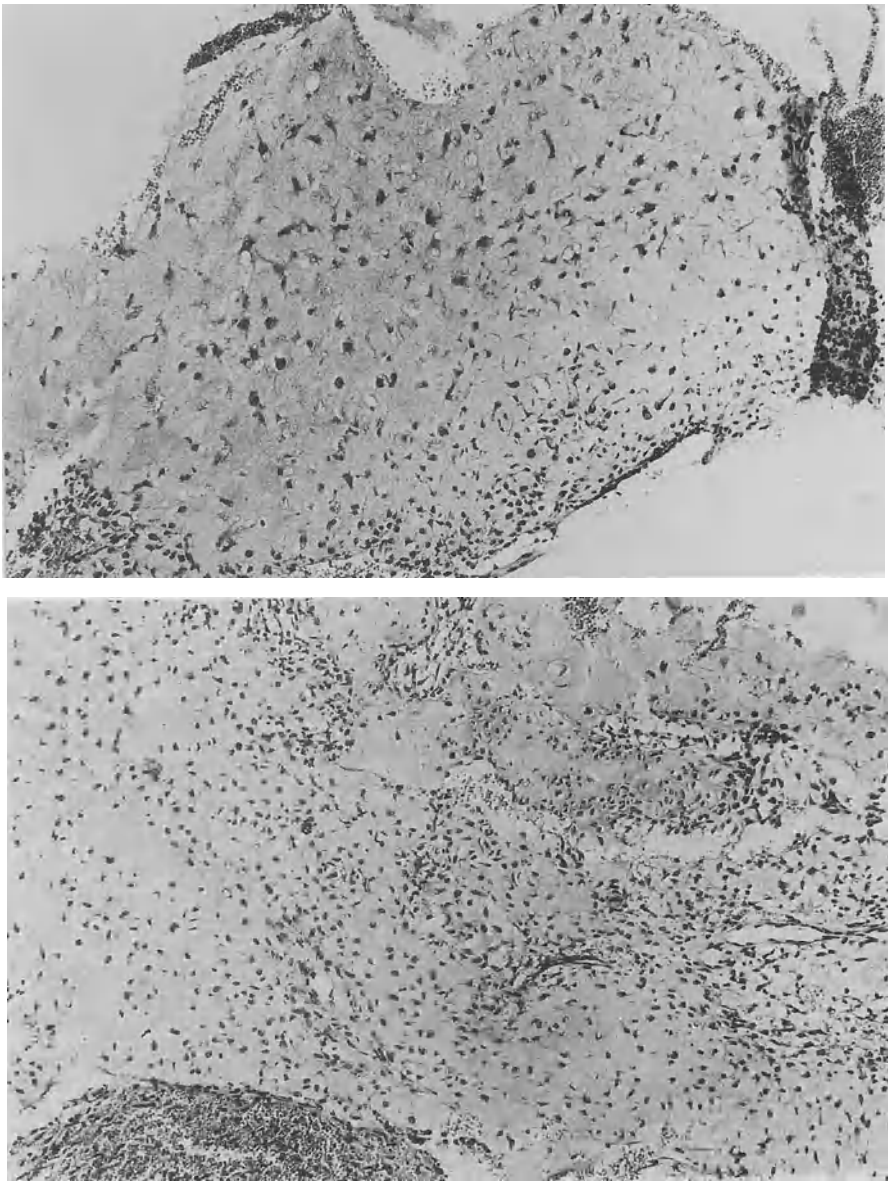


Fig.19.3. a Chondroma, distribution of chondrocytes, H&E, ×300. **b** Chondrosarcoma, anaplastic elements and necrosis, H&E, ×300

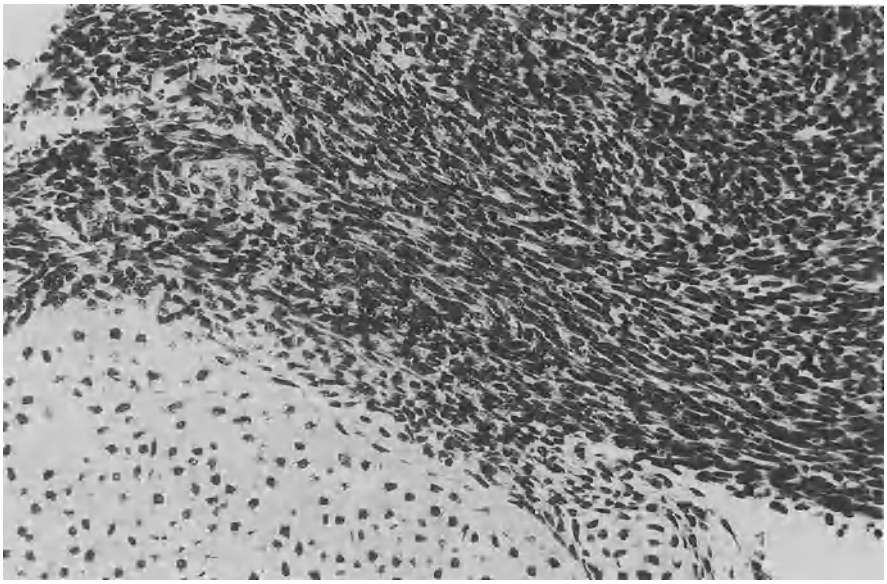


Fig.19.4. Mesenchymal chondrosarcoma, H&E, ×200

Practically speaking, the myxoid, differentiated, and mesenchymal forms [2472] are to be distinguished. The last is characterized by bundles of undifferentiated cells with cartilage islands (Fig.19.4). The cells are elongated. Immunohistochemistry testing with NSE and anti-Leu-7 is of little help in the differentiation from neuroepithelial and other mesenchymal tumors [2774].

The tumor is malignant, with local recurrence and distant metastases.

19.4 Osteoma

These tumors usually grow very slowly. They can develop superficially, as small, single or multiple exostoses of the external or inner surfaces of the skull, convexity, or base, especially on the lesser wing of the sphenoid. Reports of an osteoma of the internal acoustic meatus [1109] and in the nervous parenchyma [194] are exceptional.

Two pathogenetic mechanisms have been considered, traumatic and dysembryogenetic. Not infrequently have osteomas arisen at the site of trauma [685]. The dysembryogenetic hypothesis is the same as for other tumors, i.e. an origin from included embryonal residua.

A compact osteoma, solitary and typical of the cranial bones, is distinguished from a spongy osteoma, typical of the long bones. An osteoid osteoma [1275] originates from the spongiosa, produces osteoid substance, and involves successively the cortical lamina and the periosteum. Another type is the "eburneal" osteoma of the paranasal cavities, which may involve the frontal and ethmoidal sinuses and the orbit [541].

Histologically, osteoma is composed of lamellar bone tissue with few haversian canals, similar to the compacta of normal bone. Spongy osteoma is similar to the spongiosa. Sometimes, vessels are abundant and of angiomatous aspect.

All osteomas are benign tumors, but sometimes they reach large dimensions and represent real surgical problems: A personal case weighed 444 g! They appear in a wide range of ages, 3–67 years in a personal series, and there is a prevalence among females.

19.5 Osteosarcoma

Osteosarcomas are rare tumors, mainly localized in the limbs, but exceptionally also in the skull, and have a slight prevalence for young subjects and men. At origin from the meninges [1558] or from the nervous structures is very rare [1286].

Macroscopically, the tumors are irregular in shape, gray-reddish, and of variable consistency. Sometimes, the tumor is soft because of regressive events and sometimes hard because of bone neoformation. The infiltrative growth is clearly evident.

Osteosarcomas are malignant with extensive invasiveness, and produce distant metastases.

20 Vascular Tumors

20.1 Capillary Hemangioblastoma

Hemangioblastoma (Lindau's tumor) is a neoplasm which is found mainly in the cerebellum and is characterized by the progressive growth of angioblastic elements. When associated with retinal angiomatosis (von Hippel's disease), it forms the "angiomatosis of the central nervous system" [1656]. This association, known as von Hippel–Lindau disease [107], has been verified to be fairly rare [2079, 104]. It encompasses other malformative hamartoblastomatous processes such as cysts and tumors of the kidney, liver, pancreas, and adrenal glands [1605]. Syringomyelia may be associated with spinal hemangioblastomas.

The fundamental pathogenetic mechanism is thought to be a dysembryogenetic defect of mesenchyme occurring about the third month of fetal life and affecting various developing organs simultaneously. As happens in von Recklinghausen's disease, in which acoustic neurinoma presents as an isolated tumor in the majority of cases, cerebellar hemangioblastoma can be almost always found without the stigmata of von Hippel–Lindau disease [2079]. The dysembryogenetic hamartoblastomatous theory is, however, universally accepted, also in the case of a solitary hemangioblastoma [2968].

Cushing and Bailey [543] were among the first to suggest an origin of hemangioblastomas from aberrant vascular germs. Such an interpretation applies for the most common location, the cerebellum [2724]. In fact, the intense proliferation and vascularization of the area postrema which occurs around the third month of fetal life may account for the possible inclusion of undifferentiated embryonal cells, such as angioblasts, which might subsequently develop a neoplastic potential for reasons still not understood.

20.1.1 Biological Data

The frequency varies in the different series from 1.9% [543], 1.5% [863, 3136], to 0.8% [2012] of all intracranial tumors. If posterior fossa tumors only are considered, their incidence rises to 7.3% [2079].

Some 83% of hemangioblastomas are located in the posterior fossa [2012]. Besides the cerebellar hemispheres, the vermis, fourth ventricle, and medulla (especially the area postrema) are preferred locations. Supratentorial and spinal cord examples have been described, but they are less frequent. Up to the end of 1978, 23 intracerebral cases had been reported [1596].

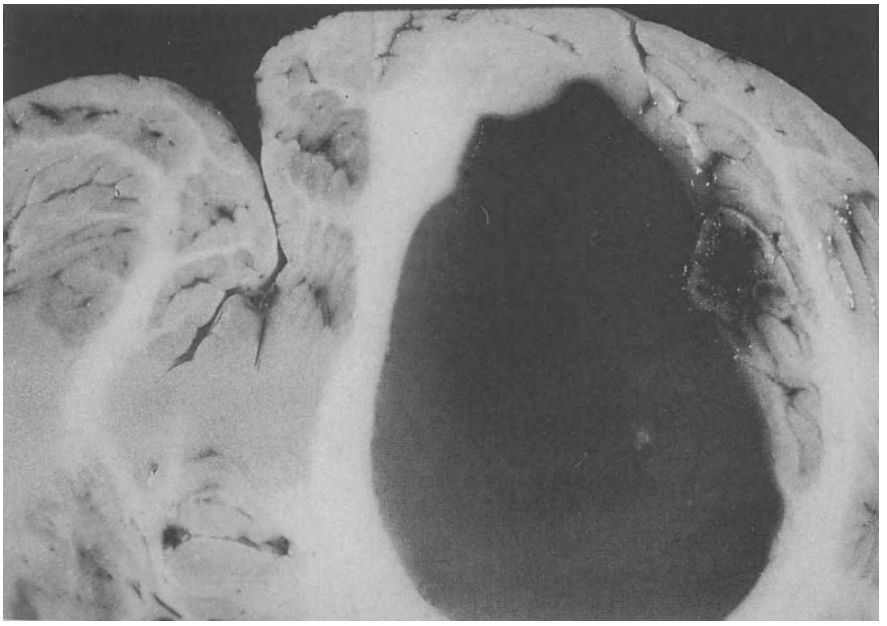


Fig.20.1. Cerebellar hemangioblastoma, large cyst with a mural nodule

Extramedullary locations involving the spinal roots or cauda equina or even peripheral nerves are exceptional. Hemangioblastomas are usually isolated tumors, but occasionally may be multiple or in the cerebellum and spinal cord or in the cerebellum and cerebrum [745].

The majority of tumors are diagnosed between 35 and 45 years of age. Children are rarely affected [768]. When the tumor is part of the von Hippel–Lindau syndrome the average age is lower, 29 years [2012].

Males are affected more frequently than females, but in some series, both sexes are equally represented [2012].

20.1.2 Macroscopic Appearance

Hemangioblastomas are nonencapsulated, mostly cystic tumors, of variable consistency but generally hard-elastic, reddish-brown or reddish-blue in colour and well circumscribed from the surrounding tissue. They are of variable dimension, from the size of a walnut to a mass replacing most of the cerebellar hemisphere. Cysts may be of various sizes and may be multiple, but usually there is a single large cyst which forms the main body of the tumor, the solid part being represented by a small mural nodule (Fig.20.1). The cysts have a yellowish or brownish fluid content which often coagulates spontaneously when it is exposed to air. The internal part of the cyst is smooth and whitish or rusty if intracystic hemorrhages occur (Fig.20.2).

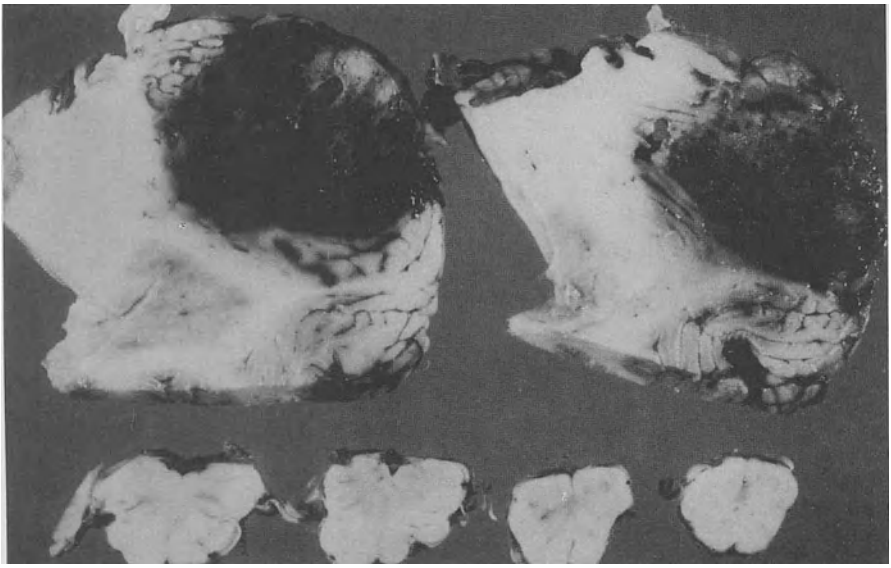


Fig.20.2. Hemorrhagic cerebellar hemangioblastoma

20.1.3 Microscopic Appearance

The main feature of the solid areas is the presence of a network of lacunae and newly formed blood vessels of different shapes, orientation, and caliber. Blood vessels vary from capillaries to sinusoidal or lacunar spaces (Fig.20.3). Reticulin staining or methods demonstrating a basement membrane highlight the blood vessel network and the intervascular cells arranged in islands or in epithelial-like cords (Fig.20.3b).

Blood vessels of the capillary type are formed by endothelial cells resting on a basement membrane in continuity with a rich argyrophilic intercapillary and interstitial network (Fig.20.4a). There are also blood vessels showing various alterations in their walls, and vascular spaces having a cavernous appearance or forming sinusoids filled with blood. Their endothelial lining is often discontinuous and fenestrated, so that some segments of the lumen appear delimited only by elements of the surrounding interstitial stromal tissue.

The endothelial cells of the capillaries and lacunae are usually swollen, isomorphic, and with hyperchromatic nuclei. Stromal cells have an epithelioid appearance or are polyhedrical, with clear, hypochromatic nuclei often containing a prominent nucleolus. In paraffin sections, their cytoplasm usually shows variable vacuolation up to the formation of a large single vacuole delimited by a plasma membrane (Fig.20.4b). Frozen sections stained with Sudan black and examined under polarized light may demonstrate the presence of sudanophilic birefringent material. Not infrequently, however, lipids are absent, and the cytoplasm is pale, homogeneous, or finely granular. Fat droplets are easily seen under the electron microscope (Fig.20.5). Because of their resemblance to the

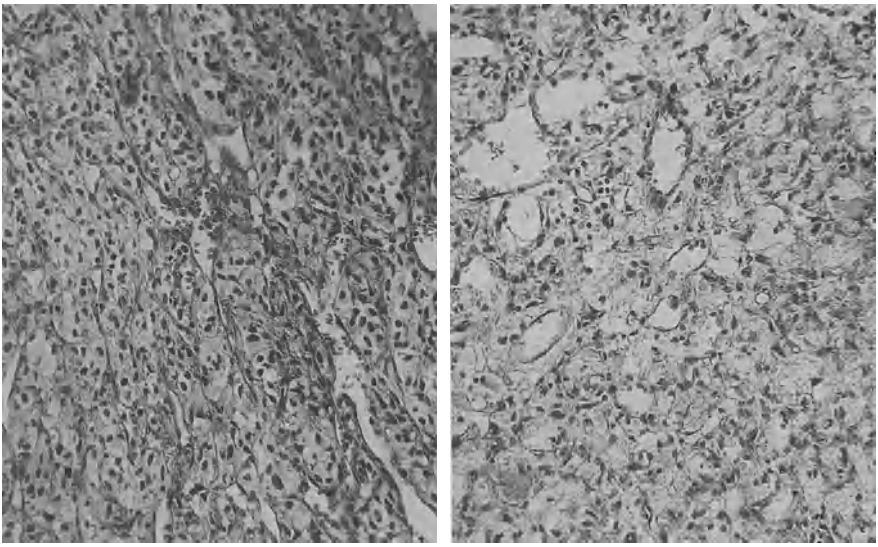


Fig.20.3a,b. Cerebellar hemangioblastoma, many capillaries intermingled with intermediate cells, arranged in islands or cords, H&E, ×200 [2486]

foamy cells seen in some dysmetabolic conditions, they were called by Lindau (1926) [1656] and Lozano and Costero (1926) [1701] "pseudoxanthomatous."

The nuclei of this cell type are usually fairly uniform but sometimes show a discrete pleomorphism (Fig.20.6). In some cases, giant uni- or multinucleated cells may be present. Mitotic figures are generally not present.

The nature of the interstitial cells has been discussed for a long time and remains controversial. In general, the prevailing idea is that they derive from the pia or have an angiogenic origin [602, 1840]. The problem is made more difficult by the frequent finding of GFAP positive cells of astrocytic type in the tumors. These are generally considered as reactive astrocytes trapped in the tumor [1388, 602, 1840, 2509, 37]. Sometimes, polygonal GFAP-positive lipidized cells of stromal type without processes are present (Fig.20.7). They are vimentin-positive also and may be reactive, lipidized astrocytes [1388] or stromal elements which have taken up GFAP from the environment [602]. However, the astrocytic component may be somewhat conspicuous [1842], even though the aspect of a mixed glioma or angioglioma is never achieved [253].

On the basis of the main morphological features, cellular, capillary, and cavernous variants of hemangioblastoma are distinguished [543]. The former is characterized mainly by stromal cells, which are positive for vimentin [2513] and therefore hardly distinguishable from astrocytes. Their positivity for fibronectin [1470] permits, on the contrary, such distinction.

The tumor, as already noted, has no capsule, but it is constantly sharply delimited from the normal nervous tissue (Fig.20.8). Its limit with healthy tissue is marked by the presence of masses of small blood vessels, and often there is an intense reactive gliosis with the presence of GFAP-positive astrocytes in the peripheral parts of the tumor.

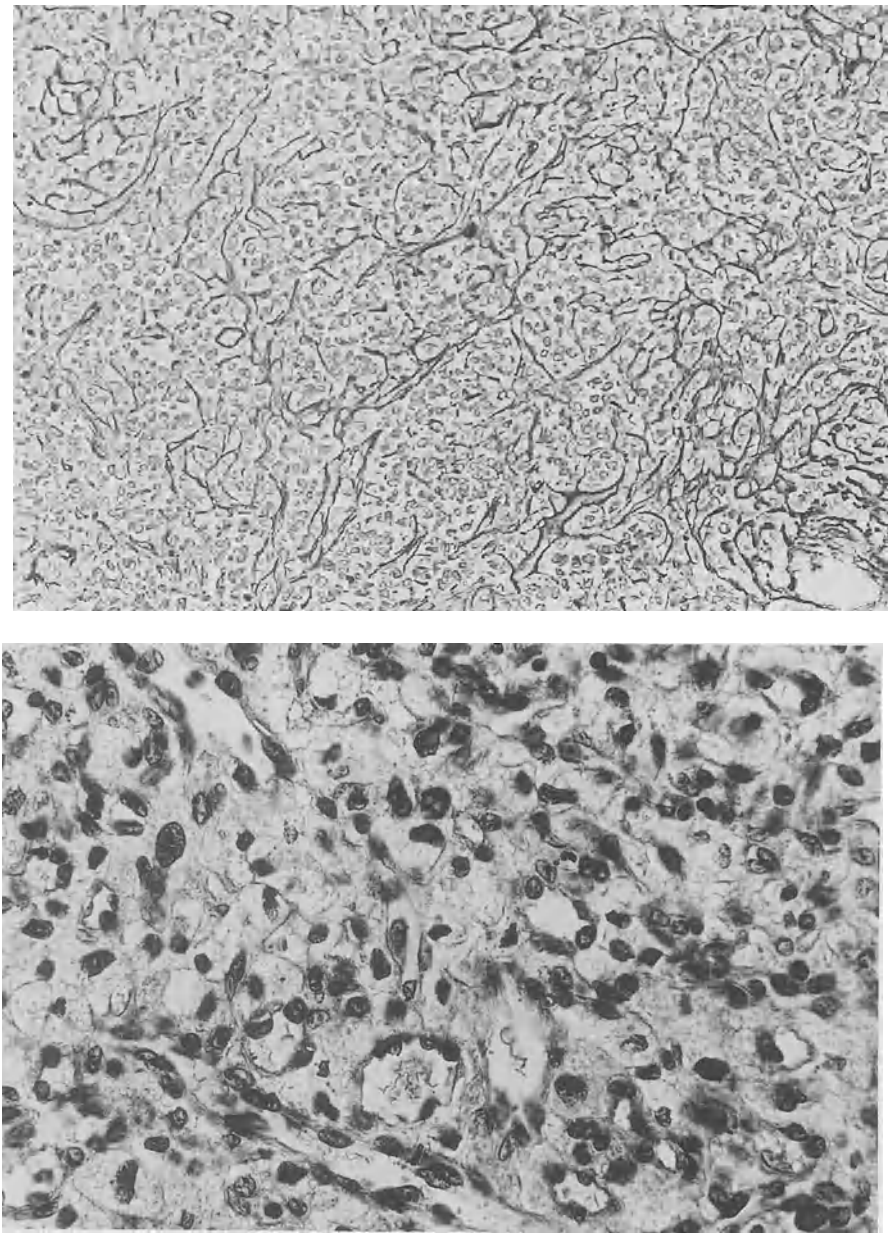


Fig.20.4a,b. Cerebellar hemangioblastoma: **a** rich argyrophilic network, Gomori, ×200; **b** intermediate cells with granulous and vacuolated cytoplasm, H&E, ×400

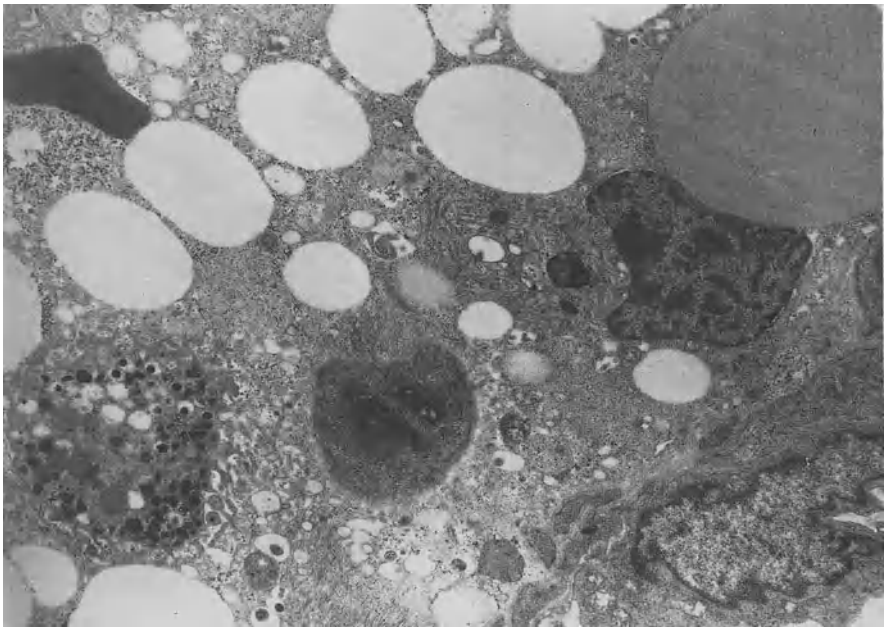


Fig.20.5. Cerebellar hemangioblastoma, fat droplets in the cytoplasm of intermediate cells, ×4000

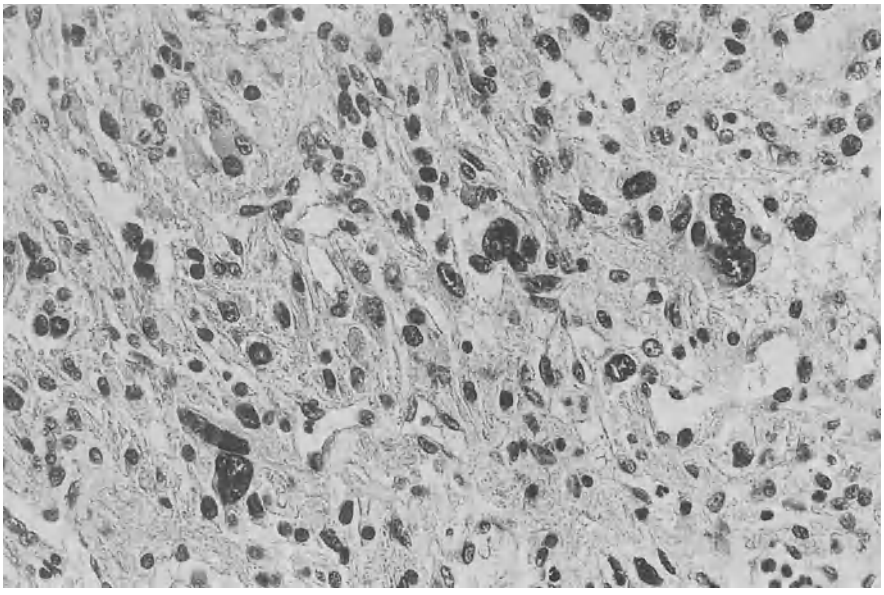


Fig.20.6. Cerebellar hemangioblastoma, nuclear polymorphism, H&E, ×400

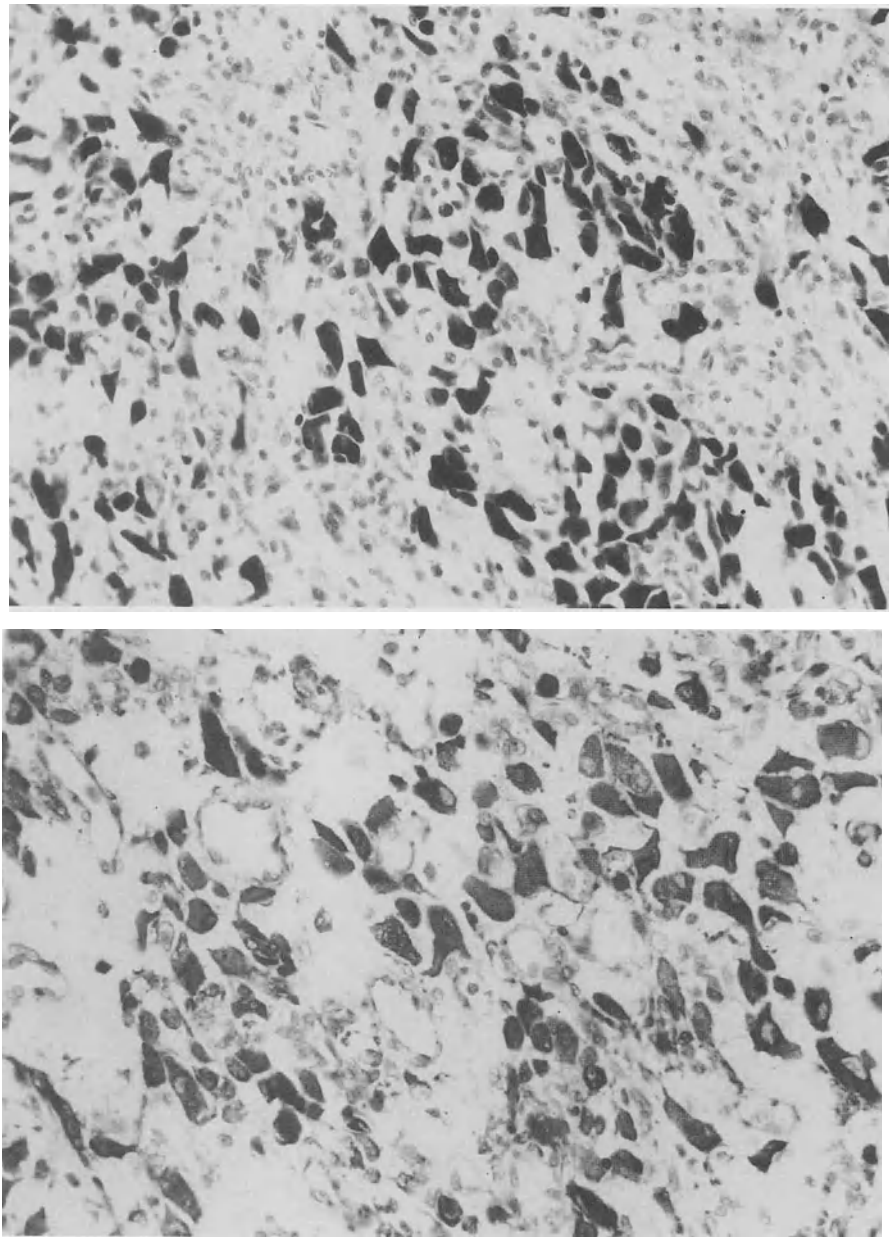


Fig.20.7a,b. Cerebellar hemangioblastoma: **a** GFAP-positive and **b** vimentin-positive cells, PAP-DAB, ×400

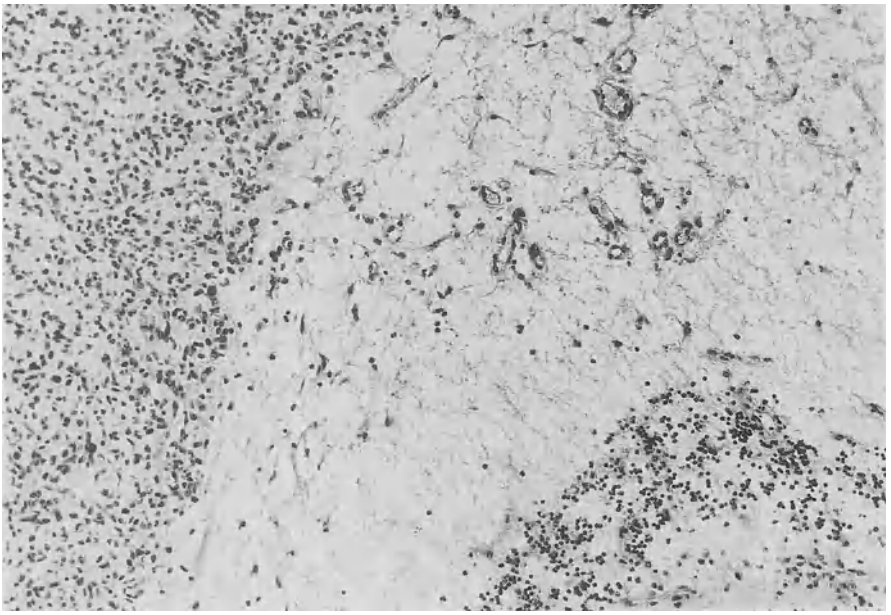


Fig.20.8. Cerebellar hemangioblastoma, sharp limits of the tumor, H&E, ×200

20.1.4 Regressive Events

The most constant and important regressive events are cystic and fatty degeneration, hemorrhage, and hyalinization.

The formation of cysts is thought to be due to the transudation of plasma from blood vessels, with a more or less constant supply of intracystic fluid [543], explaining why aspiration is usually unsuccessful. The wall of the cyst is formed by fibrous glia and may contain Rosenthal's fibers, and also hemoglobin degradation products if hemorrhage has occurred.

Syringomyelia may develop in association with hemangioblastomas of the spinal cord [718], through a process similar to that leading to cyst formation. Others believe it is a primary feature of von Hippel–Lindau disease [1194].

Hemorrhage is constantly present, as a discrete erythrocyte seepage into the tumor parenchyma and/or massive and extensive bleeding.

Erythrocytes are found free within the tissue between the capillaries and the vascular lacunae, and also between the stromal elements where, by confluence, they may give rise to pools with no limiting endothelium.

Hyalinization processes are common.

20.1.5 Electron Microscopy Study

Three cell types are recognized: endothelial cells, pericytes and stromal cells [372, 404, 1366, 2704, 417, 1150, 1152, 1153 , 1154, 2625, 1344].

Stromal cells, besides vacuoles, vesicles, and lipid granules [1154], show features reminiscent of endothelial cells, such as microfilaments, serrate junctions, basement membranes, and Weibel–Palade bodies, although in lesser quantities, probably because they derive from common mesenchymal angiogenic cells [1150]. Pericytes do not contain Weibel–Palade bodies and derive from nonangiogenic mesenchymal cells. Factor VIII/RAg demonstration in stromal cells is controversial, with positive [1330] and negative observations [1840]. It is possible that there is a loss of antigen or an insufficient concentration of antigen [1150]. It must be added that the occurrence of Weibel–Palade bodies in stromal cells has also been questioned [2625], and a leiomyoblastic differentiation has been found both in pericytes and in stromal cells [1344]. Pericytes are more abundant than in the capillaries of the brain, muscle, and lung. They have a contractile function and probably regulate the size of the capillary lumen [1152]. A large number of mast cells is found in this tumor in relation to the endothelial and stromal cells. They continuously degranulate in the intercellular spaces, and the heparin released may be an important factor in the proliferation of blood vessels [1150].

Endothelial cells contain large pinocytic vesicles situated close to the nucleus and surrounded by bundles of microfilaments and Weibel–Palade bodies. The large vesicles which derive from the invaginated plasma membrane have no known function [1153].

20.1.6 Metastasis, Recurrences, Prognosis

Hemangioblastomas are biologically benign tumors, even when histologically they show a tendency to infiltrate the surrounding tissue [2724]. A permanent cure can be obtained by complete surgical removal. Recurrences can arise with incomplete surgical removal or after a simple evacuation of the cyst. In some instances, it is difficult to establish whether it is a real recurrence or a multiple neoplasm. Recurrences, however, have also been reported also after an apparently total removal [2174]. Five years after surgery, 89% of patients were in good condition in a recent series [2012]. There are no examples of tumors which have undergone malignant change, not even in the exceptional cases of subarachnoid dissemination [1913]. An angiosarcoma of hemangioblastic derivation has never been reported.

20.1.7 Associated Polycythemia

The genetic relationship of tumor angioblasts with embryonal angioblastic tissue, apart from the morphological resemblance, is underscored by the finding of polycythemia in some cases [2660], with a return to normocythemia after tumor resection, and by the presence of islands of erythropoiesis in the tumor parenchyma [1792, 994].

A substance similar to erythropoietin, the hormone regulating erythropoiesis which is associated with polycythemia, has been found [2967, 1105, 1292] in the cysts and in the tumor. Furthermore, 120–500 nm secretory granules which may be erythropoietin or its precursors have been found in stromal cells [1259, 57]. Cells immunohistochemically positive for erythropoietin and renin have also been found in the tumor [244].

20.1.8 Differential Diagnosis

The similarity between the cellular type of hemangioblastoma and paraganglioma of the cauda equina has already been remarked upon. Another distinction must be made in respect of metastatic renal cell carcinoma. The main problem remains that of the distinction from angioblastic meningioma (see Chap. 18). Fundamentally, the findings are in favor of an assimilation of the variant 3 of type IV angioblastic meningioma of Cushing and Eisenhardt [544], i.e. the hemangioblastic variant, with the hemangioblastoma [1192, 1389, 2420]. It is still doubtful whether transitional forms exist between meningioma of different types and hemangioblastoma [2420].

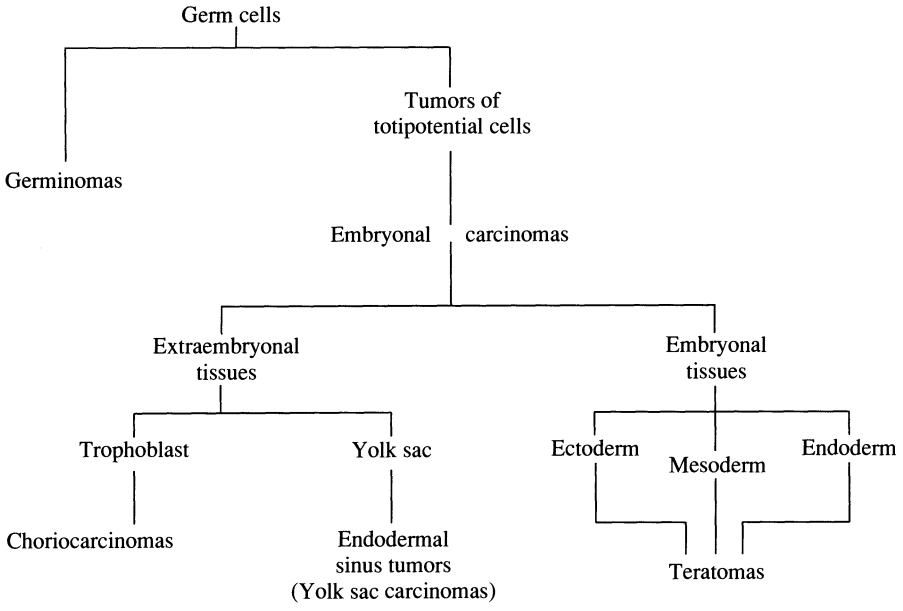
21 Tumors and Dysontogenetic Lesions

21.1 Germ Cell Tumors

Germinal cells represent one of the cell lines into which the blastoderm differentiates, the others being the somatic and the extraembryonal lines, but at the same time germ cells are capable of differentiating again toward the somatic and extraembryonal lines. After they form in the normal yolk sac, they migrate toward the gonadal folds, but if displaced, they can retain their ontogenetic potential and acquire neoplastic properties [2977].

The various germ cell tumors (GCT) correspond to embryonal stages of development. Germinomas correspond to primordial germinal cells. The extraembryonal derivatives of germ cells may differentiate into yolk sac endoderm, thereby forming endodermal sinus tumors, or into trophoblast, hence forming chorioncarcinomas. From pluripotent embryo stem cells, according to some, embryonal carcinoma originates and then immature and mature teratomas develop, which may be mono-, di-, or tridermomas [2820] (see Table 21.1). According to others embryonal carcinoma represents a further

Table 21.1. Development of germ cell tumors



stage of differentiation of endodermal sinus tumors and does not have the ability to differentiate into embryonal and extraembryonal derivatives [2795]. Still other theories exist. For example, according to the embryonal cell theory, displaced foci of embryonal cells may escape the influence of the primary organizer. According to the theory of extraembryonal cells, teratomas originating from the yolk sac are not of germ cell origin. Another theory sustains that teratomas originate from an included twin fetus [973]. The term "teratoma" can be used with two meanings. In the strict sense, it indicates tumors which contain embryonal elements of all three primitive germinal layers. In a broader sense, it indicates any cerebral benign or malignant dysontogenetic lesion.

21.1.1 Frequency, Age, Sites

GCT originate at specific points along the midline of the body, such as the gonads, or the sacrococcygeal, retroperitoneal, mediastinal, and diencephalic regions. Rarely, nonmidline tumors [2958, 1797, 1986, 1468] involving the basal ganglia, thalamus, frontal, and paraventricular regions or septum pellucidum have been reported [1797, 2798]. It has been calculated that no more than 40 cases have been described in the basal ganglia, plus 2 recent ones [2798]. These tumors have common histological features. They may be congenital, and in this case they are mainly benign teratomas. Teratomas of the third ventricle are, in fact, the most frequent congenital intracranial tumor [2964].

GCT arise in the region of the third ventricle, along a line which runs from the suprasellar cistern to the pineal region. Germinomas are mostly found in the suprasellar region followed by the pineal region and then by the basal ganglia/thalamus, while nongerminomatous tumors appear in the pineal region, followed by the suprasellar region, lateral ventricles, fourth ventricle and cerebellum [1310]. A case of embryonal cell carcinoma localized in the parietal lobe has been reported [1742B].

From the clinical point of view, hypopituitarism due to multiple hormone deficiencies, pituitary dwarfism, hyperprolactinemia, diabetes insipidus, hypernatremia, and precocious puberty may develop, especially if the tumor is suprasellar [1249].

The male/female ratio is 3.25:1 for nongerminomatous tumors and 1.88:1 for germinomas. The suprasellar region is more often involved in females, while the pineal region prevails in males [1310]. The tumors appear at the age of 10–12 years, but teratomas and choriocarcinomas are more frequent in younger children, and the incidence of germinomas peaks toward 13–15 years [1311].

GCT represent 0.5% of all intracranial tumors [25, 1294]. A high incidence, of 4%–5% of these tumors in Japan [68, 1980, 1544] and Taiwan [2623] has been noted. In Taiwan, they represent up to 5.1% [72] or even 9% of intracranial tumors. This is valid also for testicular GCT. For these tumors an increase in incidence in individuals under 30 years of age has been found since the last World War [2560].

21.1.2 Pathogenesis

There is no doubt that germinal cells are the source of GCT. However, it is not clear whether this is due to a defect of migration, to the formation of "embryonal remnants,"

or to other causes, taking into account that almost all of these tumors originate in the suprasellar region and in the pineal region.

Embryology teaches us that maturation of the diencephalic structures coincides with migration of the germinal cells from the posterior yolk sac to the gonadal crests and that after the 60th day of gestation, there are no extragonadal cells left. A simple migration error may explain the origin of retroperitoneal, mediastinal, and sacrococcygeal GCT, but for the diencephalon, such local factors as the mechanisms of regulation of gonadotrophic activity must be invoked. Neuroendocrine events at puberty may have an activating influence, and there are many observations which indicate an inductive or a transformative role of gonadotrophin on GCT.

21.1.3 Germinoma

At the suprasellar and pineal sites, germinoma is the most frequent of all GCT and represents 0.1%–3.4% of all intracranial tumors [1186].

21.1.3.1 Macroscopic Appearance

The tumor, whose cut surface is grayish-pink and friable in consistency, is at times calcified; it may appear demarcated and confined to the pineal gland but more often infiltrates surrounding areas, e.g., the roof of the third ventricle, quadrigeminal plate, aqueduct. When it develops more anteriorly, it reaches the anterior part of the third ventricle, the lamina terminalis, the chiasm, and the foramina of Monro. It may even grow into the lateral ventricles.

21.1.3.2 Microscopic Appearance

It recalls that of gonadal tumors and of mediastinal germinoma and features lobules delimited by fibrous septa containing lymphocytes (Fig.21.1a). Tumor cells may also be admixed with lymphocytes. The tumor is composed of cells of two types: large and small (Fig.21.1b). The former have eosinophilic, ill-defined cytoplasm and contain a vesicular nucleus with an evident nucleolus (Fig.21.2). Mitoses may be numerous. The small cells are lymphocytes which are clustered into groups or scattered, especially in the fibrous septa. They have been found to be mostly of the T-cell subset [2017]. Multinucleated, foreign-body-type giant cells may occasionally be present.

Not uncommonly, the histological appearance is mixed, because of the presence of teratomatous areas or of other germinal tumor elements, such as embryonal carcinoma, choriocarcinoma, etc. [1815].

The cytoplasm of the large cells contains PAS-positive glycogen granules. Under the electron microscope, apart from endodermal cells and lymphocytes, mesothelial cells and large trophoblastic cells are seen. The endodermal cells show the already mentioned glycogen granules, annular lamellae, and junctional complexes [511, 1140, 1769, 2788, 1076, 1475].

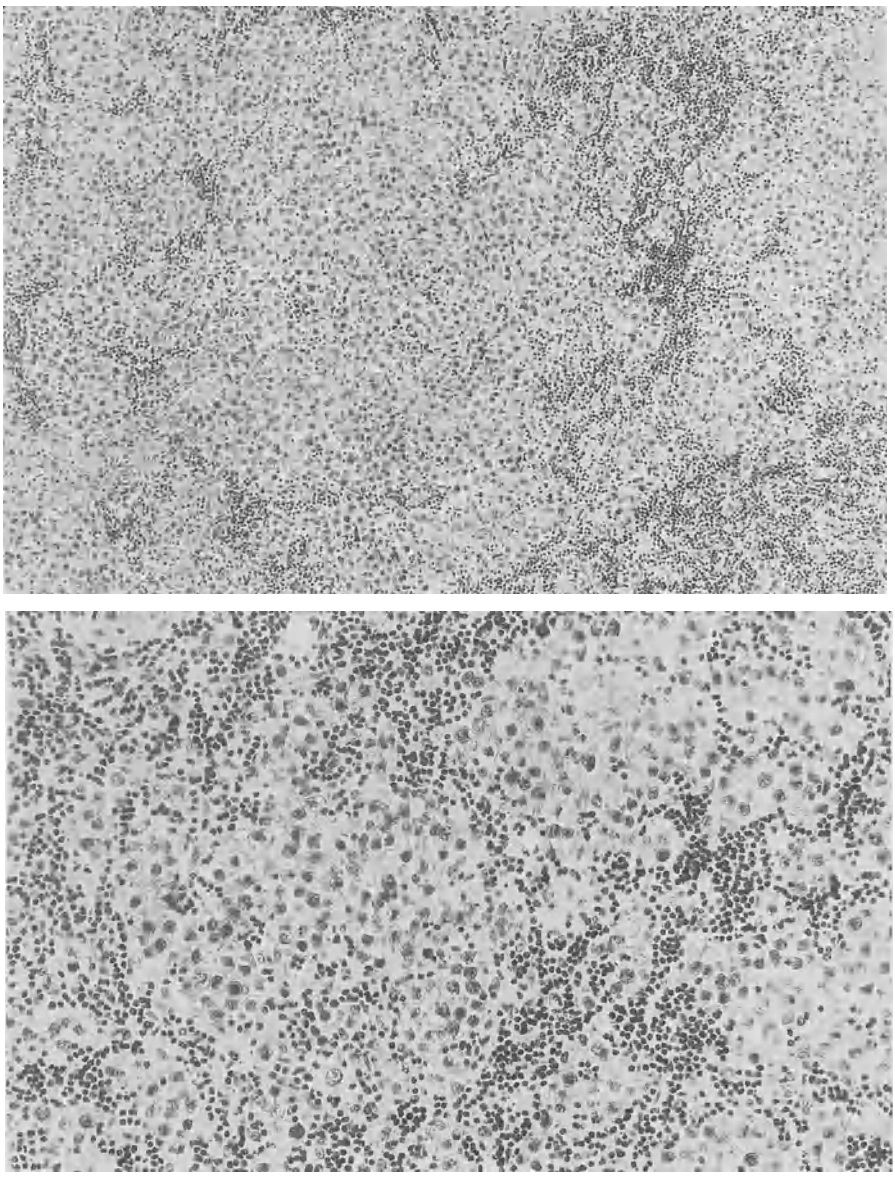


Fig.21.1a,b. Germinoma: **a** lobules delimited by septa containing lymphocytes, H&E, ×125; **b** tumor cells admixed with lymphocytes, H&E, ×300

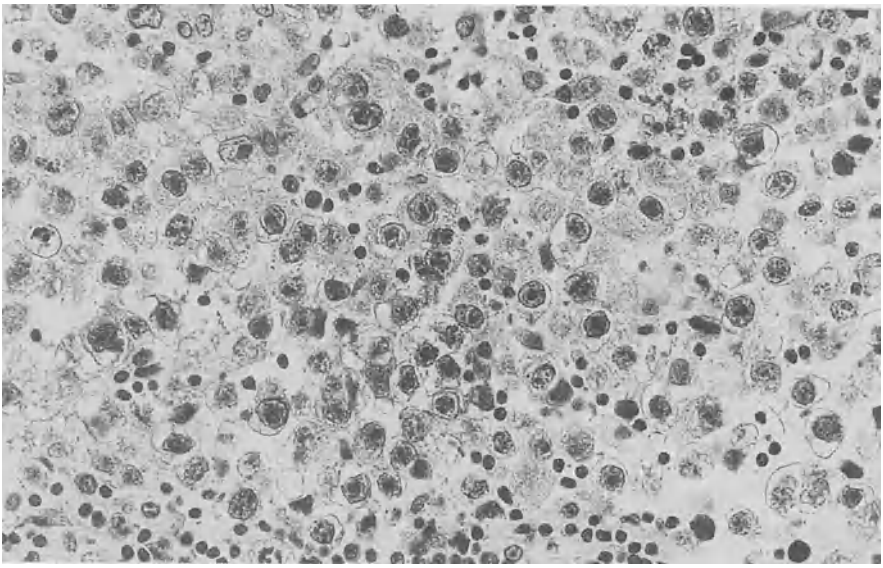


Fig.21.2. Germinoma, typical tumor cells with vesicular nucleus and evident nucleolus, H&E, ×400

21.1.3.3 Prognosis, Treatment

Germinoma is sensitive to radiation and, in general, is characterized by fairly good postoperative survival rates. Its quartile is 1.4 as opposed to 0.1 for the other GCT [1311]. Undoubted advantages resulting from advances in neurosurgery in these anatomical areas [1322] have led to suggestions that surgical procedures should be attempted before other forms of therapy [2725]. Postoperative radiotherapy has given very good results [1607]: survival at 5 and 10 years has been 75% and 69% [2446], and 85.6% [1815], respectively, whilst others reported 82% survival at 5 years [695]. It should be remembered that some series in the literature are not histologically documented. A positive response to irradiation with 20 Gy is sometimes used as a diagnostic procedure [695], but many authors do not agree.

The tumor may spread via the CSF [219] with a variable, even very high frequency [1607], so most authors advocate preventive postoperative irradiation to the entire neuraxis. According to some, this approach would not be justified when myelography and cytology results are negative [2983]. Distant metastases via the blood stream have been reported [1310].

21.1.4 Embryonal Carcinoma

The embryonal carcinoma represents 31% of the tumors of the pineal region in infancy [2105], is formed of cords or lobules of anaplastic or columnar cells (Fig.21.3), has nuclei which are vesicular and contain an evident nucleolus. Mitoses are frequent. The ep-

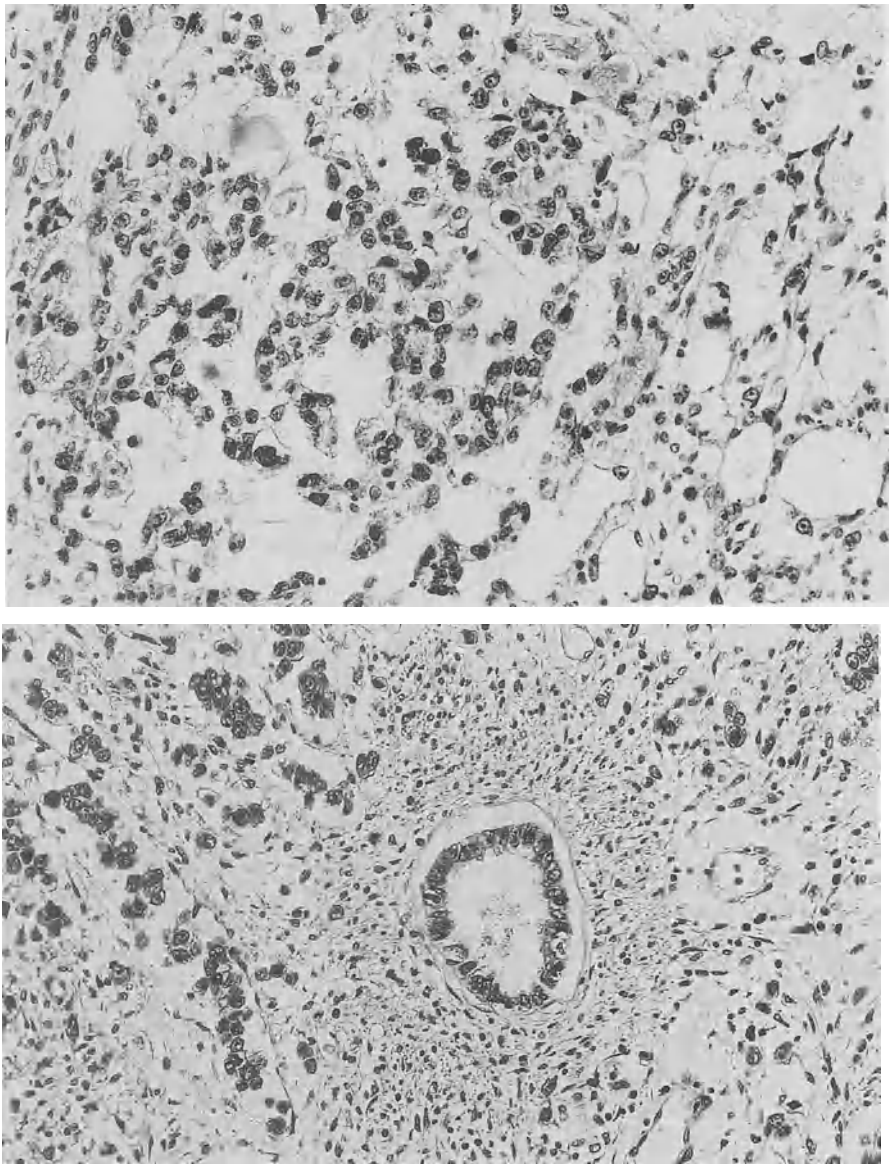


Fig.21.3a,b. Embryonal carcinoma: **a** cords and lobules of tumor cells, H&E, ×300; **b** teratomatous aspects, H&E, ×300

ithelium may take on a fibroblastic appearance, and cartilage may form within the stroma. "Embryonal bodies," likened to normal 1–2-week-old embryos, may be identified in the tumor [739].

21.1.5 Choriocarcinoma

Choriocarcinoma is a very rare tumor: Up to 1974, 34 cases had been reported [1072]. It is rarely pure and is usually admixed with other tumor types, such as embryonal carcinoma and teratoma.

It is not possible to be certain, solely on the basis of a biopsy, whether the tumor is a pure extragenital choriocarcinoma (because nonchoriocarcinomatous portions may not have been sampled) or a cerebral metastasis from a reproductive tract tumor [220]. For this reason, the number of reports of pure cases up to 1983 was only 24 [3092]. In a series of 70 cases of germinal tumors, there was only one choriocarcinoma [219].

Histologically it is characterized by the presence of multinucleated syncytiotrophoblastic cells which surround the monomorphous cytotrophoblast and cavernous blood spaces. The tumor is found in the pineal region or, more rarely, in the suprasellar location, in the lateral ventricle [1361], or in the third ventricle [1777].

21.1.6 Endodermal Sinus Tumor

This tumor is characterized by the presence of endodermal sinuses (Schiller–Duval bodies), perivascular endodermal cells, and cystic dilatations with thin walls. The tumor was described in 1968 [192], and not more than 36 cases have since been reported: 26 were located in the pineal region and 8 in the suprasellar region. A case in the thalamus has also been published [1797]. The tumor is highly malignant and features a network of cuboidal epithelium forming papillae sustained by delicate connective tissue, containing blood vessels with thin walls. Under the electron microscope, the cuboidal or irregular cells have numerous apical microvilli, lateral serrated junctions, and a delicate basal membrane. The trophoblastic cells are similar to those found in choriocarcinoma [1797]. Beside the very rare pure forms, mixed ones with endodermal sinus tumor, germinoma, choriocarcinoma, or embryonal carcinoma have been described [1294, 2420].

21.1.7 Teratocarcinoma

The teratocarcinoma is formed by embryonal carcinoma and mature or immature teratoma. Embryonal carcinomatous features occur beside the teratomatous ones [260, 1783]. Teratocarcinoma has to be distinguished from teratomas with malignant transformation [2977]. A doubtful case of association between germinoma and astrocytoma has also been reported [2019]. Embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma are highly malignant and have a poor prognosis [1310]. They tend to metastasize via the CSF.

21.1.8 Immunohistochemical and Chemical Characterization

The characterization is achieved by the immunohistochemical demonstration on tissue, and by immunochemistry on CSF and blood, of a panel of antigens such as carcinoembryonal antigen (CEA), α-fetoprotein (AFP), human chorionic gonadotrophin (HCG), and placental alkaline phosphatase (PLAP). AFP and HCG levels are raised in the serum and/or CSF not only in embryonal carcinomas and choriocarcinomas [1255], but also in teratomas [1983]. Germinomas are negative for AFP and CEA [2627, 219].

If HCG-positivity in germinomas is demonstrated, the tumor is considered to be mixed. On the contrary, germinomas are very often positive for PLAP [2627, 1255, 2986].

Germinomas have sometimes been found to be cytokeratin and EMA-positive and also vimentin-positive in different cells [1995]. This would demonstrate that intracranial germinomas may show early signs of epithelial or mesenchymal differentiation.

21.2 Teratoma

These can be subdivided into mono-, bi-, and tridermomas depending on whether one, two, or three layers participate in the neoplastic process. Epidermoids, enterogenous cysts, cerebral lipomas, and colloid cysts of the third ventricle are examples of monodermomas [2977]. Dermoid cysts are examples of didermomas. Tridermomas are in turn subdivided into mature and immature. The former may undergo malignant transformation, while in the latter it is difficult to recognize the three layers.

21.2.1 Frequency, Age, Site

Intracranial teratomas are very rare: They comprise 0.5% of all intracranial tumors [3134] and 2% of those occurring in infancy [1251]. The frequency is higher in Japan, in agreement with that of GCT in general. In the spinal cord they are even rarer, 2 out of 1322 tumors [2665]. There is a predilection for men and the first 2 decades of life. Intracranially, they favor sites in the pineal region, the suprasellar region, the pituitary fossa, and the fourth ventricle [2486, 219, 2420]. In the spine, they appear mostly in the sacrococcygeal region.

21.2.2 Macroscopic Appearance

They are mostly single, rarely double or multiple [1251]. The external appearance of typical teratomas is that of an encapsulated tumor, well demarcated from surrounding tissues (Fig.21.4). In spinal teratomas, the tumor may be less demarcated and adherent to surrounding tissues. The surface is usually smooth and nodular, the color is reddish

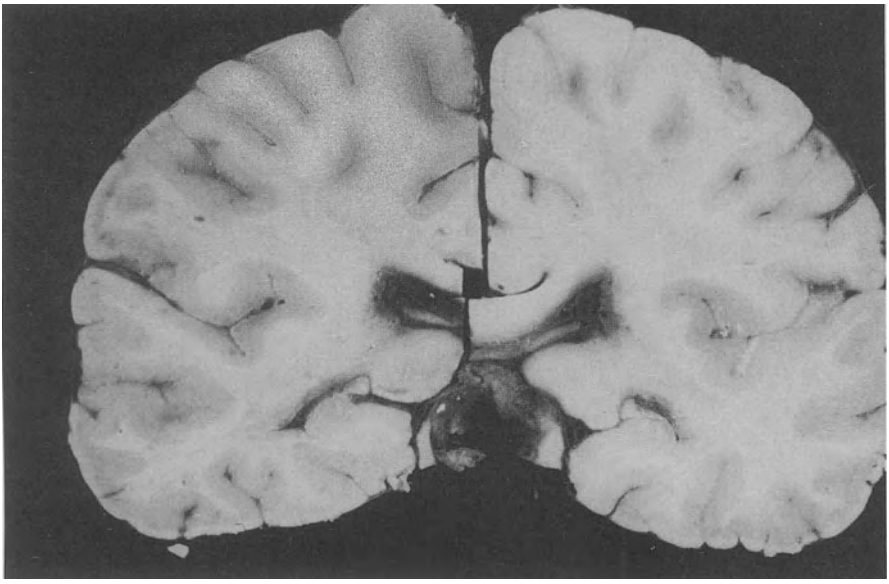


Fig.21.4. Mature teratoma of pineal region

and often variegated because of the numerous hemorrhages and many brownish cysts [3134]. The consistency varies in relation to the structures present in the tumor, but in the majority of cases it is like that of cartilage. On section, the tumor is polymorphous. Cysts occur very frequently and their content is at times similar to that of dermoepidermoids, but it is often yellowish or reddish or dark-brown, because of hemorrhages. In typical teratomas, the presence of organoid formations is a macroscopic diagnostic element. In immature teratomas the limits of the tumor are not clear-cut, and it almost constantly infiltrates the surrounding tissues.

21.2.3 Microscopic Appearance

Mature teratomas present with remarkable polymorphous features which are determined both by the presence of various organoid structures and by the extension and intensity of regressive processes. In typical forms, various mature tissues of epithelial, mesodermic, and endodermic origin may be observed [2059, 1121]. In a pineal teratoma, the presence of 15 different types of tissue was demonstrated [1850]. The tumor showed a high degree of differentiation and organization, which can reach the formation of organs, such as teeth, glands, etc. Among ectodermal structures are islands of Malpighian epithelium, cutaneous adnexae such as hair, sweat and sebaceous glands, papillary and tubular formations lined by cuboidal epithelium, and cells of neuroectodermal derivation, such as neurons and glia cells (Fig.21.5a,b). The mesodermal structures may be represented by connective fibrous, adipose, muscle (Fig.21.5c), cartilage, and bony tissues. In every case, cells of mesodermal and angioblastic derivation such as

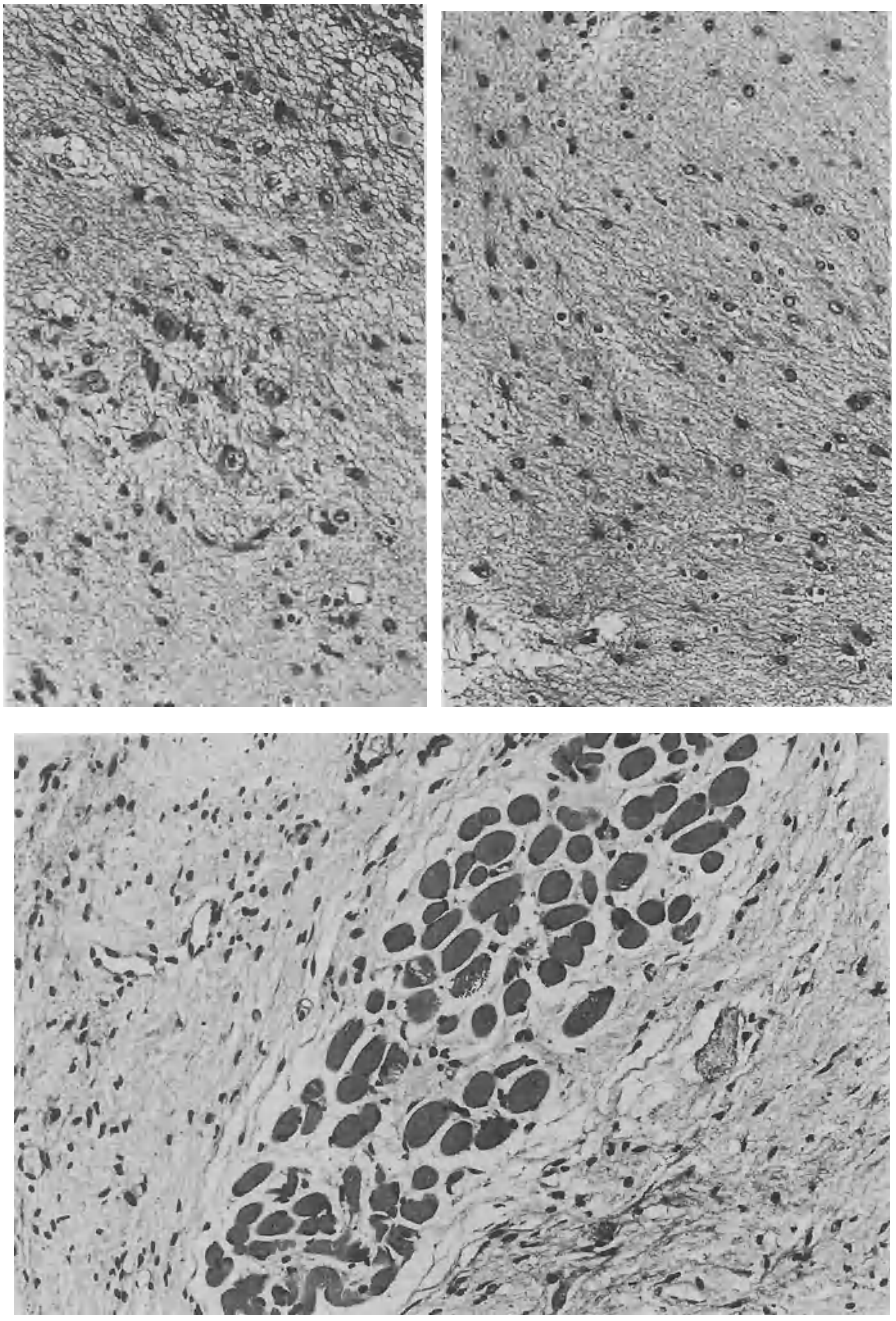


Fig.21.5a–c. Teratoma: **a** neurons; **b** glia cells; **c** muscle cells, H&E, ×300

fibroblasts, fibrocytes, lymphoblasts, lymphocytes, plasma cells, are found. Tissues of endodermal derivation are more rarely observed, e.g., respiratory and intestinal epithelia (Fig.21.6). Cysts are almost invariably found originating from areas of necrosis or hemorrhage. In immature teratomas, some of the adult structures of trilaminar derivation of mature teratomas may be found. However, the main differential characteristic is represented by the presence of poorly differentiated or undifferentiated cells.

Tubular structures, canaliculi of mucous epithelial cells, or columnar structures of undifferentiated cubic epithelium can be found. In some cases, the general features may be those of a choriocarcinoma. Then, their biological behavior is also similar. Areas with a seminomatous appearance are present, as well as cells in various stages of differentiation and more or less accentuated features of anaplasia.

21.2.4 Prognosis, Recurrence

In classical teratomas formed by mature, well-differentiated tissues and demarcated from surrounding tissues, total surgical removal is the rule. In this case, recurrences are not observed. Instead, in cases of partial removal, as often happens for the pineal region and for spinal cord locations, recurrences may occur, but after a long time. Mature teratomas are, therefore, tumors with benign biological and histological behavior. Metastases have, in fact, never been reported. Tumors with multiple nodules, as occurs in other benign malformative tumors, have instead been described.

Immature teratomas may recur and even produce metastases via the CSF or outside the CNS [219]. It is very important for the prognosis to establish whether or not germinal tumor foci occur. For example, areas of embryonal carcinoma may be found [1982, 219, 2627] or, more rarely, of choriocarcinoma or germinoma evolving toward choriocarcinoma [931]. More frequent is the finding of germinomatous areas in teratomas of the pineal region [25, 1294], suprasellar region [2650, 1294], or sellar region [2114]. Spread via the CSF is the rule in these cases, and this must not be mistaken with multicentric growths [2420].

21.3 Tumors with Muscle Cells

This section groups tumors which have in common the origin from a probable embryonal error, occurrence in infancy, affinity to immature teratomas, and presence of elements of the muscle series.

21.3.1 Medullomyoblastoma

It is a rare tumor, described for the first time in a 5-year-old girl [1767]. Eighteen cases had been described up to 1985 [445]. With the recent cases [2272] there are now 25. In a personal series, there are two such cases [2525A].

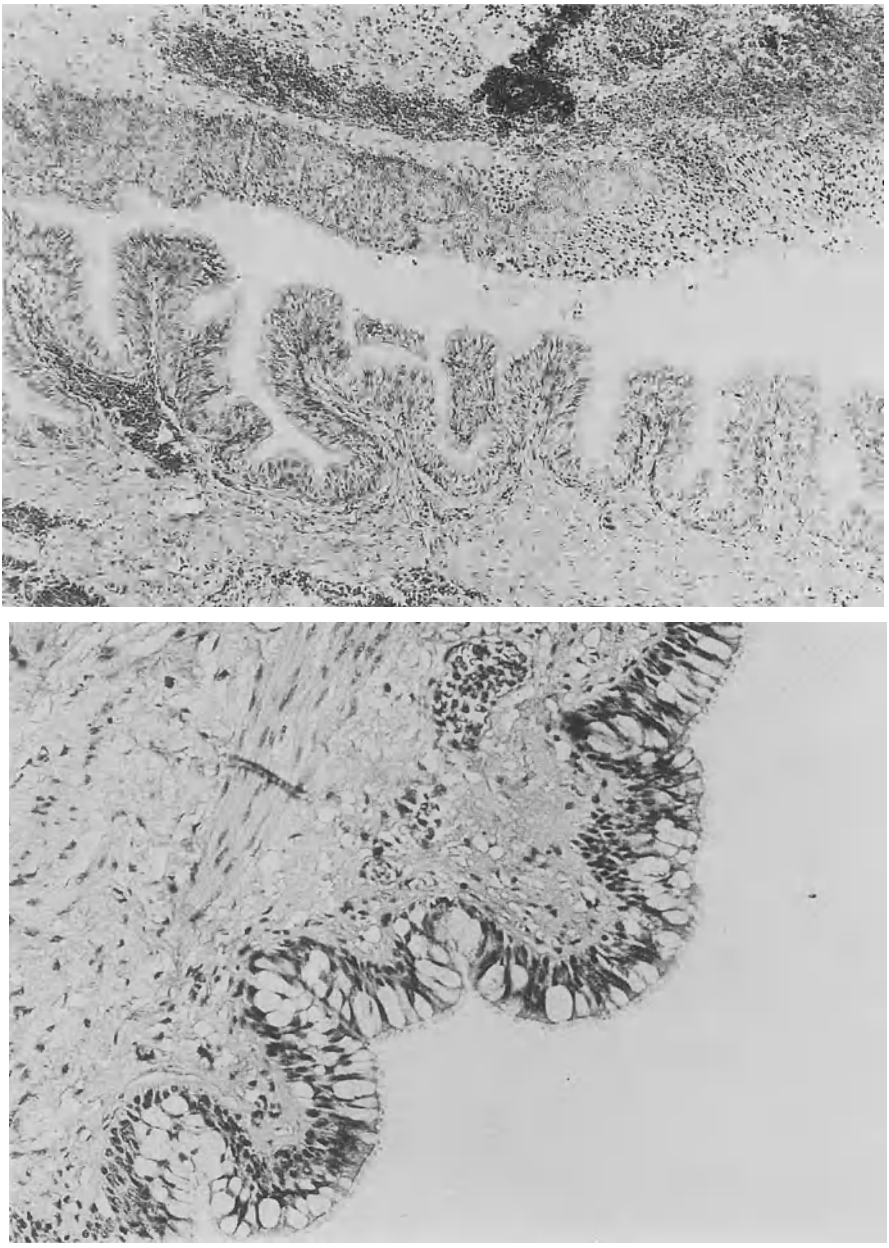


Fig.21.6a,b. Teratoma; different structures of endodermal derivation are evident, H&E, **a** ×100, **b** ×300

The tumor has the same localization and mean age as classic medulloblastoma. Two cases have been described in adults [865, 2272]. There is a prevalence of males; the M/F ratio is 3.8:1. The preoperative duration is usually short, with a mean of 3.7 months; only in a few reported cases has it been longer than 6 months [239, 1022]. The microscopic aspect is similar to that of classic medulloblastoma, with the occurrence of a muscular component. This is usually represented by striated muscle fibers, distributed in bands or in perivascular areas (Fig.21.7a). Only in two cases was the muscular component made up of smooth muscle cells [3133, 865]. The muscular component can be easily recognized in routine histological preparations for the striated aspect (Fig.21.8a). Confirmation may come from the immunohistochemical demonstration of desmin (Fig.21.8b), myosin, actin, or myoglobin, or from electron microscopy study [2675, 2976]. A neuronal and glial differentiation has been demonstrated in four cases [1908, 2634, 2675, 256], whereas a glial differentiation was seen in only one case [632]. Widespread neuronal differentiation was present in two personal cases (Fig.21.7b). A teratomatous aspect has been described in one case [445], and in some cases melanin-containing cells were found [2976, 684], bringing the tumor close to the melanotic variant of medulloblastoma.

Different hypotheses have been formulated to explain the pathogenesis of this tumor. First of all, muscle cells have been thought to originate from the metaplasia of smooth muscle cells of blood vessels [1767]. Another hypothesis considers this tumor as a form of immature teratoma [445], and still another postulates that the tumor arises from primitive mesenchymal elements capable of differentiation along multiple cell lines [1022]. It is also possible that perivascular or meningeal mesenchymal elements differentiate into rhabdomyoblasts, given the frequency of their perivascular location. On the basis of the finding of muscle cells in the meninges, accompanied by glial heterotopias in children with multiple congenital anomalies [1169, 50, 2001, 1316], Russell and Rubinstein [2420] hypothesized a deviant inductive interaction.

Another hypothesis is that of origin from multipotent endothelial cells [2976], but this must be considered as very unlikely. It is also possible that primitive pluripotent ectodermal cells show a myogenic differentiation capacity [632, 2675]. One must take into account that rhabdomyoblastic differentiation has been found in a medulloblastoma cell line [101].

Survival does not differ from that of classic medulloblastoma.

21.3.2 Primitive CNS Rhabdomyosarcoma

Rhabdomyosarcoma is the most common of the soft tissue sarcomas in infancy. It arises from primitive mesenchymal cells of many tissues. In intracranial locations, rhabdomyosarcomatous features may be found in teratomas with striated muscle differentiation, in medullomyoblastoma or in pure rhabdomyosarcomas of which 35 cases [663] have been reported in the literature. Rhabdomyosarcoma affects young subjects, 71% of the cases being under 18 years of age, and both sexes equally. The preferred site is the posterior fossa. The tumor may primitively arise from the meninges or involve meninges and neural parenchyma at the same time. It often spreads along the craniospinal meninges.

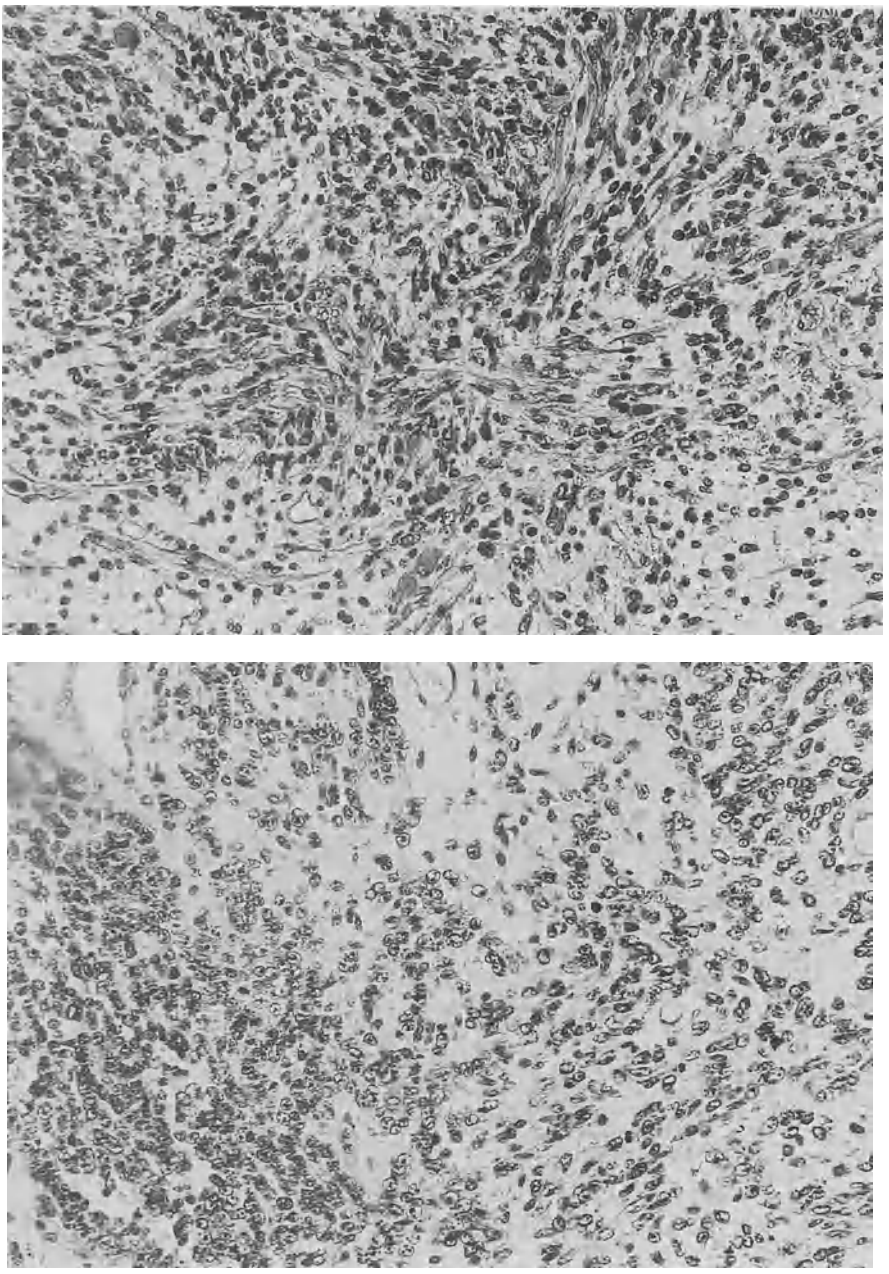


Fig.21.7a,b. Medullomyoblastoma: **a** area with striated muscle fibers, H&E, ×150; **b** tumor area with neuronal differentiation, H&E, ×150

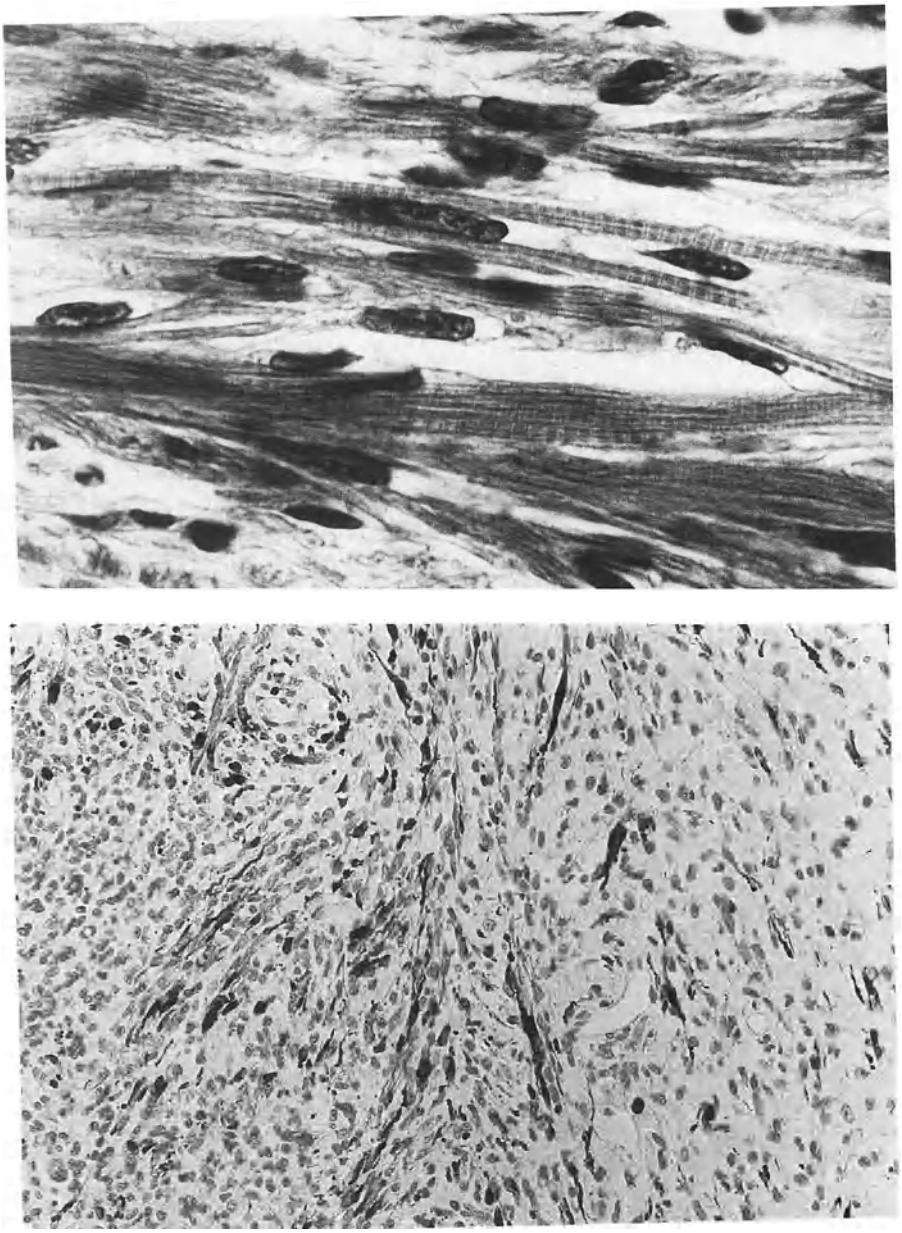


Fig.21.8a,b. Medullomyoblastoma: **a** striated muscle fibers, H&E, ×400; **b** muscle fibers are positive for desmin, PAP-DAB, ×200

The macroscopic appearance is varied, but rarely hemorrhagic [1600, 663].

The histological appearance is not different from that found in similar tumors in other parts of the body. Elongated rhabdomyoblasts with abundant eosinophilic cytoplasm with "racket" and "tadpole" appearances are present. Poorly differentiated areas in which cells have scanty cytoplasm and hyperchromatic nuclei may be present (Fig.21.9), as well as loose myxoid areas. The presence of transverse striations is characteristic and diagnostic, but they are absent in about half the cases [118].

These tumors have been subdivided into embryonal, alveolar, botryoid, and pleomorphous types [1043], but this subdivision has been criticized because of the existence of a wide spectrum of variations. Under the electron microscope, rhabdomyoblasts appear at different stages of development [2241], and thick and thin myofilaments or Z band material is observed. The myofilaments may be arranged in bundles or sparsely in the cytoplasm. It is important to note that these findings may be present without transverse striations being visible under light microscopy study.

Immunohistochemically, it is possible to demonstrate myoglobin in more than 50% of tumors [299, 1337], which correlates positively with differentiation [299, 612]. The lack of demonstration of myoglobin does not, however, exclude the diagnosis of rhabdomyosarcoma. Myosin is a more sensitive indicator and, being expressed before myoglobin during development, is also present in poorly differentiated tumors [612]; however, it is less specific. Whilst vimentin is diffusely present and, therefore, scarcely useful for diagnosis [1130], desmin may be demonstrated in Z bands or diffusely in the cytoplasm [1337].

The tumor diagnosis is usually obtained by combining light with electron microscopy and immunohistochemistry. A still controversial question regards the origin of the cells of this tumor. In general, it is thought that they are derived from the embryonal mesenchymal pericapillary cells with the capacity to multidifferentiate, which persist after birth [231]. In the CNS, they may derive from neuroectoderm, from the so-called ectomesenchyma, or from the neural crest. It must be remembered that myoblastic differentiation with the expression of receptors for acetylcholine and myofibrils has been obtained from ENU-induced glioma cell lines [1615]; these cells expressed NSE to the contrary of muscle cells of mesodermic derivation.

The prognosis is very closely related to the tumor site [719]; however, it has been found that for anaplastic or monomorphous tumors, the risk of recurrence is greater [2210]. Rhabdomyosarcoma has to be considered as a malignant tumor, survival being no more than 7 months from diagnosis and 10 months after at least partial surgical removal. The survival has been 9 months after radiotherapy and 8 months after combined treatment; however, there have been patients surviving 21, 42, and 67 months [663]. Radiotherapy with a dose of 50 Gy delivered to the tumor is generally advised, whereas the usefulness of chemotherapy is debatable. Local or diffuse recurrence, and not metastasis, is the main cause of death.

21.3.3 Other Tumors

Malignant mesenchymal tumors or embryonal sarcomas in which foci of rhabdomyoblastic or also chondroblastic [2390] differentiation may appear and gangliorhabdomyosarcoma [1174] may also be encompassed in this group. Gangliorhabdomyosarcomas also go under the name of ectomesenchymomas [1363] and originate from cells which migrated from the neural crest.

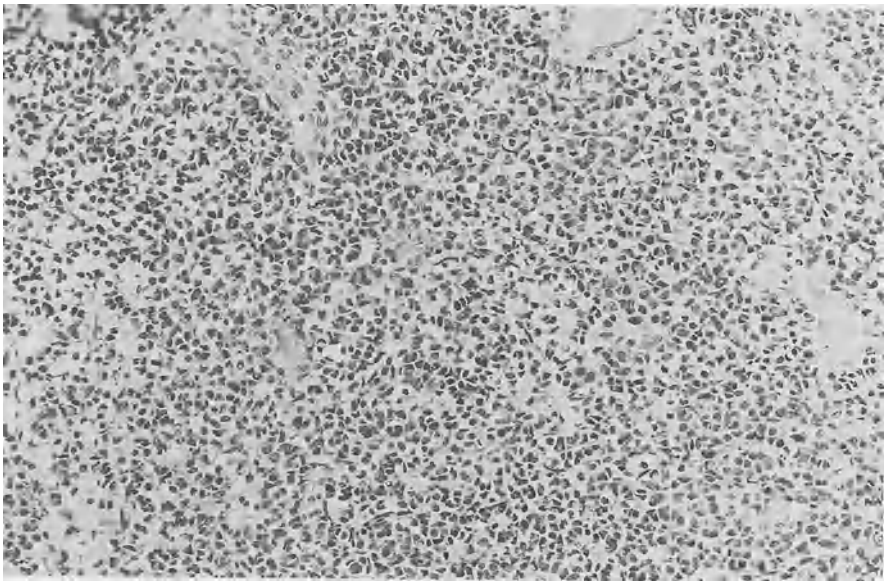


Fig.21.9. Rhabdomyosarcoma, general aspect of a poorly differentiated area, H&E, ×200

21.3.4 Rhabdoid Tumors

Tumors have been described in infancy similar to those of the kidney, characterized by a rhabdoid aspect, pure or mixed with neuroepithelial, epithelial, or mesenchymal tissue [199]. The latter tumors have been given the name "atypical teratoid tumors" [1602]. Rhabdoid tumors present before 2 years of age, are rich in mitoses, malignant, and very aggressive. In three cases localized in the posterior fossa, a cytogenetic study demonstrated loss of a gene or genes on chromosome 22 [197]. In two cases of tumor in the posterior fossa in children [439], the cells were large, monomorphous, polygonal, and positive for vimentin and EMA. It is possible that they derive from a meningothelial precursor cell, embryologically similar to the serosal mesothelial precursor cells surrounding the kidney and other organs. This explains the location of the tumor in the cerebellar meninges.

21.4 Dermoepidermoid Cysts

21.4.1 Nosography, Pathogenesis

The first descriptions of dermoepidermoid cysts were made in the last century. Generally given the name "cholesteatomas" by Von Müller [1960], bacause of the finding of cholesterol crystals in the capsule and in the cyst contents, they were also called "perlaceous tumors" [527] because of the particular macroscopic appearance.

The assimilation of epidermoid with dermoid cysts under a single heading sometimes encompassing teratomas as well has stood until today [2880], because the histological and biological differences have not been thought to be fundamental. However, such differences do exist and are sufficient to keep the two tumors separated.

The pathogenesis has variously been interpreted, but since the dysembryogenetic origin has been confirmed [2299, 267], the malformative origin has found greater consensus [1109, 3134, 693, 2420]. However, the peculiar process of embryonal divergence still remains to be clarified [1793, 1682], taking into account that, in particular cases, the pathogenetic importance, (perhaps also causal) of traumatic or inflammatory noxae has been recognized [84, 2415], especially for auricular and orbital localizations [810]. For example, the possibility of the insurgence of dermoid-epidermoid cysts in the lumbar region following lumbar puncture (especially without probe), resulting from transport and implantation of cutaneous structures within the deep tissues, has been suggested [438]. A documented case in which myelography was performed, before and after the cyst arose, has been reported [271], and this pathogenetic modality has been proven experimentally [2908] with the induction of epidermoid and dermoid cysts by direct implantation of skin in the neuraxis of an albino rat.

Like other dysembryogenetic manifestations, epidermoid and dermoid cysts are frequently associated with dysraphic conditions [1793, 1109, 2415]. In particular, spinal lesions may be uncovered by the presence of a "dermal sinus" or of spina bifida [2880] and the intracranial ones, especially those located in the posterior fossa, by related malformations [534]. The teratogenetic period has been found to be around the third to fifth week of i.u. life [2190], i.e., at the time when the neural tube closes and primary cerebral vescicles form [1109, 148, 1754]. For all the craniospinal localizations, including the intraparenchymal cysts or those located in the choroid plexuses [2469, 1109], a common origin from the leptomeninges is recognized [2469, 1109]. The case in which a thoracic epidermoid cyst was associated with a meningocele is therefore of particular importance [1431].

21.4.2 Frequency, Age, Site

Dermoepidermoid cysts are rare and represent 0.6%–2% of all tumors [1251, 1109, 2060, 148, 693, 1754, 1126, 2887, 3138].

In the personal series they represent 0.54% of all tumors. Considering that the 53 cases in the collection are all intracranial, the incidence in relation to this location rises to 1.9%. Dermoids are definitely less frequent than epidermoids.

The location varies, especially for intracranial cysts [1737, 2364], which are found both in proximity to the midline and in a lateral position. The cerebello-pontine angle is thought to be the most frequent site, the rarest one being the epiphyseal region [2668]. In a large series [1737], the frequency in decreasing order was the following: cerebello-pontine angle, chiasmatic region, Sylvian fissure, lateral ventricles, longitudinal fissure, diploe, parapontino-pituitary region, cerebellum, and multiple tumors at various locations. In particular, the basal parts of the posterior cranial fossa seem to be the preferred sites for epidermoids and the cerebello-medullary cistern and the cerebellum, for dermoids [1109].

For spinal tumors, a marked preference for the lumbosacral region was recognized, as with many other malformative processes.

The shape and size of the cysts influence their precise location. A more or less long peduncle may anchor the cysts to meninges or blood vessels. They grow by compressing adjacent parts of lesser resistance. Rarely, they develop on the outside of the cranium [3021].

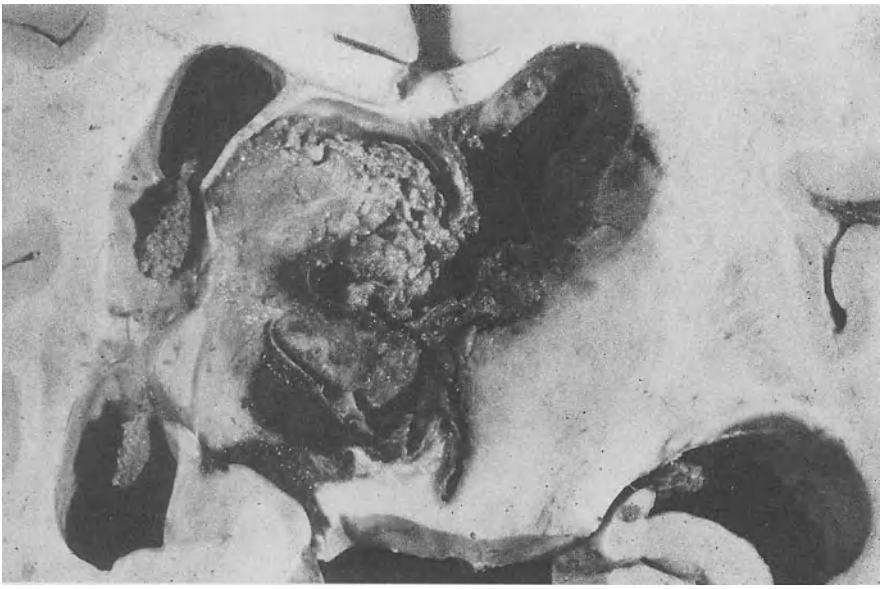


Fig.21.10. Midline dermoid cyst

Infants are more affected in some series [1251, 1682], consistent with the malformative origin of the cysts. However, the maximum incidence is found in the third and fourth decades of life for the intracranial and the second and third for the spinal cysts. The inconsistency may be due to the long duration of the cysts, which grow slowly, and patients survive even for decades [287, 168]; however, they are subject to growth spurts particularly in adult life. There are very young patients, for example, aged 6 months [1251], and very old ones, such as that of Henschen (1955) [1109], who was 78 years. It can reasonably be admitted that particular local factors play a prevalent role for the biological factors.

The age at diagnosis, in personal cases, varied between 3 and 57 years with an average of 24 years, as in other series [1697, 1109]. There is a slight male predominance.

21.4.3 Macroscopic Appearance

The tumor appears roundish and knobbly, encapsulated and well delimited, with a smooth surface. Sometimes the capsule is so thin and transparent as to allow the intracystic material to be seen. The color is usually whitish, and the consistency variable, mostly hard-elastic. On the cut surface, one or more cysts can be seen with a wall of variable thickness. In dermoid cysts (Fig.21.10), the inner surface shows papillae, and hairs, singly or in tufts (Fig.21.11), are visible together with material formed by amorphous greasy yellow masses of gland origin and by whitish, lamellar, friable debris produced by epithelial desquamation. In epidermoids (Fig.21.12), the wall is thinner and

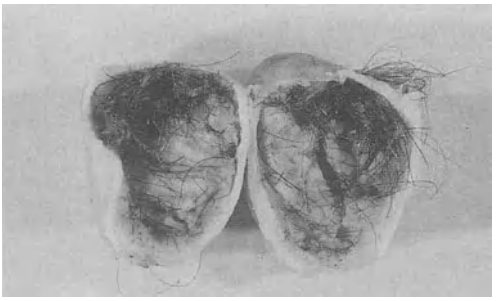


Fig.21.11. Hairs in a dermoid cyst

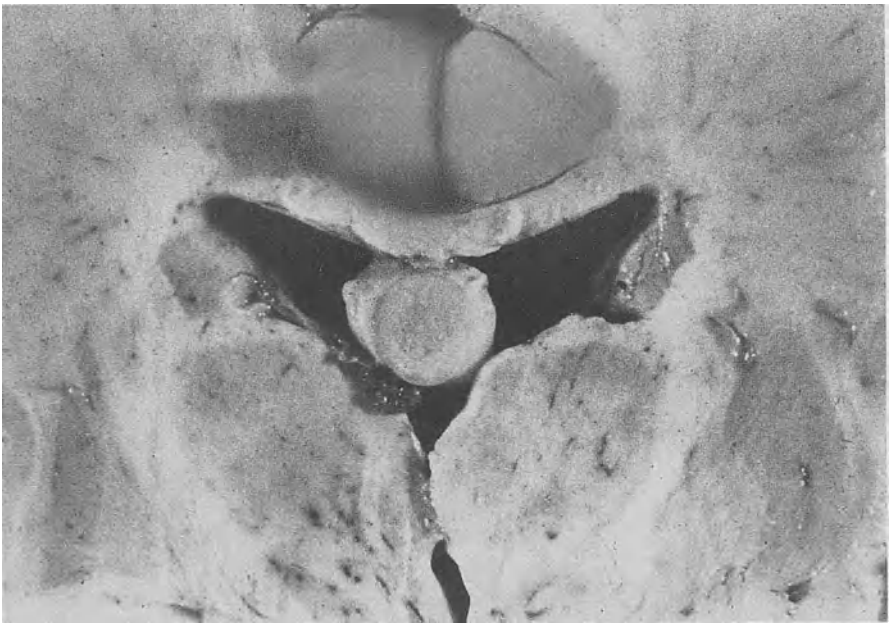


Fig.21.12. Midline epidermoid cyst

the content is almost always whitish, lamelliform, and squamous. In rare cases, the content may be liquid. Calcareous concretions can be found in the cyst wall.

21.4.4 Microscopic Appearance

In epidermoid cysts one finds, from outside inwards, a reaction zone, an epithelial lamina, and the cyst content. The reaction zone may be glial, gliomesodermic or simply mesodermic in relation to the site. In the last, hemorrhages are frequent. Lymphocytic and plasma-cell infiltrates, both around blood vessels and free in the tissue, are constantly present; less frequently, there are polymorphonuclear neutrophil or abundant eosinophilic infiltrates. Fibroblasts, macrophages, and calcifications are present as well.

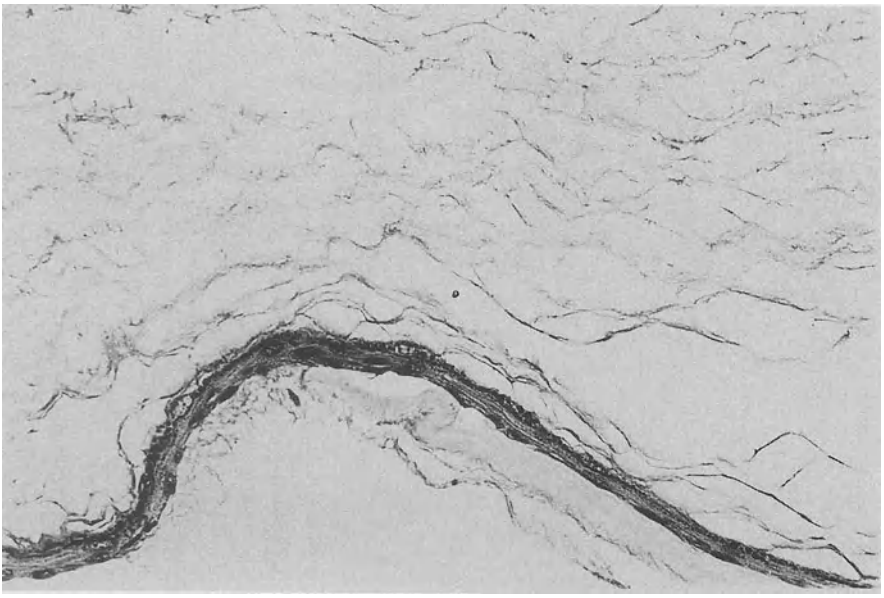


Fig.21.13. Epidermoid cyst, epithelial lamina and desquamation product, H&E, ×200

The epidermal layer is formed by a linear epithelial lamina with 1–3 layers of cells (Fig.21.13); rarely, in oblique cuts, it appears as 8–10 layers. When compared with normal epidermis, the stratum lucidum and corneum are frequently missing. The granular layer instead is almost always variable but present [2364]. The malpighian layer is constantly present and is often represented by a single row of cells. The cytoplasm is frequently scanty and vacuolated. The friable and whitish material forming the content of epidermoid cysts contains large quantities of cholesterol and fat.

In the dermoid cyst, a dermal tissue occurs between the reaction zone and the epithelial lamina. Numerous sebaceous glands, of great diagnostic importance (Fig.21.14), are usually found. The epithelium is multistratified and interlocked with the crests of papillae in the subepidermal region, which is formed by dense connective tissue. The various epithelial layers are well represented, particularly the malpighian layer, which is very wide. The granule cell layer may be interrupted in places, and is formed by elongated cells parallel to the surface of the cyst, whose cytoplasm is often rich in basophilic granules. The epithelium, generally, does not show substantial differences from that of normal skin.

21.4.5 Prognosis, Sequelae

The surgical removal of extraparenchymal dermoepidermoid cysts is usually technically simple. Instead, in intraparenchymal cases, especially spinal, it is difficult or impossible to carry out a complete excision. When the capsule has been completely removed,

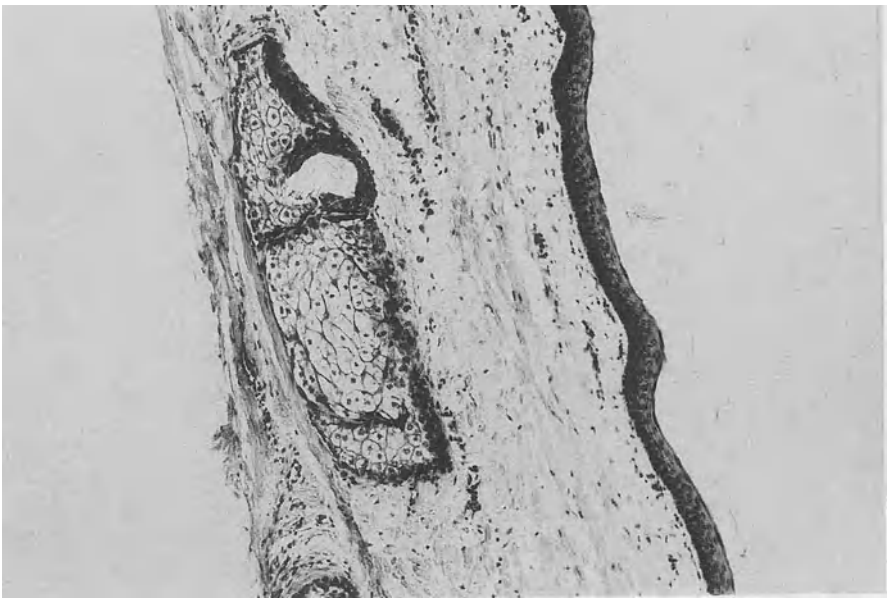


Fig.21.14. Dermoid cyst, epithelium and glands, H&E, ×200

recurrences are not observed, while in the partially ablated cases, recurrences do occur but usually long after the original operation.

Metastases have never been observed. The carcinomatous transformation of an epidermoid and the sarcomatous or carcinomatous ones of a dermoid are possible though exceptional events [1109, 3134, 2880, 945].

Aseptic inflammatory reactions of meningoencephalitic type to cholesterol are possible. These may arise both spontaneously, following rupture of the capsule because of necrosis, or following operation [147].

21.5 Craniopharyngioma and Epithelial Cysts

21.5.1 Embryogenetic Aspects

Craniopharyngioma may be considered among the tumors which have caused the most discussion in neuropathology, in relation to their embryologic origin.

The tumor which is today given the name "craniopharyngioma" had already been described in 1857 by Zenker [3117], in his presentation of an autopsy case of a cystic suprasellar lesion containing cholesterol crystals and squamous epithelium. The term "craniopharyngioma" was coined in 1932 by Cushing [541], who referred to the embryologic hypothesis formulated in 1904 by Erdheim on the origin of the tumors from remnants of the craniopharyngeal duct. In the formulation of his hypothesis, Erdheim

started from some observations of neuroembryology on the development of various structures of the hypophyseal region carried out years previously by Rathke and Luschka.

In 1838, Rathke described an irregular, globular invagination at the base of the skull, in the roof of the primitive stomodeum. From this structure, since then eponymously defined as "Rathke's pouch," the anterior portion of the hypophysis or adenohypophysis originates. Between the third and fourth week of gestation, the roof of the primitive stomodeum, which is lined by ciliated simple columnar epithelium, invaginates dorsally in the region immediately anterior to the oropharyngeal membrane, giving rise to Rathke's pouch. The pouch later becomes elongated and forms the orohypophyseal (or craniopharyngeal) duct, which undergoes progressive obliteration in the subsequent weeks. Towards the seventh week the duct is almost completely obliterated, remaining patent only in its cranial part, which is defined "hypophyseal pouch." At the same time, the infundibulum, which is lined by neuroepithelium, becomes elongated and protrudes posteriorly and inferiorly from the floor of the third ventricle, making contact with the hypophyseal pouch. In the meantime, the mesenchyme separates the base of the skull from the oropharynx, giving origin to the sphenoid bone and to the sella turcica.

Inside the hypophyseal pouch, the epithelium undergoes numerous infoldings until the pouch is occluded. As a consequence of epithelial proliferation, the pouch shows an anterior and superior rotational movement. The anterior and posterior walls of the folded pouch give origin to the anterior and intermediate lobes of the adenohypophysis. A small portion of the anterior wall further folds upwards, surrounds the infundibulum, and gives rise to the "pars tuberalis".

As has been said, the craniopharyngeal duct becomes obliterated, and as a rule it disappears. However, in 1860, Luschka described the presence of epithelial cells of squamous type in the infundibular region, which Erdheim interpreted as due to a phenomenon of aberrant persistence of embryonal residua of the craniopharyngeal duct. According to Erdheim, the upward rotational movement of the hypophyseal pouch, associated with the persistence of residua of the craniopharyngeal duct, is the cause of their dislocation in a suprasellar position along the anterior and lateral surface of the infundibulum. These nests of squamous cells could sometimes develop a proliferative capacity, thus giving rise to craniopharyngiomas.

Frazier and Alpers (1931) [818] and Cushing (1932) [541] referred to this pathogenetic hypothesis. The latter author was the first to use the term "craniopharyngioma," thinking that the cell remnants from which the tumor originated arose from an "imperfect closure of the hypophyseal or craniopharyngeal duct." Other authors agreed with this interpretation [3136, 909, 910, 1964, 2192, 907, 1853], but the dysembryogenetic-malformative hypothesis on the origin of the tumor was not accepted by everyone [1718, 2391, 2418]. The strongest criticism was that presumably squamous epithelial cells were not primitively present but derived by metaplasia from adenohypophyseal cells. It has in fact been demonstrated that the implant of "pellets" of tar compounds in the adenohypophysis of the rat may cause squamous metaplasia and also the development of epitheliomas [420].

The possibility was hypothesized of the squamous metaplasia of hypophyseal cells, in particular of the pars tuberalis, as the basis of the origin of craniopharyngiomas, by demonstrating the presence of squamous cells in 333 of 1364 normal pituitaries [1718]. According to these authors, squamous metaplasia has a progressively greater incidence in every later decade of life. However, subsequent observations have demonstrated nests of squamous cells even in the adenohypophysis of neonates [957]; in this case, it would be more opportune to speak of a congenital origin of such nests rather than of metaplasia. An attempt to unify both theories, dysembryogenetic and metaplastic, has recently been made [1336, 2846]. Two histologically distinct types of tumor are noted: an infantile one, resembling the epithelium of the tooth and of the oral mucosa of dysembryogenetic origin and an adult one lacking some of the histological characters of the former and with a tendency to form palisades and calcifications of probable metaplastic origin from adenohypophyseal cells.

The resemblance to the tooth is at the basis of a third hypothesis sustained by different authors [153, 1342, 2583, 44], i.e., the origin of the tumor from an aberrant migration of tissue from the enamel. In this direction, the term "adamantinoma" or "ameloblastoma" with which the craniopharyngioma was often defined [518, 818, 1265] would be more appropriate. Such a relationship is demonstrated by the recognition, though rare, of tooth elements or even of well formed true teeth

amongst the neoplastic tissue [153, 2193, 1342, 44]. However, other authors [2418] believe that craniopharyngioma cannot be considered identical to the adamantinoma of the jaw because of numerous histological differences.

The dysembryogenetic theory of Erdheim, reenacted by Cushing, maintained that nests of purely intrasellar squamous cells should give rise to tumors with the same frequency found in a suprasellar location, and it has been criticized [2420]. Pure intrasellar craniopharyngiomas have never been reported. Similarly, reports of craniopharyngioma of the pharyngeal hypophysis are lacking, even though nests of squamous cells have been described at this site. Craniopharyngioma could be likened to epidermoid cysts which can be found in proximity to the midline along the neural axis and of likely malformative origin, i.e., to heterotopia of ectodermal elements which occurred during the closure of the neural groove. Also, the distinction between craniopharyngioma and suprasellar epidermoid cysts would be histologically unfounded [2192].

The embryological considerations on the origin of the hypophyseal structures above mentioned are also relevant to explain other cystic malformations found relatively frequently and usually in the hypophyseal region [818, 150, 2598, 184, 909, 2418, 2324]. They are small, purely or mainly intrasellar cysts covered by cuboidal epithelium and discovered at autopsy. In rare cases they can, however, be quite large and cause an endocrine symptomatology or that of the empty sella syndrome [932, 3100, 1466, 117, 2929, 1984, 2728, 2383].

These structures are defined as "cysts of Rathke's fissure" because they are supposed to originate from Rathke's pouch, of which they represent the postnatal residue [3136, 2418, 1171, 1172, 3100, 1814]. They have a possible common embryological origin with craniopharyngiomas with which they, in fact, share histological features. In this sense, they would corroborate the dysembryogenetic hypothesis of Erdheim on the origin of craniopharyngioma.

21.5.2 Incidence

Craniopharyngiomas represent 1.2% of all intracranial tumors [3138]. They can affect both sexes and all ages in equal measure, showing, however, a predilection for the first 2 decades of life; more than half the cases, in fact, occur in children and adolescents.

Considering patients under 20 years of age, they represent from 8% to 13% of all cerebral tumors [123]. A peak in patients between 6 and 10 years of age has been reported. Craniopharyngiomas have also been described in neonates [1265, 2418], and the rarity of such observation is supposed to be due to the slow growth of the tumor. A bimodal age incidence with a second peak between 50 and 70 years has been reported [2418, 1336, 2192, 383, 1853]. When all suprasellar tumors are considered, the incidence of craniopharyngioma in children and adults increases to 54% and 20%, respectively [352].

The association with other oncotypes is an extremely rare event. A case of a suprasellar craniopharyngioma associated with a cystic temporal astrocytoma was reported [384]. The association in different individuals of the same family of gliomas and craniopharyngiomas has been reported as well in two families [2966]. The contemporaneous presence of arteriovenous cerebral malformations at different sites has also been noted [1932, 2689].

21.5.3 Site

The site is typically suprasellar. In a large series encompassing only adults, this site appears in 94% of cases [2192]. The contemporaneous intrasellar development is present

in 18% of cases at diagnosis but increases to 31% at autopsy [2192]. The pure intrasellar location is discussed [2418, 1853]. Russell and Rubinstein (1971) [2418] describe rare cases of dumbbell-shaped tumors developing through the diaphragm of the sella turcica. The intrasellar development of the tumor leads in general to compression or even to the destruction of the hypophysis.

Rarely has the presence of an ectopic hypophyseal gland been described in association with a craniopharyngioma [605]: In this event, the ectopic position of the gland is not supposed to be congenital but secondary to the growth of the tumor with consequent dislocation of the hypophysis.

From the primitive suprasellar site, the tumor may subsequently expand and involve adjacent structures such as the optic chiasm anteriorly in 35% of cases [2192], and the posterior, anterior, and middle cranial fossae in decreasing order of frequency [1932]. It has been demonstrated [1853] that the variation of the length of the optic nerves and hence the position of the chiasm may condition the direction of development of the tumor. Prechiasmatic craniopharyngiomas would tend to expand toward the anterior cranial fossa. On the contrary, when the chiasm is situated very anteriorly, the tumor develops mainly toward the interpeduncular fossa below, and toward the floor of third ventricle above.

Preferential sites in relation to age have been described [1336]: In children, craniopharyngioma grow predominantly suprasellar, while in adults it grows more commonly behind the sella, above the dorsum sellae, and in the interpeduncular cistern. This site difference is related to the developmental lines of the cerebral structures along which, as the cerebral hemispheres enlarge, the third ventricle and the brain stem occupy a more dorsal and caudal position in relation to the sphenoidal plane. In an exclusively intrachiasmatic case, the malformative nature of the lesion in relation to an ectopic migration of squamous cells from the hypophyseal peduncle inside the chiasm has been hypothesized [673].

The local invasiveness of craniopharyngioma appears to be more frequent than usually thought. The percentage of tumors involving the anterior, middle, and posterior fossae increases to 5%, 2%, and 4%, respectively, when autopsy cases are considered [2192].

Growth through the tentorium as far as occupying the cerebello-pontine angle has exceptionally been described [1932, 42]. Another case with abnormal extension to the nasopharynx, oropharynx, and orbits was also reported [1740].

Craniopharyngioma does not, as a rule, infiltrate the neural parenchyma; it shows extraneural growth only, even though it can have strong adhesions to the nervous tissue due to an intense reactive gliosis and to tumor digitations into the neural parenchyma. Direct invasion of the cerebral parenchyma has, however, occasionally been described, with destruction of the hypothalamus, basal ganglia, and brain stem [1265, 1011, 2959].

21.5.3.1 Intraventricular Tumors

The upward development of the tumor may lead to involvement of the third ventricle and cause internal hydrocephalus because of blockage of the CSF circulation. In the majority of cases, the tumor grows in the suprasellar cistern until it invaginates the floor of the third ventricle [965], in fewer than 4 of 100 cases [1932]. Sometimes the tumor cyst may rupture into the ventricular system. A true communication between the tumor cyst and the ventricle has also been described [2281].

Pure intraventricular growth is very rare [640, 388, 2411, 965, 2536]. Occasionally, it is not a primitive, intraventricular tumor, because a peduncle formed of blood vessels and stroma and even without traces of neoplastic tissue may represent the connection between the extra- and intraventricular growth [2536].

Some semantic confusion about pure intraventricular craniopharyngiomas arises from the histological similarity with epidermoid cysts of the third ventricle, which in some series are included among colloid cysts in this location [388].

As for the pathogenesis of pure intraventricular craniopharyngioma, it has been hypothesized that it develops from epidermoid cells situated in the floor of the ventricle in the region of the tuber cinereum [2411, 965]. The pure intraventricular craniopharyngioma presents some histological peculiarities, such as an absence of calcifications and of cysts [2411, 965], but they have not been confirmed in other reports [388, 2536].

21.5.4 Clinical Aspects

Apart from focal neurological signs, the most important clinical symptoms are those of intracranial hypertension. They are, in general, more pronounced in children [1500, 1167] and are attributed to the greater tendency of the tumor to grow above the sella toward the third ventricle until the foramina of Monro become obstructed.

Visual disturbances are very frequent. Apart from papilledema, visual, perimetric, and other deficits (uni- or bilateral temporal hemianopia, homonymous hemianopia, optic atrophy, etc.) are present. Other negative effects are due to endocrinopathies: loss of libido due to a deficiency of FSH and LH and a picture of hypothyroidism due to deficiency of TSH [2781]. In children, precocious puberty [352], diabetes insipidus, obesity, and hypothyroidism are often observed [1167]. The deficit of stature is characteristic [383]. A rare manifestation of craniopharyngiomas in adults is the amenorrhea-galactorrhea syndrome [69, 869]. This is caused by hyperprolactinemia, whose genesis is related to a deficit of secretion of prolactin inhibiting factor, due to compression of the hypophyseal peduncle by the tumor.

Intraventricular craniopharyngiomas have a different symptomatology. Endocrinopathies are, in fact, rare, and among these may be diabetes insipidus. Similarly, visual disturbances due to involvement of optic pathways are rare or absent. Characteristic and precocious is instead the symptomatology due to obstructive hydrocephalus with headache and progressive dementia [2411, 473].

Lastly, the rupture of the cysts may cause an aseptic meningitis due to the irritating action of keratin or cholesterol [2144].

Beside clinical manifestations, laboratory results have to be briefly mentioned. The most frequent sign is represented by calcifications on a plain skull X-ray. These may be present in at least 47% of adults [2192] and up to 80% of children [1336, 383]. Much more frequent in the suprasellar region, they have also been described within the sella [1336]. In this case, the incidence is at least 4 times greater than that found with pituitary adenomas [352]. Other details which may be found on a plain X-ray of the skull are changes of the sella [2192]. In children, the enlargement of the sella is very frequent, while in adults, the erosion of the dorsum is more typical [1336].

CT scan imaging has further refined the diagnostic investigations, permitting a higher percentage of positive findings than the straight skull X-ray [3087]. The more characteristic densitometric alterations are three: calcifications, cysts, and "enhancement" after contrast medium administration [352]. Of great help is MRI.

21.5.5 Macroscopic Appearance

Craniopharyngioma presents as two main types: solid and cystic (Fig.21.15). The cystic type is more common, but both may coexist. In an adult series [2192], 60% of the

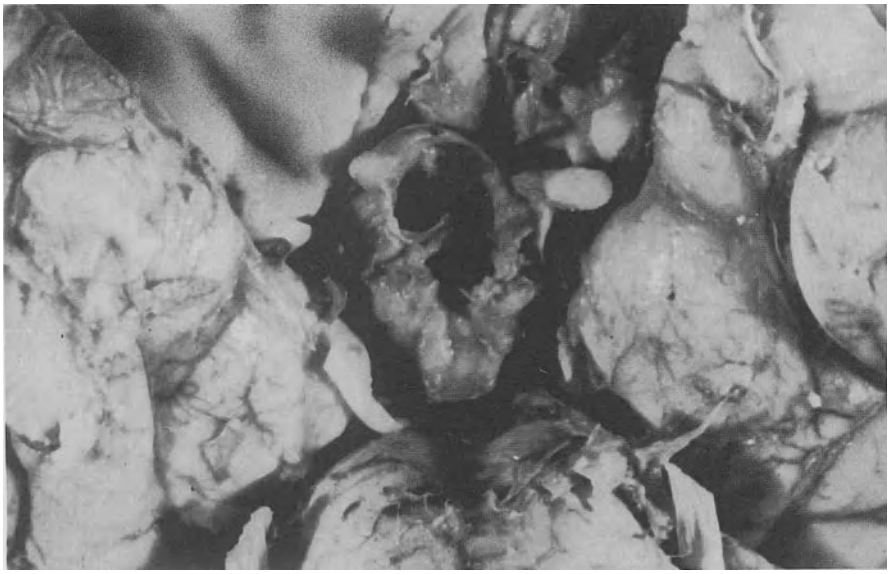


Fig.21.15. Cystic craniopharyngioma

craniopharyngiomas were purely cystic, 9% predominantly cystic, and 15% mixed. In a series of adult and infantile cases together, the solid type prevailed [2418]. The cysts may be of various dimensions, involve only the region of the tuber cinereum, or may expand and damage surrounding structures to reach remarkable dimensions [1466, 2281, 1985]. As previously seen, in the rare event of supra- and intrasellar development through the diaphragm of the sella, the tumor takes on a dumbbell shape [2418].

The tumor has, in general, well defined borders (Figs.21.16, 21.17) but may present clear adhesions to surrounding nervous tissue, in which it elicits marked reactive gliosis. It is therefore debatable whether a limiting capsule is present [473].

The average dimension at the time of operation is 3.5 cm [2192]. The surface is smooth or irregularly nodular. If the tumor is predominantly of the cystic type, it can simply be formed by a thin translucent membrane, while the solid component is reduced to an intramural nodule bulging in the cyst. The solid parts have a gray-red color and show an increased consistency, caused by the presence of calcifications. On the cut surface, they are gray and granular and often contain multiple foci of calcification, bone, and deposits of degenerated fat.

The cyst content is variable: In the majority of cases, it is dense, green-brown, greasy, and very rich in cholesterol crystals. In other tumors, instead, the cysts contain a clear, amber, gelatinous, or even dense or pasty fluid.

21.5.6 Microscopic Appearance

Two components may be distinguished, cellular and cystic. Craniopharyngioma can be defined as an "epithelial microcystic tumor" [2391], formed by nests or trabeculae of

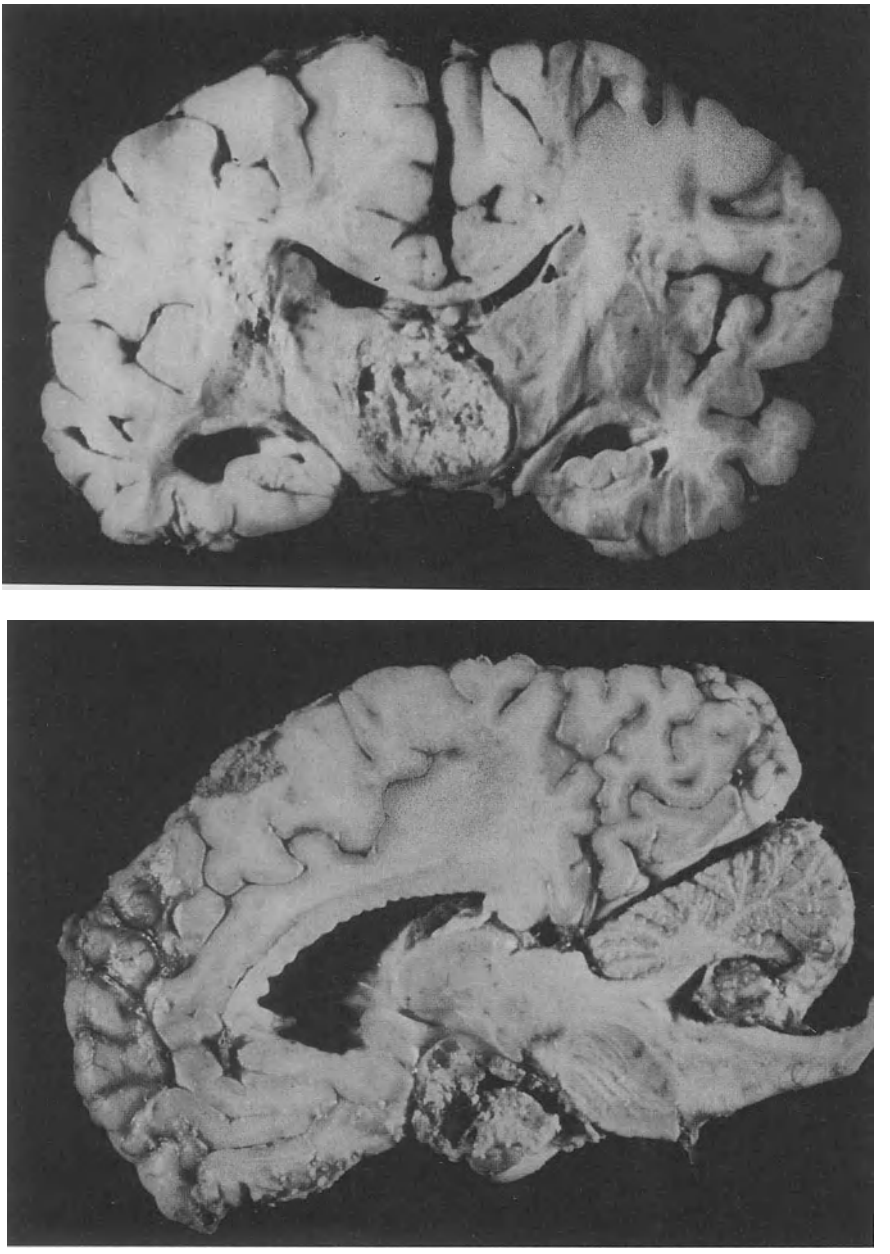


Fig.21.16a,b. Craniopharyngioma: **a** in coronal section; **b** in sagittal section

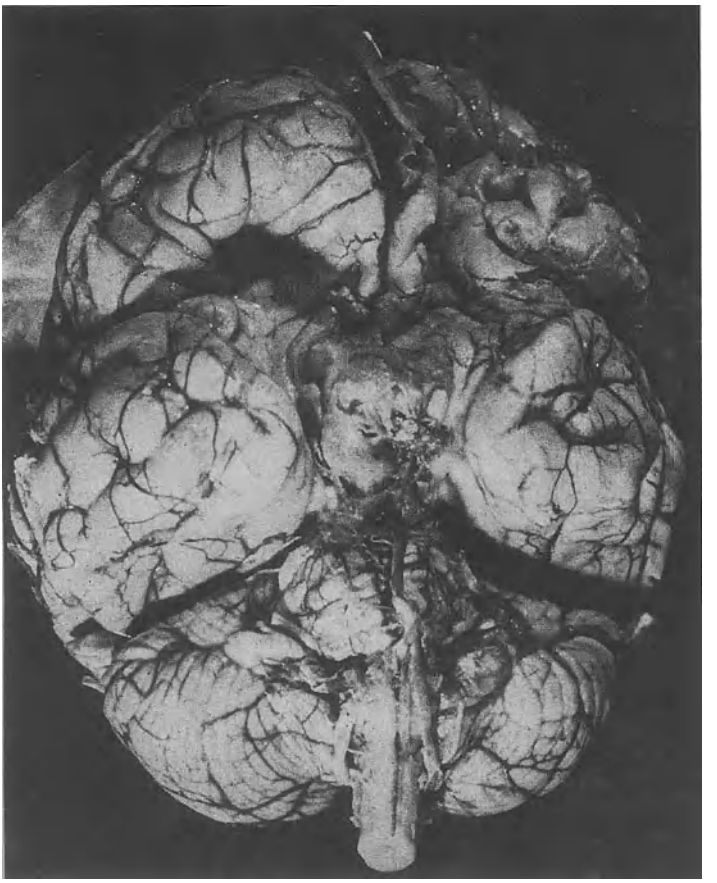


Fig.21.17. Craniopharyngioma from the skull base

variously anastomosed epithelial cells separated by a vascular connective tissue stroma (Fig.21.18a). Cells within nests and in the trabeculae have a polygonal appearance like those of the squamous epithelium and are often multilayered. In these cases, it is sometimes possible to recognize differences between the various layers, almost as if the cells take up the arrangement found in the epidermis. A columnar, cuboidal, intermediate, and spinous cell layers are recognizable [2486].

The columnar cells have a central nucleus with longitudinal intracytoplasmic fibrils like the cells in the basal epithelia [2418]. The columnar cell layer delimits the periphery of the nests and rests on a basement membrane which, in turn, separates the epithelial nests from cystic spaces or stromal trellises (Fig.21.18b). The squamous epithelium often shows features of full "maturation," giving rise to whorl structures and to foci of keratinization, sometimes with the formation of true keratin pearls (Fig.21.19a).

Beside areas with squamous epithelium, other areas have been described, often in the same tumor, in which the columnar cells take up a ramified or stellate appearance

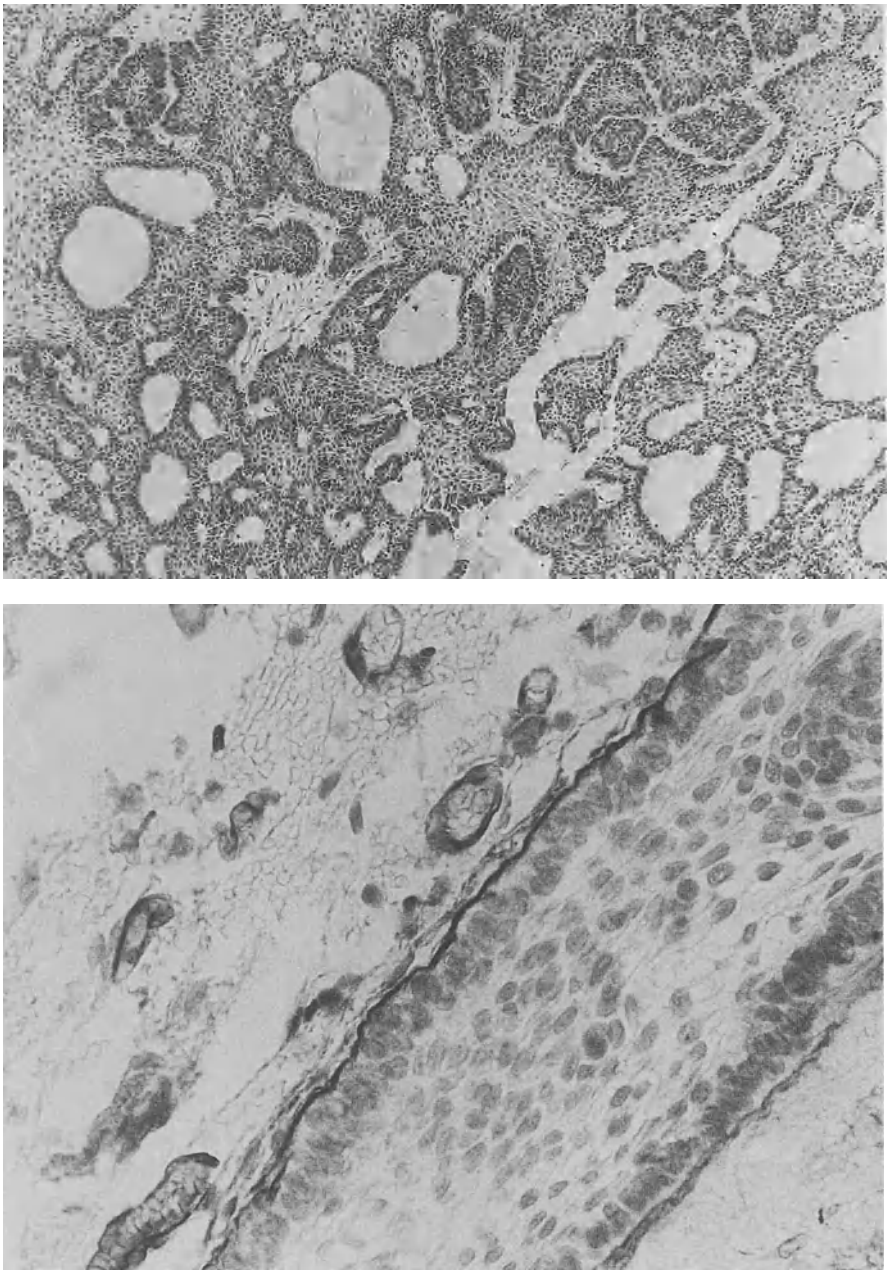


Fig.21.18a,b. Craniopharyngioma: **a** epithelial nests and trabeculae with cysts and stroma, H&E, ×150; **b** basement membrane between epithelial nests and stroma, laminin PAP-DAB, ×400

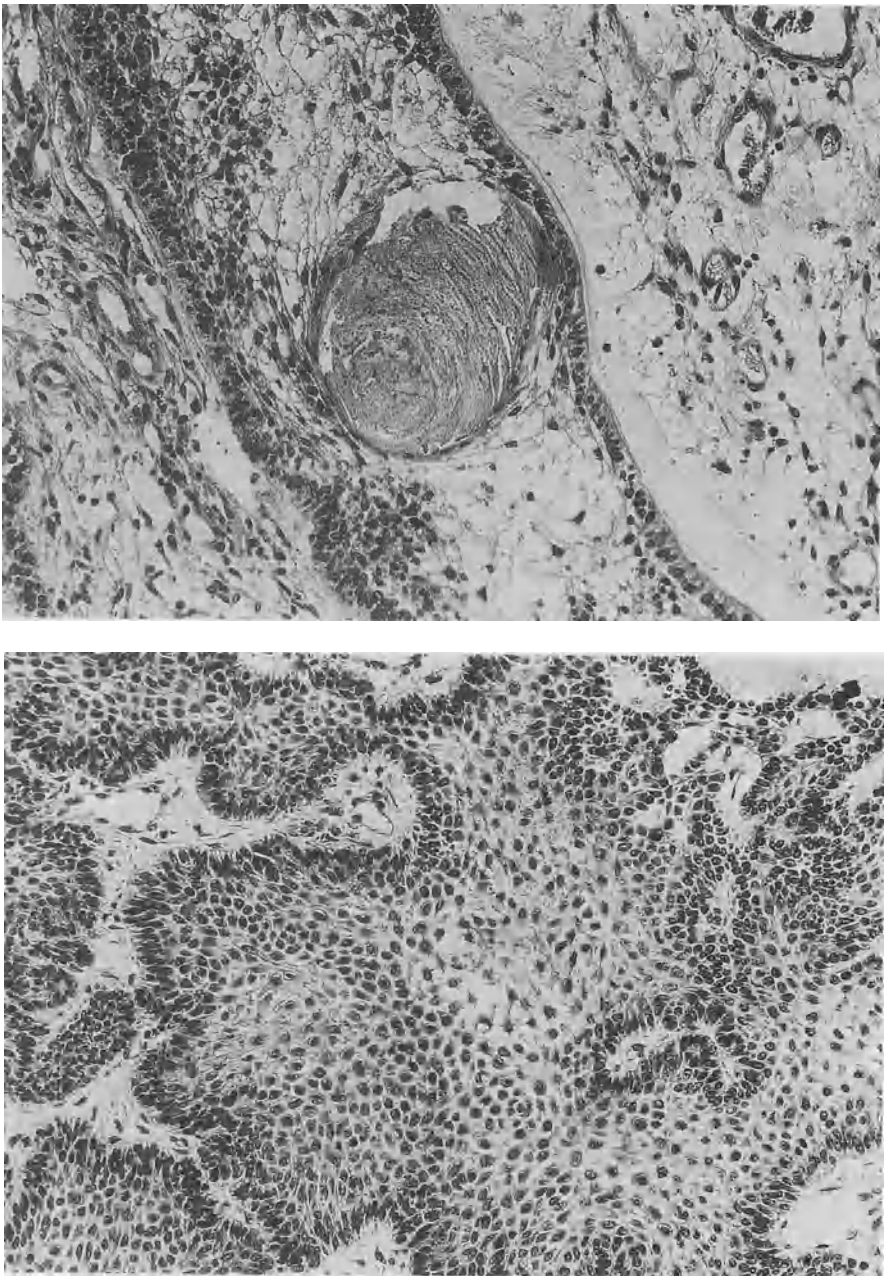


Fig.21.19a,b. Craniopharyngioma: **a** keratin pearl, H&E, ×400; **b** "adamantinomatous areas," H&E, ×400

and show numerous thin prolongations. These cells appear dissociated because of the presence of a finely fibrillar matrix and, consequently, give the tissue a trabecular appearance, maintaining reciprocal points of contact only through thin prolongations. The inner zones of these areas often undergo degenerative changes, so that the most centrally situated cells lose their fine cytoplasmic processes. The tissue then takes up a cribriform appearance because of the presence of numerous microcysts. These areas are often defined as "adamantinomatous" (Fig.21.19b), in that the resulting tissue is reminiscent of the appearance of adamantinomas of the jaw [153, 2193, 153, 1342, 2583, 44].

Similarly, the extreme similarity of the stellate cells of these areas with the reticular stellate cells described in the pulp of the tooth during tooth formation has been stressed [518, 909].

The origin of craniopharyngioma from the primitive stomodeum [722] could itself facilitate odontogenesis within the tumor. In fact, rare observations on craniopharyngiomas in which tooth formation was evident have been made [153, 44, 153, 1342, 2583]. In one case [44], admixed with tumor tissue, 20 teeth were present, the majority of which were well formed.

The term "adamantinomatous" is also used by some [818] to refer to areas in which columnar cells form palisades, which recounts the arrangement described for ameloblasts of the enamel. This reference is, however, improper because in craniopharyngioma the cells tend to be stratified, while the ameloblasts are arranged in a single layer [2418]. Russell and Rubinstein [2418] defined as adamantinomatous those tumor areas in which trabeculae of degenerated and dissociated columnar cells take up an appearance similar to that of the mesenchymal tissue produced by ameloblasts during enamel formation. In their opinion, therefore, the analogy is only descriptive and not embryological. However, others maintain that ameloblasts may as well be considered epithelial in nature, despite their resemblance to cells of the connective tissue, and sustain the correspondence (not only descriptive but also embryological) between ameloblasts and the stellate cells of craniopharyngioma [909].

Adamantinomatous areas often arise within squamous areas or are surrounded by a single layer of columnar pseudostratified cells resting on a thin basal membrane. In other cases, cell nests may be formed by areas with adamantinomatous features in whose center squamous cells are found.

The mixture between the two cell types, seen on light microscopy study, gives evidence of a common origin, the stellate cells deriving from the squamous ones because of degenerative phenomena. The limits between areas with one cell type and areas with the other cell type may also be clear-cut, whereas in still others, transition zones may be found. Often the tumor may be totally squamous or adamantinomatous. Some authors [1336, 2846] believe that two different histological types of craniopharyngioma can be distinguished. One type is typical of children but can also be observed in adults, and it is analogous to that described above. A second, rarer type occurring in adults is characterized by an epithelium which forms islands, delimits small cysts, and lies immersed in a connective tissue matrix or makes contact with nervous tissue. Neither keratinization nor calcifications are observed, and cell degeneration and the formation of large cysts are rare. This second type originates by metaplasia of suprasellar nests of squamous cells, as described by Luse and Kernohan [1718].

Craniopharyngiomas with a papillary appearance (Fig.21.20) have recently been described in adults [916]. They constitute a subtype, per se, with particular clinical and histological characteristics and a worse prognosis.

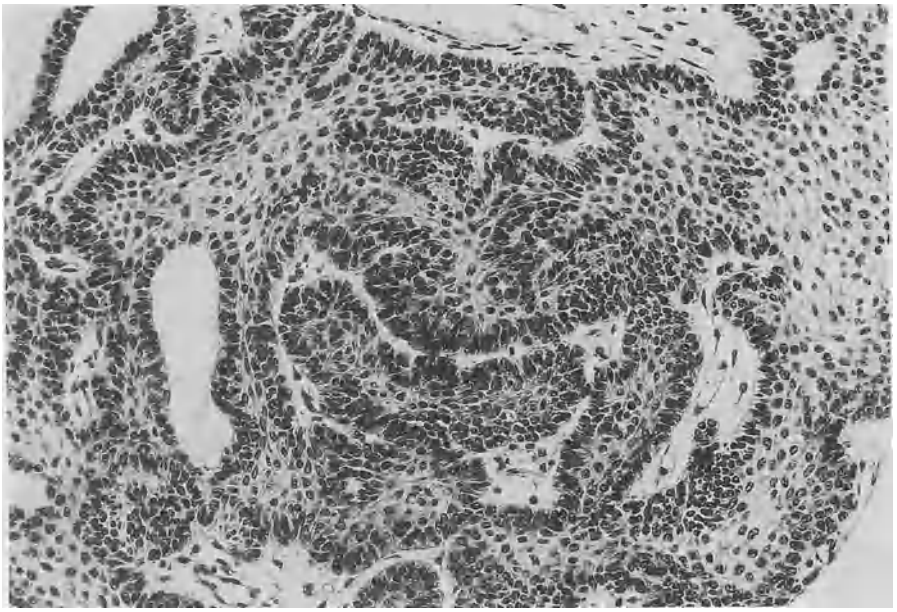


Fig.21.20. Craniopharyngioma, papillary appearance, H&E, ×400

21.5.6.1 Electron Microscopy and Immunohistochemistry

Tumor cells are extremely variable in dimension, shape, and relations [909, 443, 1668, 2935, 1853]. Common and constant characteristics are the extreme richness in cytoplasmic organelles, the presence of complex junctional apparatuses, and the abundance of tonofilaments. The cells possess notable quantities of glycogen, osmiophilic secretory granules and lipid inclusions. The smooth and the rough endoplasmic reticulum and the Golgi apparatus are well developed, and there is a large number of mitochondria. Microtubules are occasionally found. The nuclei sometimes present invaginations of the envelope, while the chromatin is mostly arranged peripherally.

The cell surface is provided, especially in the central part of the trellises, with numerous microvilli among cells of polyhedral aspect ("prickle cells") (Fig.21.21). The microvilli of juxtaposed cells delimit extracellular spaces of variable amplitude, sometimes with a microcystic appearance. Two types of intercellular junctions can be recognized, more numerous tight junctions and desmosomes formed by a thickening of juxtaposed membranes about 400 nm in length and 30–40 nm wide. Bundles of short and poorly developed 50–70 Å tonofilaments frequently project on desmosomes (Fig.21.22). Bundled or scattered tonofilaments may also be seen in the cytoplasm, especially in maturing epithelial cells sited in the center of the trellises. The cells at the periphery, with a lesser number of tonofilaments, have a cylindrical shape and rest in a single layer on a basement membrane outside which connective tissue or cystic spaces are found. The nuclei are oriented perpendicularly to the basement membrane. These cells have hemidesmosomes toward the basement membrane and develop complete desmosomes between each other. A large number of desmosomes and interdigitations between the cytoplasmic processes are visible between cells situated immediately internally to the cylindrical cells.

Stellate cells in the center of the epithelial nests, loosely arranged and elongated, show the same ultrastructural features. They are rich in tonofilaments and desmosome type junctions among

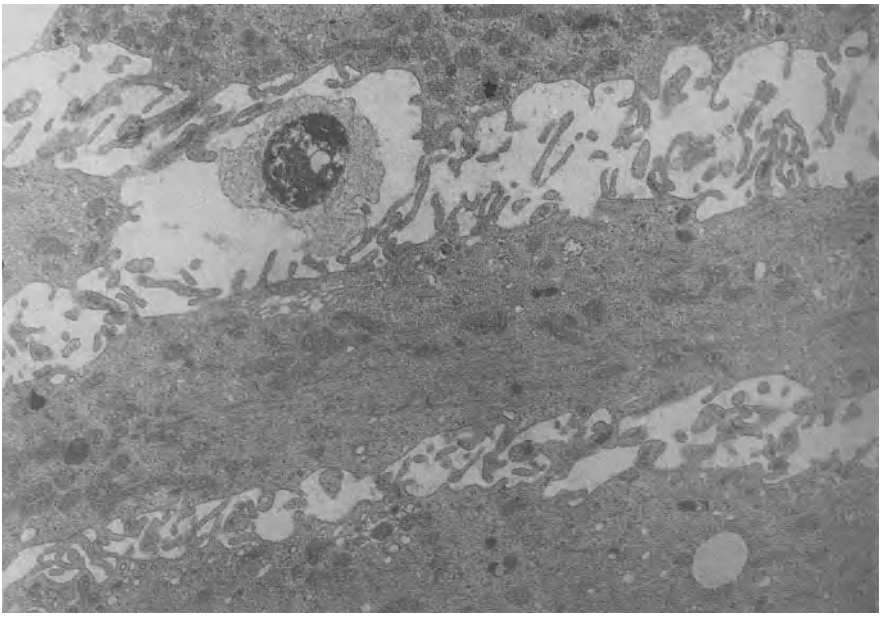


Fig.21.21. Microvilli and "prickle" cells, ×40,000

the long and thin cytoplasmic processes, which sometimes delimit more or less large cystic spaces. The stellate cells derive from a regression of polygonal cells due to the marked expansion of the surrounding extracellular spaces [909]. Their resemblance to cells of adamantinomas and ameloblastomas of the mandible has already been emphasized [909].

A finely reticular material, different from that of the basement membranes delimiting some cysts, is observed along the cytoplasmic membrane of stellate cells, close to the cyst lumen (909). Analogous material has been found in some superficial epithelia including squamous cells of the skin undergoing keratinization.

Keratinization has been discussed for a long time from the histochemical point of view, as related to the presence of acid mucopolysaccharides, sulfhydrylic groups, and sulfur bridges [804]. Keratohyaline granules have also been described in the cytoplasm of some cells with light microscopy study [909, 2192]. Some authors [2849, 3136], however, deny the existence of the keratinization process, rather characteristic of the so-called suprasellar epidermoid cysts, with which craniopharyngiomas have been confused [2418]. A possible distinction between craniopharyngiomas and epidermoid cysts, however,[2192] would not be based on the presence of keratin, but on the finding of adamantinomatous areas, which are lacking in epidermoid cysts. In the absence of such areas, the only differential criteria are the "greater tendency" to stratification and keratinization shown by epidermoid cysts.

Ultrastructurally, the tonofilament masses represent the molecular substrate of keratohyalin [443, 910, 1565, 1668, 2935, 1853, 2454]. The cells situated in the center of the epithelial trellises show "massive fibrillary hyperplasia" [443] and degenerate. The tonofilament bundles become extremely thickened (up to 200 nm) and are arranged without order in the cytoplasm. When the cells die, the masses of tonofilaments take up the features of electron-dense bodies corresponding to the keratohyalin granules seen under light microscopy. The debris of disintegrated cytoplasmic organelles participates in the process [443]. The process of keratinization in craniopharyngiomas is different from the analogous process in the epidermis, only because it does not occur in an orderly manner [909].

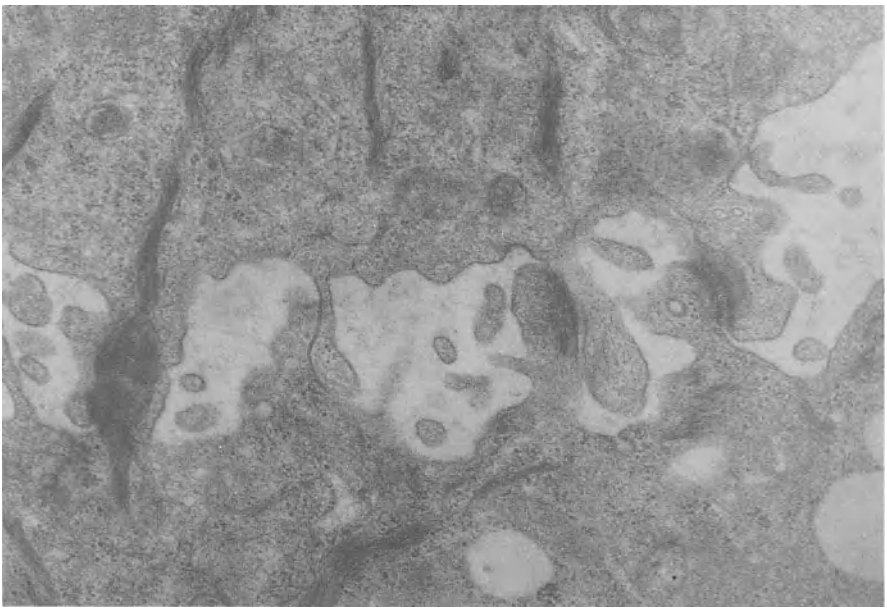


Fig.21.22. Tonofilament and desmosomes, ×40,000

Antibodies to keratin have confirmed immunohistochemically the presence of cytokeratin in craniopharyngioma, in the cytoplasm of both squamous and stellate cells. A positive reaction was also observed in squamous cell nests in the pars tuberalis of the normal hypophysis and in the cylindrical cells delimiting the intrasellar microcysts of the pars intermedia (Rathke's cleft cysts). On the contrary, the cells of the normal and tumor adenohypophysis and tissues of neuroectodermal derivation did not react. It should be remembered that in a normal and a tumor hypophysis, microfilaments, but not tonofilaments, can be demonstrated [1496].

21.5.6.2 Calcification

Closely correlated with keratinization is the process of calcification. It is a frequent occurrence and a point of distinction from adamantinomas of the jaw [909]. Its incidence is very high, up to 75% of cases in series comprising only adult cases [2192] and even higher in series including children [1336]. It can be so marked as to be seen on a plain skull X-ray.

Microscopically, it more often involves adamantinomatous areas (35%) but may also be found in squamous areas (15%), in the stroma (13%), and in the surrounding neural parenchyma (11%) [2192]. The histological type, typical of adults [1336] and considered of metaplastic origin, does not contain calcifications and keratin. Both characteristics are also absent in the papillary variant [916].

Investigation by X-ray microanalysis [2935] has demonstrated that the calcified areas contain Mg, P, and Ca, with the greatest peak for P. Diffraction studies have demonstrated that the Ca is present as hydroxyapatite crystals [1565]. In general, the calcification process takes place in areas in which masses of keratin are demonstrable [2418]. Under the electron microscope, calcium deposits are found in proximity to such masses but also in intact cells [909] or in cystic spaces apparently devoid of keratin [909, 1853]. The calcium aggregates recall the morphology of hydroxyapatite crystals of bone.

The genesis of the calcification process has been documented ultrastructurally [1565, 2454]. The cells undergoing keratinous degeneration lose their complement of organelles, the cytoplasmic membrane, and often also the nucleus. In the cytoplasm, needle-shaped apatite crystals become demonstrable among the tonofilaments and within vesicles lined by a 150–500 nm membrane. The vesicles, perhaps degenerated mitochondria, are the primary focus of deposit of the hydroxyapatite crystals, analogous to what is observed in the formation of psammomatous bodies in meningiomas [1663]. The coalescence of vesicles and calcified tonofilaments leads to the formation of large, calcified bodies. The tonofilaments are likely to orient the precipitation of the hydroxyapatite crystals. The process of calcification may extend in some cases to the production of true lamellar bone [2418].

21.5.6.3 Cystic Component

The cystic component of craniopharyngioma may prevail, and the solid part can be confined to a small intracystic node.

The cysts may be subdivided into three varieties according to the lining cellular component. Stromal cysts are more often of microcystic type and contain eosinophilic clots and sometimes aggregates of foamy cells (Fig.21.23). They are recognized ultrastructurally by the basal columnar cell lining with a continuous basement membrane on the luminal side. Such cells are considered to correspond to the cells of the germinal layer of the epidermis [909].

In loose adamantinomatous areas, microcysts derive from the coalescence of small, extracellular, dilated spaces. Also, the cells delimiting the cyst are of the basal columnar type, but the basement membrane is situated on the side opposite to the lumen. The cells have long processes connected by junctional complexes [909, 2935] and are often covered, on the luminal side, by the reticular material described previously. A third type of cyst, also affecting the epithelial component, originates from the maturation and subsequent exfoliation of degenerated squamous cells (Fig.21.24a). These cysts are delimited by a stratified squamous epithelium and often contain keratin debris and calcium deposits. Ultrastructurally, the squamous cells of the luminal rim show numerous microvilli [909, 2935] and are occasionally covered by a rim of keratin [909].

The microcysts mostly belong to adamantinomatous areas, and the cysts of large dimension may be lined by squamous epithelium and only rarely by stellate cells [2418]. More frequently, however, the macrocysts are lined by various cell types at the same time, sometimes demonstrating transitional forms between squamous and adamantinomatous elements [2192]. The cysts in adamantinomatous areas and those resulting from maturation have been examined under the scanning electron microscope [2935]. Microvilli were easily visible in both. Stellate cells often showed numerous vesicular processes on the luminal surface, indicating exocytosis or pre-keratinization.

The stromal component of the craniopharyngioma is discretely vascularized, and, apart from microcysts, it is also the site of regressive changes such as myxoid degeneration and calcifications [2192, 2391, 2418, 3136].

Stromal microcysts are due to local vascular changes with consequent colliquative necrosis and also extravasation of proteins and fluid because of the increased capillary permeability. Ultrastructural investigations have demonstrated numerous capillary abnormalities [1139, 1853, 2935]. Capillaries are immersed in an extracellular matrix rich in collagen, and the basement membrane is often reduplicated. The endothelial cells contain pinocytotic vesicles, filaments, microtubules, and often Weibel-Palade bodies [1139]. The intercellular junctions are well developed; however, they do not give rise to "tight junctions" [1853].

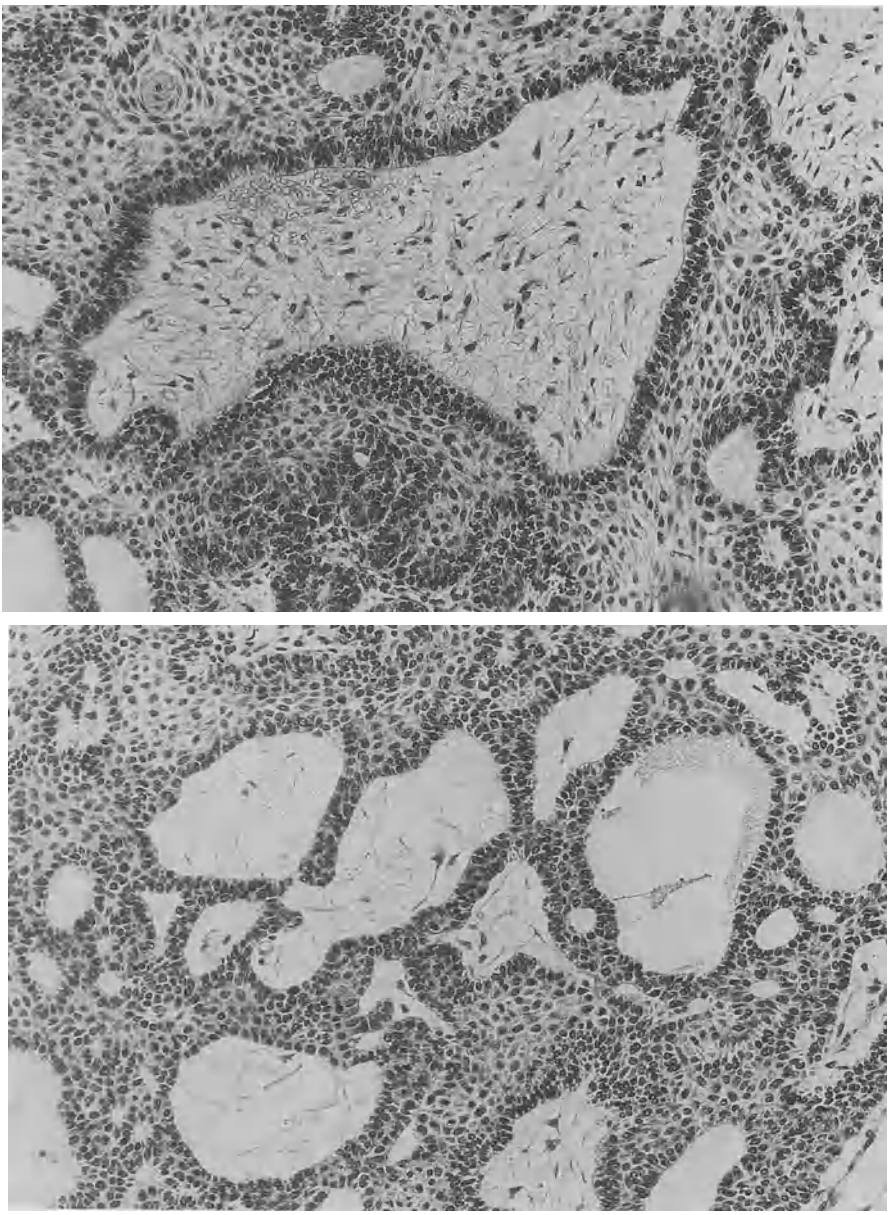


Fig.21.23a,b. Craniopharyngioma, stromal cysts in evolution from **a** to **b**, H&E, ×300

Fenestrations formed by small 50-nm pores, which favor the exit of liquids and proteins to the extravasal spaces, are frequently observed. The fenestrated capillaries could arise from a proliferation of blood vessels originating from adjacent sites like the hypophysis and hypothalamus whose system of capillaries has fenestrae [1853]. Alternatively, they are characteristic of the tumor, on the basis of the finding of fenestrated capillaries in tissues similar to craniopharyngioma, like the skin [1139].

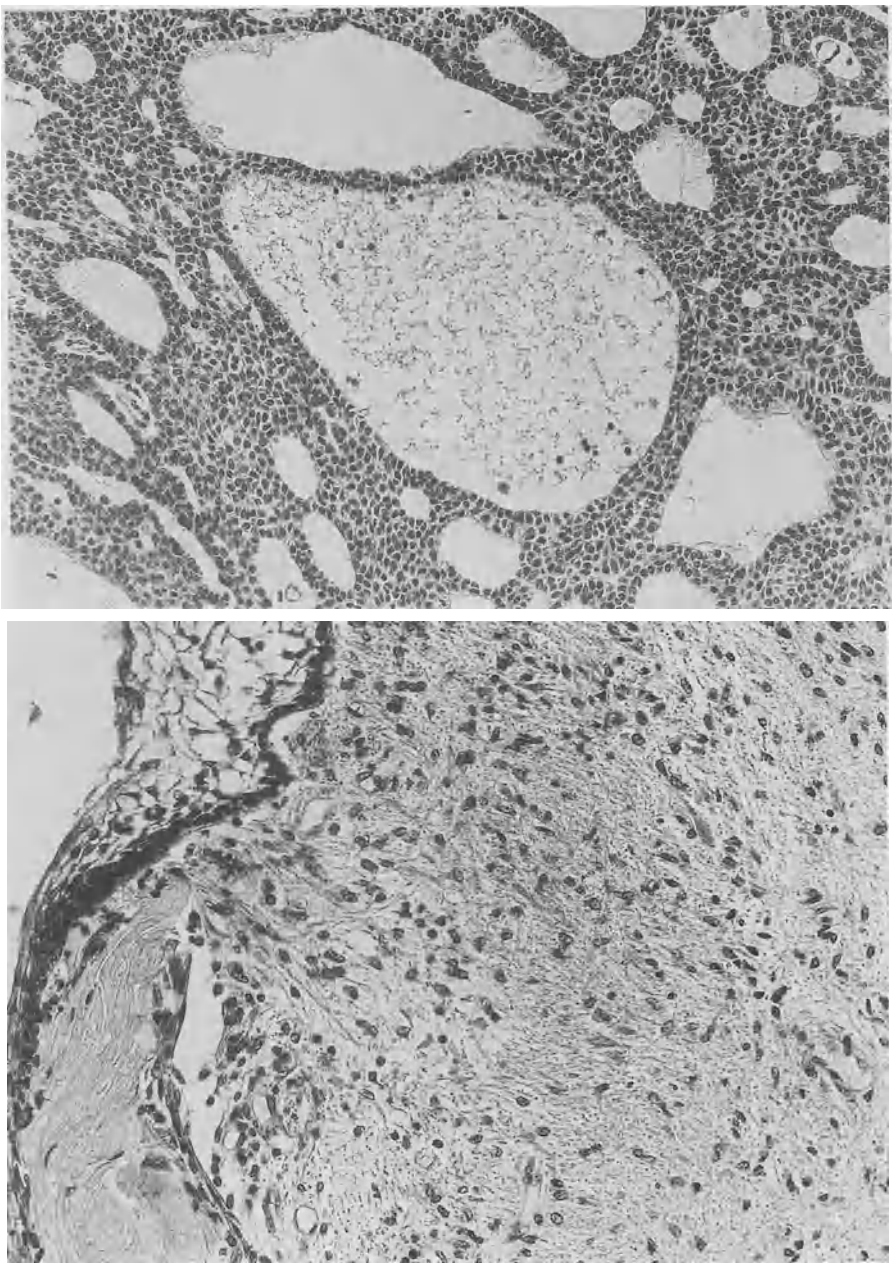


Fig.21.24a,b. Craniopharyngioma: **a** epithelial cyst, H&E, ×300; **b** reactive gliosis with Rosenthal's fibers around the tumor, H&E, ×200

21.5.7 Adjacent Tissue

Although the tumor is circumscribed and occasionally shows an apparent capsule, numerous adhesions with blood vessels, cranial nerves, or the arachnoid–pial surface of the brain are present. The relationships between tumor and brain parenchyma vary in the different patterns. Sometimes, the tumor grows in association with cerebral tissue without compressing or eliciting any reaction. In these cases, the neural tissue surrounding the tumor appears malformed and constituted of bundles and streams of small glial cells, like those seen in other precocious congenital malformations [1336]. More often, however, the neural parenchyma is compressed or the site of an intense fibrillary reactive gliosis. A subependymal astrocytic reaction has also been described in rare cases of craniopharyngioma with intraventricular growth [965, 2536]. The fibrillary gliosis is often associated with numerous Rosenthal's fibers (Fig.21.24b) [3136, 2391, 2418], similar to those seen in cerebellar astrocytomas [909]. Inflammatory cells, lymphocytic infiltrates, and foreign-body-type giant cells may be observed within the tumor and in the adjacent cerebral parenchyma [3136, 1336, 2192, 2418]. Both gliosis and chronic inflammation have been related to the release of keratin and cholesterol from the tumor [1668, 2192]. Even though the cholesterol is produced by a mechanism of cellular degeneration and subsequent colliquation, in vitro observations demonstrated that it is actively produced from viable cells of the tumor [1668]. Similarly, in tumors produced by intracerebral implantation of oral epithelium in the rat, an accumulation of cholesterol crystals was observed at the viable periphery of the tumor and not in the necrotic center [2908]. An increased cholesterol production has been found in vitro in cultures of craniopharyngioma which featured an aggressive behavior both in vivo and in vitro [1668].

An aggressive clinical behavior with a tendency to invasiveness and local infiltration has been repeatedly stressed [1011, 2391, 2958]. This is in part due to the impossibility of a radical surgical extirpation due to the location of the tumor. However, the growth of small prongs of neoplastic tissue (Fig.21.25) within intensely gliotic areas, which in the past were erroneously attributed to carcinomatous degeneration [2418], may impede total removal and be responsible for recurrences [909, 1853].

Although malignant degeneration has never been observed in the prongs [2391, 2418], atypical features have sometimes been identified at the ultrastructural level [1668].

21.5.8 Relationships of Craniopharyngioma with Rathke's Fissure Cyst

Recently, cases of suprasellar craniopharyngioma have been described in which some cuboidal and columnar cells featured well developed cilia or vacuoles filled with PAS-positive material [1814, 977]. In one case, squamous and columnar cells were resting on the same basement membrane and showed transitional features between the two types [1814]. Furthermore, two different histological features in dumbbell craniopharyngiomas have been described [2418]: The suprasellar portion was formed by typical squamous elements and the intrasellar one, by a cuboidal or ciliated epithelium. The importance of these observations derives from the fact that analogous features (cylindrical ciliated cells and mucin secretory granules) are characteristic of the so-called Rathke's cleft cyst [150, 2599, 184, 3100, 1387, 2929, 634, 635]. As has been said in the embryogenetic section, it is thought that intrasellar residua of Rathke's pouch, occasionally found only postmortem (13%–22% of all autopsies), may give rise to small cysts or to structures like glands between the anterior and intermediate lobe of the hypophysis [635, 977, 2418]. Very rarely, the cysts may become symptomatic, as in 63 cases reported up to 1982 [2728]. Likely, in these cases, the cellular residua start

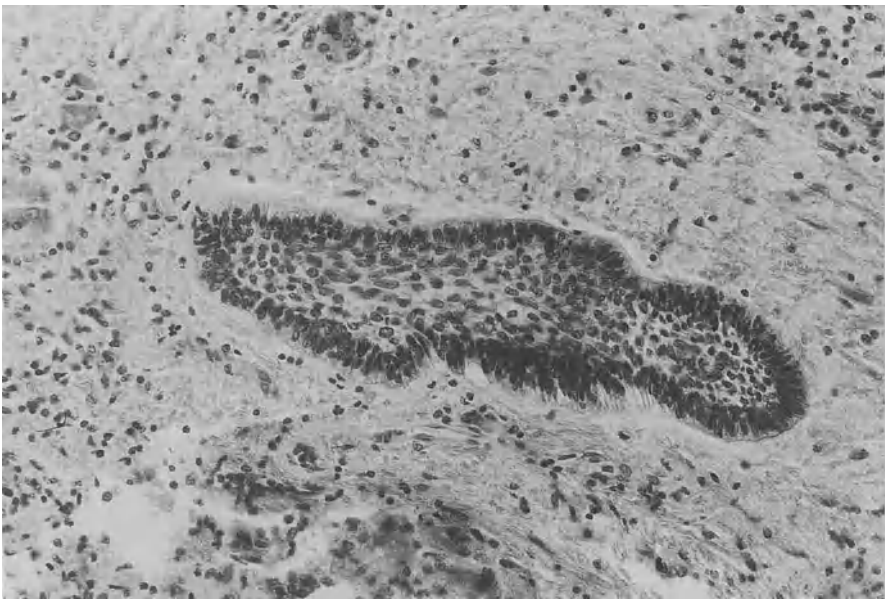


Fig.21.25. Craniopharyngioma, prong of epithelial tissue in an area of gliosis, H&E, ×300

again to proliferate and form cysts filled with mucin. The expansion of the cyst, usually intrasellar, but with suprasellar extension in a third of cases [2383], may cause hypopituitarism, compression of chiasm, obstructive hydrocephalus, and sometimes the "empty sella" [932, 3100, 117, 2929, 1467,2728, 1984, 2383]. The finding of completely suprasellar cysts is very rare [2383, 2418]. These cases can be distinguished from craniopharyngioma even on macroscopic grounds because their content is fluid and mucinous and not of the "machine oil type."

In the majority of cases described, the histological appearance is constant: The cyst wall is composed of a single layer of cuboidal or ciliated columnar epithelium containing signet ring cells and resting on a basement membrane (Fig.21.26a). The cells have cilia with a typical 9+2 microtubular arrangement, microvilli, and junctional complexes of ependymal type [634]. PAS- and mucicarmine-positive material is present both within cells and in the cystic cavity [977]. Calcifications are mostly absent [3100, 2383], with exceptions [977]. Keratin and cholesterol deposits are also lacking. The wall may contain chronic inflammatory cells [117, 2383]. In one case, amyloid has been demonstrated in the stroma underlying the basement membrane, likely due to the presence of peptides released by the compressed hypophysis [481].

Beside these frequent aspects, numerous histological variants have been reported, often within the same cyst. The epithelium may be simple columnar or pseudostratified, cuboidal, cylindrical with or without cilia, or vacuolated and may form papillae with intraluminal projections or intraparietal glandlike structures [2636, 634, 977].

Rarely, isolated foci of squamous cells with keratinization, ultrastructurally identical to the analogous cells of craniopharyngioma [3100, 1466, 634], have been described [2636, 3100, 1387, 2929, 634, 977]. The ultrastructural study of cells from a cyst in culture has furthermore revealed cellular elements with transitional characteristics between squamous cells and cylindric cells, either ciliated or containing secretory granules [3100].

If, then, in their more typical histological aspects, craniopharyngiomas and cysts of Rathke's cleft may be easily differentiated, it should be remembered that the distinction between the two lesions is important because of their different clinical behavior. In contrast to craniopharyngiomas, Rathke's cleft cysts do not have an invasive appearance, do not recur, and can be surgically treated by simple drainage and opening of the wall [481, 634]. In mixed cases, it is, therefore, impor-

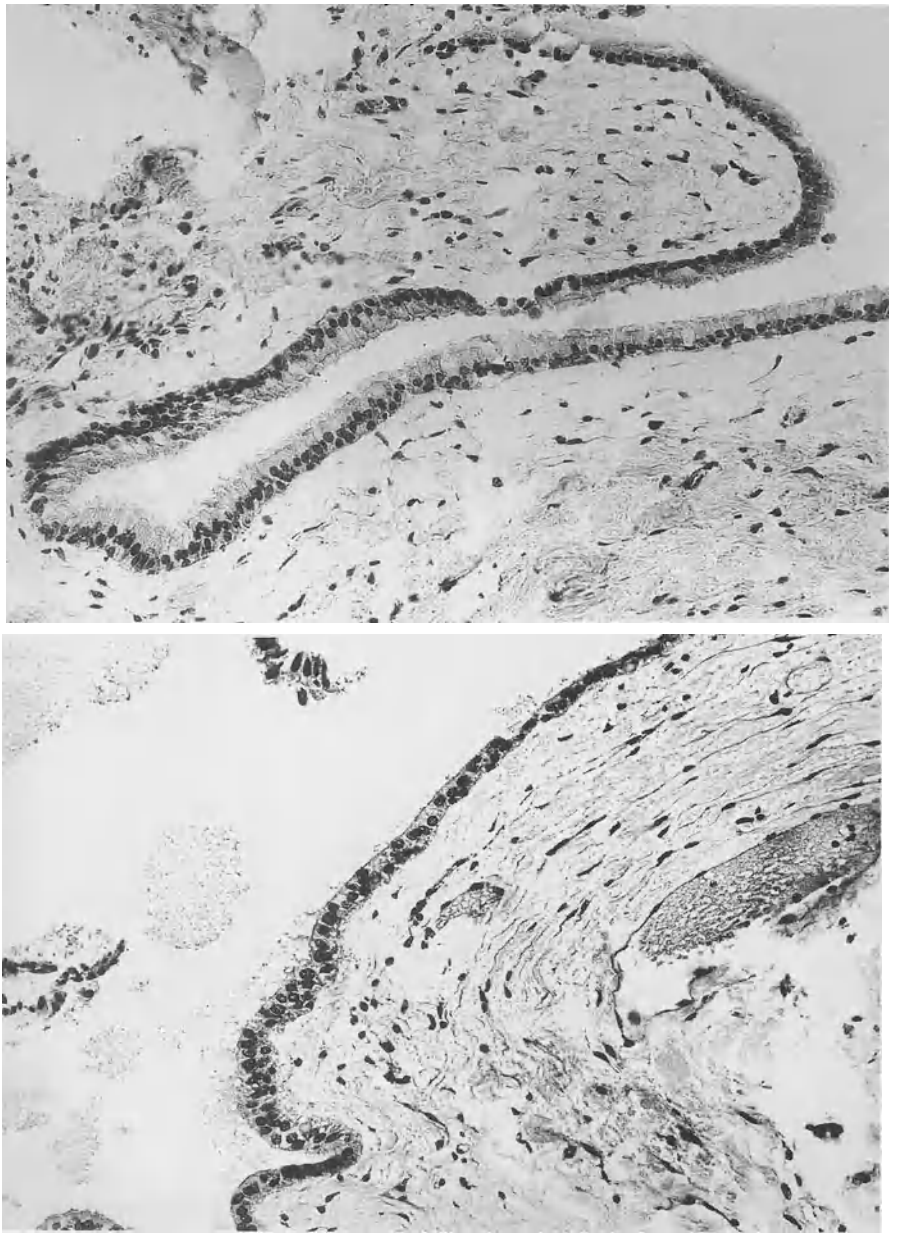


Fig.21.26. a Rathke's pouch cyst, H&E, ×300; **b** colloid cyst, columnar epithelium, H&E, ×300

tant to evaluate the predominant epithelial type before attributing the tumor to one of the two oncotypes. It has been reported that symptomatic cysts of Rathke's cleft containing squamous epithelium have a more aggressive behavior, tend to recur, and behave, in practice, like craniopharyngiomas [2383].

The existence of cases with intermediate characteristics between craniopharyngiomas and Rathke's cleft cysts is considered in general as an index of the common embryological origin from remnants of the epithelium of the stomodeum [2418, 1171, 1172, 3100]. However, histological findings typical of Rathke's cleft cysts, i.e., cilia, mucin, and acid mucopolysaccharides, may also be found within neuroepithelial structures (choroid and ependymal epithelium) [2636, 634]. A mixed origin for the cellular elements of the cysts, beginning with neuroepithelial residues for columnar epithelium and with residues of the epithelium of the stomodeum for the squamous elements, has therefore been proposed [634,635]. As an alternative, the squamous component could have a metaplastic origin from the cuboidal or columnar epithelium [2418].

The possible origin from the neuroepithelium is confirmed by the histological similarity of these cysts with colloid cysts of the third ventricle. These structures, which are today mostly considered as nonexclusive of the third ventricle and with a possible manifestation on the midline along the whole neuraxis [2635, 1138, 910, 2637, 17, 1038], would then be different from Rathke's pouch cysts only for the exclusively ventricular situation.

The origin of colloid cysts themselves is still hotly debated. The classic view is that they are of neuroepithelial origin [2635, 2418,634]; however, analogies with the epithelium on the basis of ultrastructural findings have been observed [1139, 910, 1134, 907, 1932, 3087, 1038], as well as the presence of various cellular types, columnar, ciliated, columnar nonciliated, stratified squamous. Squamous cells of colloid cysts furthermore possess tonofilaments [907] and tight junctions of the macula adherens type which are not characteristic of the neuroepithelium and are found instead in cysts of Rathke's cleft and in craniopharyngiomas.

On the basis of the histological findings, craniopharyngioma, Rathke's cleft cysts, and colloid cysts of the third ventricle could have a common embryological origin from the epithelium of the primitive stomodeum. The three neoplasias may therefore be framed in a "continuum," differing from each other on the preponderance of a certain cellular type and on their anatomical location.

21.5.9 Prognosis, Treatment

The choice of the optimal therapeutic approach for craniopharyngioma is still very controversial. Three choices have been put forward: surgery, radiotherapy, and chemotherapy. The evaluation of the results of treatment from the literature is not straightforward for two reasons: (1) The follow-up period is often too limited, and (2) series based on more than one therapeutic protocol are very rare.

The need for surgical intervention is universally recognized; however, there is disagreement with respect to the extent of surgery. The "radical" operation offers, on average, 80% long term control of the neoplasm [1801, 1359, 2776, 1167, 2604, 48, 1853, 2781]. Recurrences are usually observed within 2 years [383]. However, there are reports of recurrences after some decades from an operation which was otherwise judged to be radical [1336]. The best results are obtained with noncalcified tumors with a diameter under 3 cm [2604].

The radical operation is criticized by various authors [2192, 1933, 352, 2846, 383, 780, 1746] because of the subsequent severe neurological and endocrine damage. It has, however, to be remarked that the same histological characteristics of the tumor, with the formation of prongs in the surrounding neural parenchyma and the absence of a limiting capsule, renders the term "radical" improper [383]. In the Toronto group's experi-

ence, over 60% of craniopharyngiomas in childhood can be totally resected with minimal significant morbidity and mortality [1169A]. Radical surgery is recommended by the vast majority of pediatric neurosurgeons [2442A]. On the other hand, subtotal removal alone is not useful in the control of the tumor: The survival at 5 and 10 years is 34.9% and 27.1%, respectively [1746]. These figures notably improve if subtotal removal is associated with radiotherapy [2192, 48, 1933, 352, 2846, 383, 780, 1746], and in this event it becomes 89% and 76%, and the incidence of recurrence at 10 years is below 25% [383]. In a series of 37 children [781], failures after total removal were 57% versus 7% in patients undergoing more conservative surgery. In series including only adult cases, however, the 5-year survival after subtotal removal and radiotherapy is only 50% [2192]. Though craniopharyngioma is a theorically radioresistant tumor [352, 2791], the results given above demonstrate the efficacy of radiation treatment. Some authors have proposed associating radiotherapy with the most conservative surgical treatment so as to limit the damage to the hypothalamus and optic tracts [1933, 2846]. It is thought that the main effect of irradiation is to decrease the amount of fluid within the cyst [1167]; however, there are histological data which demonstrate the total destruction of the tumor after radiotherapy [1500,48]. The doses usually employed are around 5000–6000 rads, with fractionation (200 rads/day). There appear to be no differences in the survival figures in relation to the histological type [1746].

Radiotherapy itself is not, however, immune from possible negative effects. There are reports of mineralization of the basal ganglia, frontal lobes, and hypothalamus [780], late necrosis, and occlusive angiopathy [48, 1933, 780]. The development of astrocytomas [2689] and of meningiomas [1933] has also been described. Within the confines of radiation therapy for craniopharyngiomas with a marked cystic component, endocavitary irradiation (brachytherapy) by means of various types of isotopes (^{32}P, ^{198}Au-, ^{90}Y, ^{186}Re) has been proposed [1467, 1980]. The dose at the wall is 30,000–40,000 rads. In both series, the follow-up demonstrated obliteration of the cysts.

From all these experiences, it can be deduced that the best results are obtained by total surgical removal; however, the larger the tumor, the greater is the damage to intracranial structures. On the other hand, radiotherapy may lead to other damage to the nervous structures. The only solution is to remove the tumor surgically when it is still small, that is after an early diagnosis [3096]. It must be taken into account that the clinical features of adamantinous and squamous papillary tumors are different in adults and children [11].

The intratumor injection of bleomycin during operation has been proposed as an alternative to radiotherapy [2791]. Such a drug has in fact been demonstrated to be very efficacious in the therapy of squamous cell carcinomas, especially in cystic tumors.

21.6 Neuroepithelial and Nonneuroepithelial Cysts

21.6.1 Colloid Cyst of the Third Ventricle

These lesions also go under the name of neuroepithelial or paraphyseal cysts, as it is generally thought that they originate from the paraphysis. This structure has the appearance of a racemose gland, is present in the human embryo measuring from 17 to 100

mm, and then disappears. At the same time, the diencephalic ependymal pouches develop, and both these and the paraphyseal pouch may become isolated as closed vesicles and give rise to colloid cysts. This interpretation is valid for the colloid cysts of the anterior part of the third ventricle. Although this is the most frequent and most important location, neuroepithelial cysts have also been found elsewhere, for example, in the fourth ventricle and in the lateral ventricles. Six cases from the literature plus a personal case have been reviewed [590].

Not everyone agrees that the cysts originate from the paraphysis. Some authors believe that they originate from the choroid plexus [1087] or from the plexus and ependyma [2635]. According to some, the origin of the third ventricle cysts are identical to that of cysts of the lateral ventricles, only the location is different [590]. They arise from an embryonal ependymal diverticulum as telencephalic or diencephalic cysts. Actually, they develop because of folding of the neuroepithelium in or outside the ventricle and therefore could originate wherever there is an ependymal lining. In relation to the third ventricle, these authors maintain that the cysts arise from the paraphysis, which is nothing else but the choroid plexus [2633].

21.6.1.1 Frequency, Age, Site

Colloid cysts of the third ventricle are more frequent in pathological than in neurosurgical series. In autopsy material, cysts were found in more than 50%, 66.2%, and 50% of telencephalic, diencephalic, and myelencephalic plexuses, respectively [688, 2633]. However, the majority of these cysts are asymptomatic. They represent 0.5% of all brain tumors [1234], are very rare in infancy and appear prevalently in males. Adults are more usually affected.

Neuroepithelial cysts may originate at all sites at which neuroepithelium normally exists. The literature has numerous reports of cysts with diverse locations, even in the cauda equina [1928]. However, as it has already been said, those of the third ventricle may have a particular clinical importance.

21.6.1.2 Macroscopic Appearance

The cysts are spherical, of various dimensions and strongly adherent to the surrounding tissue. In the third ventricle, they adhere to the stroma of the choroid plexus in correspondence to the foramen of Monro. The content is usually dense and hyaline.

21.6.1.3 Microscopic Appearance

The cyst is usually lined by an often ciliated, cuboidal or columnar epithelium (Fig.21.26b). Sometimes, however, the epithelium may be lacking. The content of the cyst is PAS- and mucicarmine-positive. A similar reactivity, but in small droplets, has been found in the cytoplasm of cells lining the cysts [1949, 2633], as may be observed in the choroid plexus and in the ependyma [2633].

Under the electron microscope, the cyst epithelium has been demonstrated to be of ependymal type [1715, 2824].

In a case report [507], the epithelium was formed by cells of two types. In some areas, these were cuboidal or columnar, intermittently adherent to each other by means of "apical bars." The intercellular spaces were filled with a proteinaceous fluid, and the cytoplasm was rich in organ-

elles. In other areas, instead, the cells were ciliated and contained abundant mitochondria and cilia. These had the usual 9+2 tubular arrangement, while others were abnormal.

21.6.2 Spinal Enterogenous Cysts

These cysts are lined with columnar, intestinal-type epithelium (Fig.21.27) and are located in the spinal canal, usually but not always in an extramedullary situation [1062].

They may be intra- or extradural [18], and they are usually situated in the cervical and dorsal segments. The lining epithelium is columnar and PAS-positive, sometimes formed by goblet cells containing mucus, or sometimes featuring foci of squamous hyperplasia [2391, 1813].

The origin of these cysts has been much discussed. According to some, they are similar to gastroesophageal cysts, and this would be supported by the existence of simultaneous vertebral anomalies. According to others, instead, their pathogenesis would have to be considered together with that of Rathke's pouch cysts and with that of colloid cysts of the third ventricle.

21.6.3 Arachnoid Cysts

The characteristics of these cysts are a thin wall and a situation between the inner layer of the dura and the arachnoid membrane. They contain a clear and colorless or xanthochromic and strongly proteinaceous fluid, are relatively frequent, both in adults and children, and are found mainly in the Sylvian fissure, in the cerebellopontine angle, along the midline in the posterior fossa, or in the cerebellar hemispheres. In the spinal cord, they may be both epi- and subdural, are posteriorly situated in relation to the dorsal nerve roots, and may be multiple [343]. The wall is formed by a collagenous membrane covered by arachnoid cells. The adjacent neural tissue may sometimes appear atrophic and gliotic.

The origin of arachnoid cysts is variable. They may result as a consequence of episodes of leptomeningitis or following trauma, even at birth, or be of malformative origin [2301]. They may be clinically silent or may become large and cause hydrocephalus.

21.7 Lipoma

Craniospinal lipomas belong to the group of rare tumors of the nervous system. Nevertheless, since the last century they have raised notable interest because of their origin, which is still being debated at present.

Virchow [2942] considered lipomas the result of hyperplasia of adiposomeningeal cells, whereas for Gowers [986] they represented a degenerative process of neural structures. Bostroem [267] put them into the same group as dermoepidermoid cysts derived from a dysembryogenetic defect,

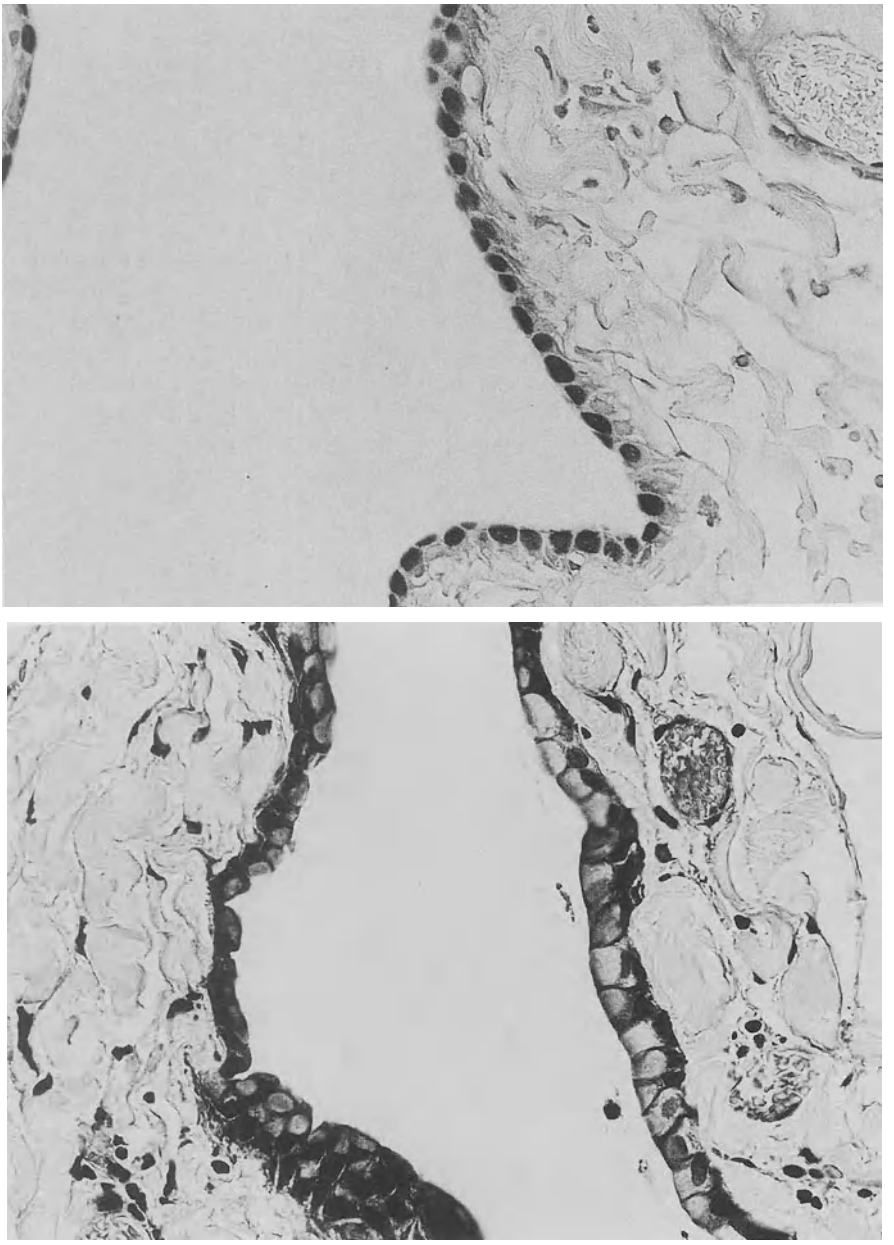


Fig.21.27a,b. Spinal enterogenous cyst. **a** PAS-positive goblets, PAS-hematoxylin, ×400; **b** positivity for cytokeratin, PAP-DAB, ×400

characterized by remnants of adipose cells of embryonal type. Of the same opinion later were others [2928] who connected lipomas with the persistence of meningeal embryonal mesenchyme. Subsequently, Scherer [2474], followed by others, took up and developed this hypothesis and thought that lipomas derived from the primitive embryonal mesenchyme as a result of the transformation of multipotent cells present around the capillaries. Because the mesenchyme of both mesodermic and ectodermic origin participates in the anlage of the leptomeninges, the idea that lipomas had to be considered as hamartoblastomatous processes of ectodermal origin [696] was also put forward. It has been observed that lipomas which develop some time after gastrulation contain only adipose tissue, whilst those which arise immediately after are characterized by the presence of mesodermal derivatives such as bone. Lastly, those related to a disturbance which occurred before or during gastrulation feature neuroectodermal elements in addition to mesodermal ones [2954].

In favor of the dysontogenetic concept of the origin of these tumors are their topography and their frequent association with dysraphic anomalies and various malformations. For example, the concomitant presence of pes cavus [137], of subcutaneous lipomas at the site corresponding to the spinal lipoma [696, 859], of a pilonidal sinus [317], of spina bifida, of osseous defects and meningomyelocele [3119, 2345] have been described.

Despite the fact that the dysembryogenetic concept is today accepted by the majority of researchers, a classification on an embryological basis does not appear sufficiently documented. However, from the practical point of view, it is useful to subdivide these tumors according to a topographic criteria into cranial and spinal, midline and lateral, intradural and extradural [2743]. There are elective locations, such as the corpus callosum, which form the majority of cases in various series.

21.7.1 Frequency, Age, Site

Lipomas are rare even if not exceptional tumors. They represented no more than 0.5% of all intracranial tumors in the collection of Bailey [107]. Only 4 intracranial lipomas were found in a series of 5000 autopsies [2954]. Thirteen cases have been reported [318A].

The lesions are seen most often in the corpus callosum [1109, 3136, 3119], and they are frequently associated with dysraphic abnormalities [1372]. Other reported sites include the infundibulum, quadrigeminal plate (especially its caudal part), choroid plexuses of the lateral and third ventricles, basal and convexity cisterns, spinal cord (extending from a few to several segments, especially in relation to the posterior funiculi [1498, 2474, 3134, 852, 1049, 318, 1372]). Recently, two lipomas localized in the mesencephalic tectum and rostral pons, associated with Pickwick's syndrome, have been reported [2620]. Extradural lipomas are more frequent in the middle and lower thoracic segments, while the intradural ones are located at the upper thoracic, cervical and conus–cauda equina level [930, 2200].

The age of occurrence is difficult to establish because they may appear in the young and in patients of middle age, but may also be found incidentally at autopsy. On the other hand, in the literature, some lipomas in the senile [1728, 3088] and infantile age group [2415] have been reported.

Both sexes are equally affected.

21.7.2 Macroscopic Appearance

They have a roundish or flattened, variable shape adapted to the site at which they are located and are of different sizes, from that of a pea to voluminous masses. Generally, they are translucid in appearance, yellow, soft-fattish in consistency and are demarcated from the surrounding tissue by a connective tissue capsule. In some cases, the capsule is lacking, and they seem to infiltrate the neural tissue which, however, does not show histological features of a true neoplastic infiltration. Lipomas of the corpus callosum sometimes occupy a large part of this structure, which appears more or less malformed up to complete agenesis. Lipomas of the third ventricle may grow and cross the foramen of Monro. Spinal lipomas appear elongated in the direction of the cord to which they are tenaciously attached, so that their surgical removal is practically impossible.

21.7.3 Microscopic Appearance

Histologically, they show the classical structure of mature adipose tissue, organized into lobes and lobules, with connective fibrous tissue bands. In frozen sections, methods for staining adipose tissue constantly demonstrate lipid material, mostly triglycerides, in the cell cytoplasm. In some cases, smaller cells with a hyperchromatic nucleus and acidophilic granular cytoplasm, similar to embryonal adipose cells, are seen among the mature adipocytes [107]. When the number of such cells is high, the structure of the tumor is similar to that of the xanthomas. The fibrous connective tissue bundles, besides subdividing the parenchyma into lobes and lobules, at the periphery of the tumor orient in parallel and form a capsule. When the connective tissue is particularly abundant, these tumors acquire features of fibrolipomas. The blood vessels are scarce and are mostly represented by small arterioles and venules, but in rare cases they may be very numerous and show an angiomatous appearance [2954]. Calcifications have frequently been described as roundish concretions both in the capsule and in the surrounding tissue [3119, 376, 3088]. The presence of mature bony structures has been reported in some cases [376].

21.7.4 Prognosis, Treatment

Lipomas are histologically and biologically benign tumors. Total removal leads to complete cure without recurrence, but the site and mode of growth frequently impede total excision. From the practical point of view, spinal lipomas have a greater importance because they more frequently give rise to clinical symptoms [2832].

21.8 Hamartomas, Ectopias, and Ectopic Tumors

21.8.1 Hamartoma of the Hypothalamus

By definition, hamartoma is a benign, nodular, tumorlike mass formed by a mixture of differentiated tissues normally present in the organ in which it is found, but in an abnormal location [24, 2318, 1645]. This lesion is rare in the CNS and is most frequently found near the hypothalamus.

Macroscopically, it appears as a mass with well-defined contours which projects from the floor of the third ventricle into the meninges. It is often connected by means of a peduncle to the tuber cinereum and to the mammillary bodies [2318, 1667], or it is free or has more points of attachment to the hypothalamus [116, 2051, 2621]. It is whitish, hard, and homogeneous in appearance.

Histologically, it is composed of neurons of different shapes and sizes (Fig.21.28a,c). According to some, they do not resemble those of the hypothalamus [1182, 3142], but others believe they do [1654, 2240, 533]. Myelinated and nonmyelinated fibers [2037], a normal glial component, and sometimes gliosis are found among the neurons (Fig.21.28b).

The hamartoma is mostly found in children and is associated with precocious puberty. This association has been explained either by the existence of anatomical connections with the hypothalamus [2318, 3069, 1645], by the presence of LH-RH [1347, 535] and of GDH-RH [533] in the neurons of the hamartoma itself, or by compression on the hypothalamus [45].

The efficacy of surgical treatment for the endocrine syndrome is controversial [1347, 2322], even if the development of microsurgery has allowed marked improvements in surgical results [1347, 1546].

Hypothalamic hamartoma may be associated with multiple congenital anomalies: small or absent olfactory bulbs, absent hypophysis, hypoplastic adrenals and thyroid, cryptorchidism, cardiac and renal malformations, sindactylia, anal atresia, etc. (Hall-Pallister syndrome). It sometimes presents histological characteristics closer to a tumor so that its differentiation from a gangliocytoma or ganglioglioma becomes difficult.

21.8.2 Granule Cell Tumors

They have been described by Abrikosof (1926) [7], may occur in almost all organ systems, and are nodular in shape and mostly benign. Their cell origin has not yet been fully clarified: Striated and smooth muscle cells, fibroblasts, Schwann cells, histiocytes, and mesenchymal cells have been considered as the cell source. Most probably they derive from Schwann cells [1956, 427, 1934].

A granular cell accumulation may be found in the posterior pituitary stalk and in the infundibulum as hamartomatous lesions, the so-called choristomas or tumorettes [2600, 346]. Sometimes they change into tumor.

Very rarely, they occur intracranially, in the sella region [154, 2912], or intracerebrally [452]. They show mostly a malignant behavior, and histologically their nature

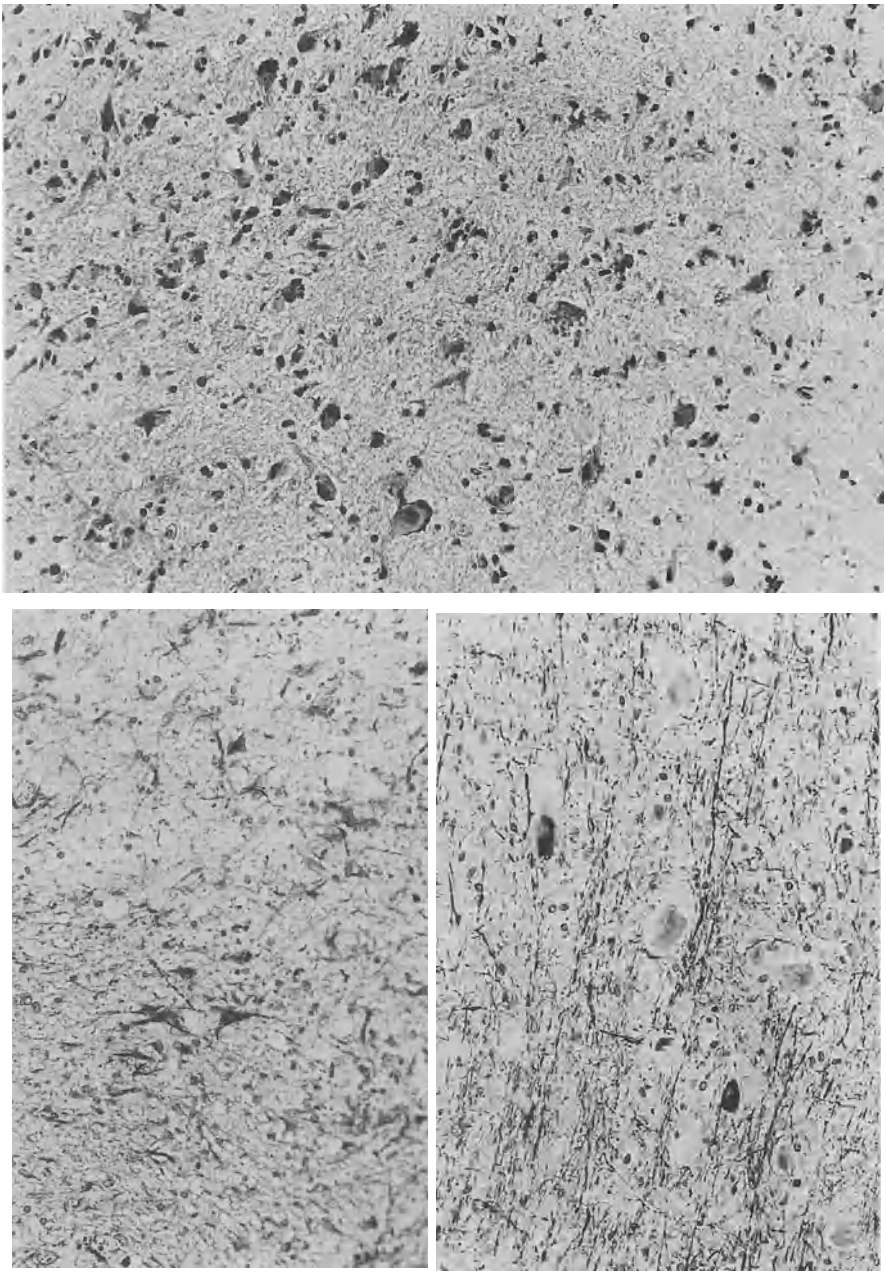


Fig.21.28a–c. Hamartoma of the hypothalamus: **a** abnormal neurons and glial cells, H&E, ×200; **b** GFAP-positive reactive glia cells, PAP-DAB, ×200; **c** neurons positive and negative for NF, SM 31, PAP-DAB, ×200

stretches from the astrocytic [2573, 1490, 633] to the mesodermic and mesenchymal [1965, 1183].

The tumor has a high cell density and is composed of large and small cells, with a cytoplasm containing PAS-positive granules (Fig.21.29), infiltrating the nervous tissue. The cells accumulate around vessels. Immunohistochemistry reveals contrasting results, showing positive staining for GFAP in some cases and for histiocytic markers in others. In the case studied by Claassen et al. [452], there was a positive staining for α_1-antichymotrypsin and with MB2 antibody for B cells, and a negative staining for GFAP, indicating a "lymphoma-like" character. Immunoelectron microscopy demonstrated in a case a positive GFAP-staining in some granular cells devoid of filaments, indicating the astrocytic origin of these cells [2937A].

Even though the tumor is associated with a short survival, good responses are seen with radiotherapy.

21.8.3 Meningeal Gliomas

There is no doubt as to the existence of ectopic glial nests in the meninges, especially in children. They are usually found in the vicinity of the foramina of Luschka or in the sacrococcygeal segments of the spinal cord and more rarely on the convexity of the cerebral hemispheres. Gliomas may arise from these nests. Their identification is, however, difficult, because one must exclude exophytic growth of a hemispheric astrocytoma. Rare cases in which the meningeal origin of the tumor was definite and others in which doubt could be present have been recorded [2420].

The same considerations are valid for the rare intradural extramedullary gliomas reported, while many doubts envelop the cases of primary meningeal gliomatosis.

21.8.4 Ectopic Gliomas and Neural Hamartomas

Rare examples of hamartomas or masses resembling astrocytoma have been described at various sites: The orbit, pericranium, submandibular and sacral extraspinal regions. There are exceptional reports of intraabdominal neuroepithelial tumors, for example, ependymomas of the ovary and of the broad ligament [1449, 161] and astrocytomas of the endometrium [3106, 1709, 1642].

The "nasal glioma" deserves particular mention. This term was introduced for the first time by Schmidt (1900) [2537] to indicate intra- and/or extranasal glial tumors. It is very rare, as only 55 cases had been described up to 1950 [221].

It has been hypothesized that this neoplasm could have the same origin as the encephalocele. It is known that in the 3–5 week old embryo, the anterior neuropore is open and connected with the nasal area through a path of epithelial cells. The brain may herniate at this site, and thus when the skull closes, neuroectodermal tissue remains isolated outside it. The closure of the skull may be incomplete so that a glial duct remains connected with the frontal cortex. Not every author agrees with this interpretation, especially because only a few of the tumors have been shown to contain neurons. However, it has to be noted that neurons when present could have undergone regressive changes. A

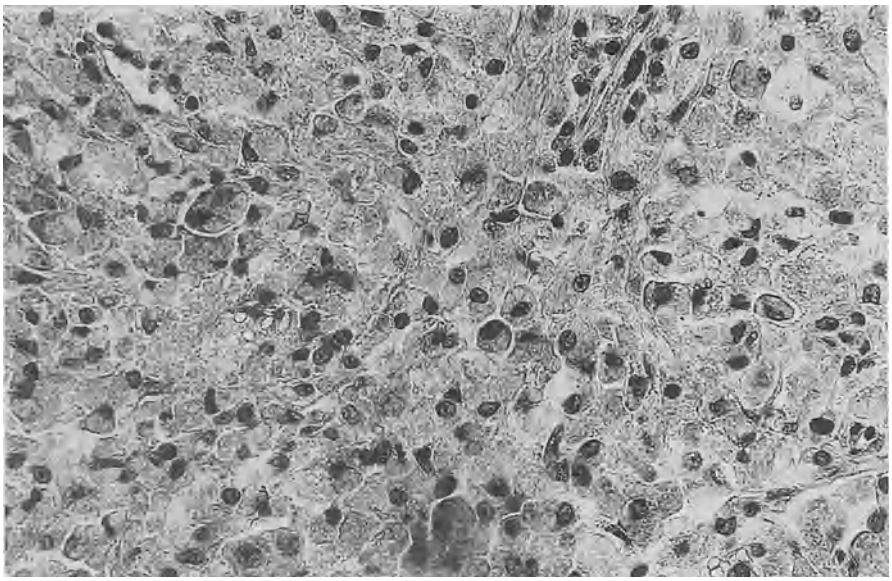


Fig.21.29. Granule cell tumor, H&E, ×200

good demonstration of the encephalocele theory was given by Smith et al. [2673], who rejected the possibility that the tumor could originate from a teratoma or from heterotopias because of the existence of a connection between the tumor and the brain. They reviewed 88 cases from the literature and added 5 of their own. The tumor was present since birth in 38 of 48 cases. It was extranasal in 60%, intranasal in 30%, and intra- and extranasal in 10%.

Histologically, it is formed by fibrous and gemistocytic astrocytes and by a vascular connective stroma. Neurons may be present in some cases. Mitoses are not observed. The tumor has a capsule formed by astrocytic processes, fibroblasts, and connective tissue. The tumor is usually surgically removed with good results. The risk is that of meningitis, especially in cases with an intracranial connection.

In the past years, some tens of cases have been added.

21.9 Vascular Malformations

They are partly hamartomatous and partly hamartoblastomatous lesions, formed by mesenchymal structures and vascular elements. They can be observed in the encephalon and spinal cord, in the meninges, and more rarely in the bones of the skull or vertebrae. The first organic classification of these lesions was that of Virchow [2942], which influenced subsequent research and nosography. Among the main classifications are those of Cushing and Bailey [543], Bergstrand [174], and Dandy [560].

Cushing and Bailey [543] were the first to separate by scientific criteria the cerebral vascular malformations of hamartomatous character from true blood vessel tumors. Telangectasias, venous and arteriovenous angiomas were distinguished from hemangioblastomas. The main distinction was that in malformations, the neural tissue is present in the intervascular spaces, while in general it is absent in tumors, where instead it is replaced by collagen or reticular stroma. It should be furthermore remembered that vascular malformations show a frequent tendency to calcify [187, 2172], and angioblastomas rarely do.

The incidence of vascular malformations in autopsy material varies from 0.1% to 4% of all tumors [1298].

21.9.1 Capillary Telangectasias

Very often, they are unexpected autopsy findings and may easily be overlooked because of their small size. They are found mostly in adults, preferentially in the pons, less frequently in the cortex and white matter, cerebral peduncles, and dentate nucleus. In some cases, they are multiple.

Macroscopically, they appear as pinkish punctated areas, sometimes similar to petechiae. Microscopically, they are formed by dilated capillaries with a saccular appearance. Their wall is thin, devoid of smooth muscle or elastica, with a tenuous collagen reinforcement. Normal neural tissue is present between the capillaries.

It is rare for capillary telangectasias to cause spontaneous hemorrhages. This eventuality is, however, fatal if the malformation is located in the brain stem. Under the heading of capillary telangectasia, Russell and Rubinstein [2420] put the "calcifying hemangioma" of the temporal lobe [2172], already considered as a telangectasia [2911].

21.9.2 Cavernous Angioma

This malformation often gives rise to neurological symptoms, both when it is located in the cerebral hemispheres and when in proximity to the ventricles and in the spinal cord, and may be a frequent cause of hemorrhage, especially in neonates. The incidence is very variable in different series: It has been calculated to be between 5% and 13% in autopsy series [2642]. Asymptomatic examples uncovered at autopsy also exist.

The age more frequently affected is the third–fourth decade, with an equal distribution among the sexes [2947]. The possibility of diagnosing the lesion precociously has recently been achieved with improved imaging quality, for example with MRI, and this has slightly modified the age incidence at diagnosis. After the 164 patients studied some years ago [2947], another 166, 41 of whom were under 18 years of age, have been reported [1122]. Seventeen patients between 18 months and 16 years of age [1830A] and 19 between 7 months and 17 years of age [2578A] have also been reported. The lesion is preferentially supratentorial, in particular, the rolandic fissure, the temporal lobe, and, less frequently, basal ganglia and the walls of the third ventricle. Below the tentorium, the preferred sites are the pons, less so the cerebellum, and rarely the spinal cord.

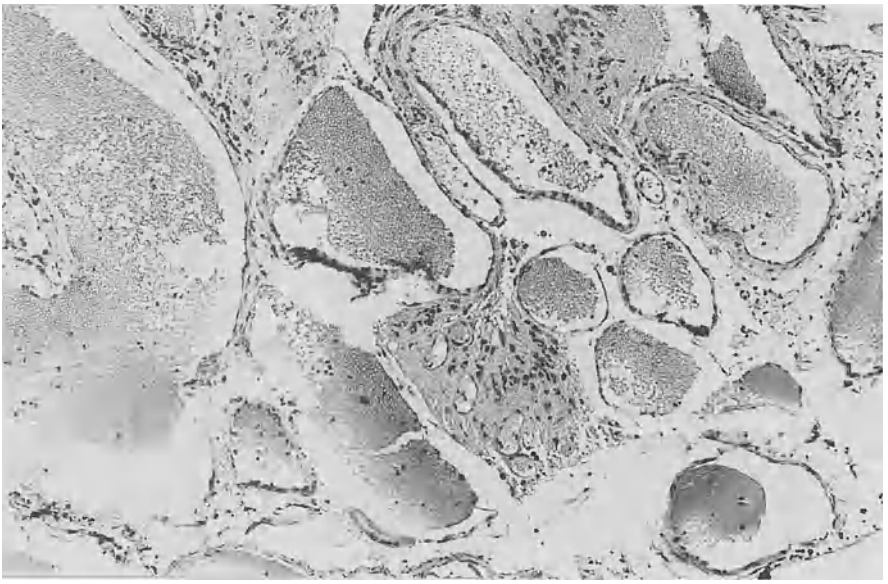


Fig.21.30. Cavernous angioma, H&E, ×150

The lesion is usually single, sometimes multiple, and may also have a familial incidence [923, 1089] or be associated with similar malformations in other organs. It is variable in size, even reaching conspicuous dimensions, and well circumscribed, has a lobulated appearance, and is dark red in color. On the cut surface, it may show cavities of various dimensions and sometimes calcifications. The surrounding neural tissue is yellowish.

Microscopically, cavities of various sizes, lined by endothelium and with a collagenous wall which may even be very thickened, are seen (Fig.21.30). Elastic fibers may be seen [2642]. Gliotic neural tissue and macrophages containing iron pigment, a result of previous hemorrhages, may be found between the cavities. There are thrombosis and organization phenomena with heavy reticulin production. In the tissue surrounding the lesion, there is no increase in blood vessels and, therefore, no supplementary blood supply. This is thought to be one of the reasons why the cavernous angioma may not be seen on angiography [2965].

21.9.3 Arteriovenous Malformation

The lesion is also known by the improper name of arteriovenous angioma or arteriovenous aneurysm: In fact, it is neither a tumor nor an aneurysm.

Its incidence varies between 0.5% and 1% of all tumors [3138]. It is already present in infancy and may cause hemorrhages, but it usually manifests itself in adulthood [1319]. There are observations in favor of a higher risk of spontaneous hemorrhages in

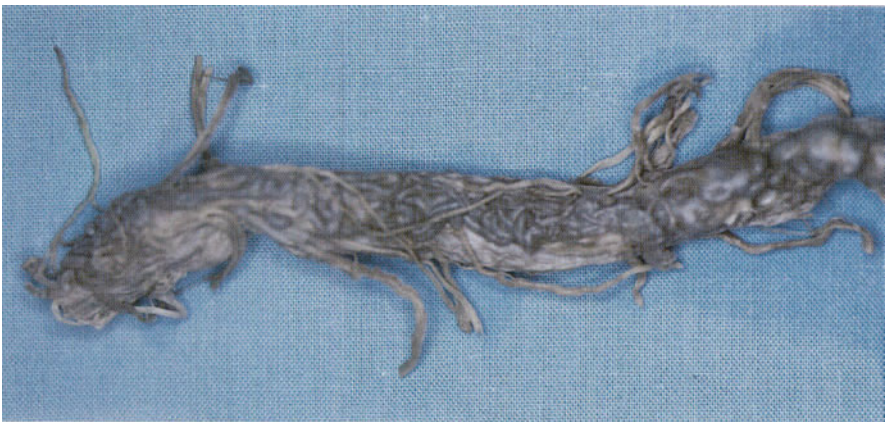


Fig.21.31. Venous angioma of the spinal cord

arteriovenous malformation (AVM) in infancy and of a high incidence of hemorrhages as a first symptom of cryptic AVM. Percentages and risk factors have been accurately calculated [989, 3043]. Men are slightly more affected than women.

The preferred site of the AVM is often the territory of the middle cerebral artery, where the mass has its base on the meninges and its apex in the depth of the parenchyma. Other arteries may also be implicated. The venous drainage occurs through superficial and deep venous channels, for example, the system of the veins of Galen. At this point, the aneurysmatic dilatation of the central vein of Galen has to be remembered [2572, 1298].

The cerebellum is rarely implicated, but often it may be the site of cryptic AVM which are demonstrated after the hemorrhage. In the personal series, there are 13 cases of this type. The spinal cord is rarely involved. On the other hand, AVM may be found in the dura, especially in women over 40 years of age.

AVM may exceptionally be multiple [1298]; sometimes, instead, they are associated with single or multiple so-called berry aneurysms [3043], which involve the blood vessels supplying the AVM. It has not been established whether they are produced by the malformation itself or whether they are secondary to increased blood flow.

The AVM appears as a wormlike packet of blood vessels, which pulsate at operation, and is covered by a gray-bluish arachnoid. The underlying cerebral convolutions are atrophic and pigmented because of previous hemorrhages. Calcifications related to fibrotic and atheromatous phenomena may be present, usually in the older age group.

Some are called cryptic because they are not seen on angiography, but are really AVM of very small dimension; they are found, as has been said, mainly in the cerebellum [2965]. Microscopically, altered arterial and venous-type blood vessels are present. The former show a modification of the tunicae: duplication or interruption of the elastica, thickening or thinning of the muscle layer. The veins show collagenous thickenings. The arrangement may be modified by thrombosis, calcifications, and atheroma. In the adjacent neural tissue there are infiltrates of lymphocytes, macrophages, iron pigment, and gliosis.

21.9.4 Venous Malformations

These anomalies usually affect the spinal cord and occur in both sexes between 20 and 60 years of age [3082]. In the spinal cord they lie on the dorsal surface, between the high thoracic segments and the cauda equina (Fig.21.31). In the brain they are mostly situated in the territory of the middle cerebral artery. A frontal location is the most frequent [881A].

Macroscopically, the lesions appear as wormlike convolutions. On sectioning, the cord shows penetration by venous blood vessels, atrophy, and gliosis. Veins with walls thickened by collagen and hyaline material sometimes involve both leptomeninges and nerve roots. Softening and cyst formation may be found in the cord.

These lesions may be associated with cutaneous port-wine angiomas [1298].

22 Phacomatosis and Dysgenetic Syndromes

This is a group of pathological conditions characterized by malformations involving more than one system. The skin is frequently involved, and so these diseases have also been called the "neurocutaneous syndromes," but this term does not encompass all possible pathological entities in this group; thus, the term "phacomatosis" is more widely used. This simply refers to the term phacoma (φακός = lens) which van der Hoeve [2899] gave to the small hyperplastic formations of the retina. These are genetically determined syndromes and, therefore, generally familial. In the CNS the manifestations include tumors, hamartomas, and various malformations.

22.1 Tuberous Sclerosis (Bourneville's Disease)

This is often a familial disease with an autosomal dominant inheritance with variable penetrance. The gene has been localized to the long arm of chromosome 9 [838]. However, the majority of cases arise sporadically. It should be remembered that incomplete forms are very frequent in relatives of patients so that the familial incidence is difficult to calculate.

The associated CNS tumor is the already mentioned "giant cell subependymal astrocytoma" (see Chap. 9). In the cerebral convolutions there are foci in which there is a disturbance of the cytoarchitecture with abnormal neurons and astrocytes, even of giant aspect. These are called tubers (Fig.22.1) and give the disease its name. Subependymal astrocytic foci may still be found (Fig.22.2) in evolutionary relationship with the above-mentioned tumors, and small foci of glial proliferation with heterotopias are seen. There are also rarer forms of cerebral tumors, with a variety of labels. In two children and a neonate, a hamartoma of the anterior olfactory lobe and in the olfactory germinal layer has been described. It was formed by whorls of giant glial cells and gliosis with further, sparse giant cells and small undifferentiated cells similar to the germinal cells. Cardiac tumors were also associated in these cases [586].

Full reviews on the topic are available [650, 970].

Amongst the cutaneous changes, sebaceous adenomas (Pringle's adenomas) of the cheeks, depigmented patches,"café au lait" spots, raised and rough areas of skin (peau de chagrin), and angiofibromas of the nail grooves (phacomas of Koenen) have also been described. Retinal gliomas are characteristic (phacomas of van der Hoeve). Cardiac rhabdomyomas, liver adenomas and lipomas, adenomas of the pancreas and kidney, colonic carcinomas, and more frankly malformative lesions such as horseshoe kidney and micropolycystic degeneration of the lung are often seen.

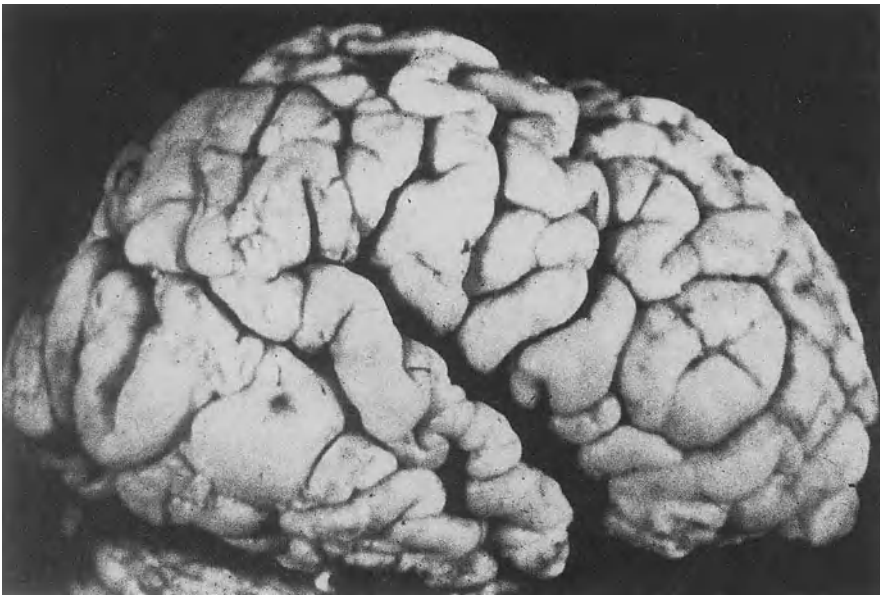


Fig.22.1. Tuberous sclerosis, cortical tuber

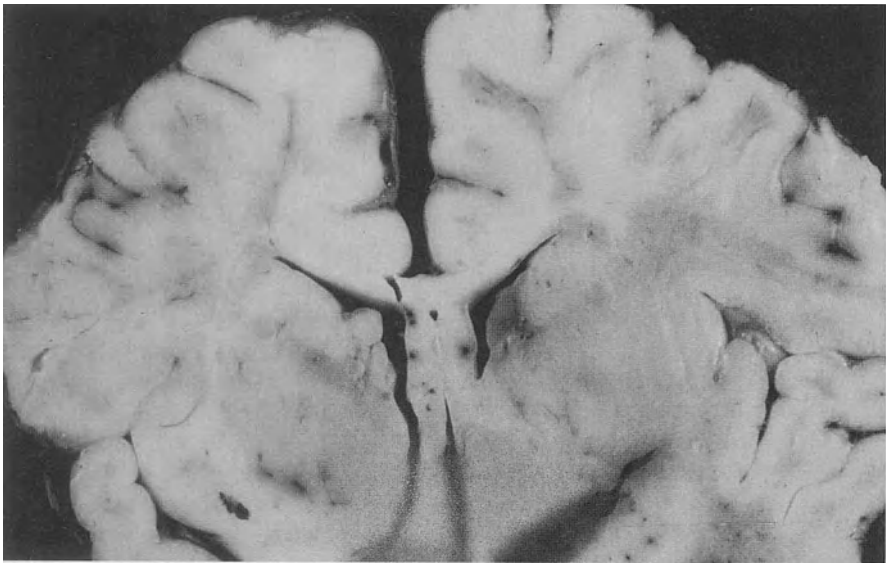


Fig.22.2. Tuberous sclerosis, subependymal nodules

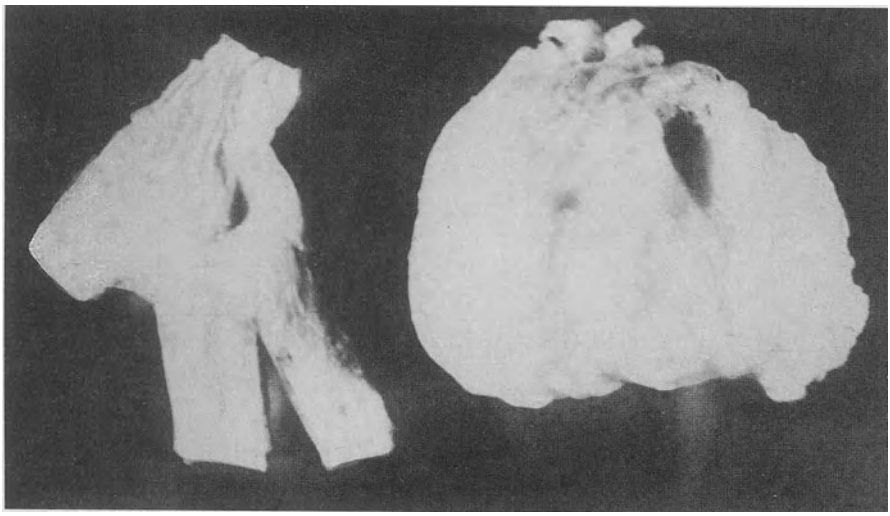


Fig.22.3. Von Recklinghausen's disease, neurinoma of Gasser's ganglion (*right*) compared with normal ganglion

From the clinical point of view, mental deficiency and epilepsy are the usual manifestations. It is possible to demonstrate the cortical tubers by means of MRI scanning [2039], confirmed by examining formalin-fixed brains with the same technique [2040]

22.2 Neurofibromatosis or Von Recklinghausen's Disease

This is a familial disorder inherited in an autosomal dominant manner, which manifests itself in two forms [2314, 2395, 1230], peripheral (NF1) and central (NF2). These differ greatly in frequency, the former having a prevalence of 0.1/100,000 and the latter of 60/100,000. Many cases are sporadic, and this disease has a high degree of spontaneous mutations [2420].

Genetic linkage studies in large families have shown that NF1 and NF2 have separate chromosomal loci (see Chap. 2). Concordant manifestations have been reported in homozygotic twins [21], and histologically identical malignant tumors have been observed in different members of the same family [2545].

Multiple neurofibromas are characteristic of the peripheral form. These may appear on peripheral and autonomic nerves or near nerve endings in the skin and viscera. When they involve the trunk of the nerve, they are of the plexiform type. Typical neurinomas may also be found, although these are mostly solitary (Fig.22.3) and very often associated with neurofibromas.

A relatively frequent event is sarcomatous transformation of the neurofibromas, which has been calculated to occur in 4.6% of patients, corresponding to an incidence

of 1/1000 [671]. It only occurs in adults and is probably related to the duration of the lesions and their number. Regardless of whether such transformation is [669] or is not [226] favored by irradiation, sarcomatous transformation is the main cause of death in the peripheral form of neurofibromatosis [2395]. NF1 also features cutaneous manifestations such as "café au lait" spots and lentigo in the axilla.

The central form [880, 1351, 1788, 3017] is characterized by bilateral acoustic neurinomas, multiple neurinomas and neurofibromas of the cranial and spinal nerves, and gliomas of the brain and spinal cord. The most frequently affected nerve is the eighth, while in the spinal canal sensory roots and the cauda equina are mostly affected. Bilateral acoustic neurinomas, however, are not necessarily associated with central neurofibromatosis [2420]. Intramedullary (see Chap. 17) and, exceptionally, intracerebral neurinomas have also been described [528].

Multiple meningiomas, usually of fibroblastic type, and gliomas, although rare, are part of NF2, and the latter may also be found in NF1. These are usually pilocytic optic nerve astrocytomas, presenting mainly in infancy. It has been calculated that a high percentage of optic nerve gliomas in infancy occur in the context of neurofibromatosis [263, 1245]. Pilocytic astrocytomas of the third ventricle may be found, sometimes with signs of anaplasia [1245, 2420]. Furthermore, cerebellar astrocytomas with signs of malignancy [1245], anaplastic astrocytomas at various sites, hemispheric astrocytomas, spinal astrocytomas, and spinal ependymomas are sometimes seen.

Other tumors may be part of von Recklinghausen's disease. Among these are pheochromocytoma, peripheral neuroblastoma, ganglioneuroma, paraganglioma and carcinoid tumor of the duodenum. This range of tumors has caused many authors to consider neurofibromatosis as a generalized "neurocrestopathy."

22.2.1 Associated Lesions of a Dysplastic Nature

There are a variety of lesions of a dysplastic nature seen in neurofibromatosis which are often microscopic and may be associated with tumors or have a tendency to grow like tumors. Their pathogenesis is difficult to identify but is almost certainly related to what was once called "dysgenesia." This in turn recalls the "Gliadysgenesien mit blastomatöse Einschlag" of Bielschowsky [198], not specific for von Recklinghausen's disease but found in other forms of phacomatosis such as tuberous sclerosis.

Dysplasia associated with central neurofibromatosis involves the Schwann cells, glial cells, and meningeal cells. In the first instance, there is intramedullary schwannosis, situated in the posterior horns and characterized by Schwann cell foci and reticular fibrils, in continuity with neurinomas of the root. Perivascular schwannosis in the spinal cord is seen in relation to ependymomas, meningiomatosis, and meningoangiomatosis, which may be seen outside the context of neurofibromatosis. Abnormal nests of glial cells may be found associated with the dysplasia mentioned above. Nests of ectopic ependymal cells may be seen associated with ependymomas, syringomyelia and calcification [2420]. These nests of glial cells have an evident cytoplasm and pleomorphic nuclei of astrocytic nature and sometimes contain blepharoplasts [2420].

Dysplastic lesions in the cerebral cortex and the basal ganglia have been fully described in six cases [3036]. They have pleomorphic and multinucleated glial cells with blastomatous features but no mitotic activity. They are immunohistochemically negative except for S-100 protein and have been defined as "glial microhamartomas."

Among the various dysplastic lesions associated with NF1 are the "subependymal glial fibrillary nodules," represented by small protuberances in the ventricular wall and containing a proliferation of fibrillary glia. They recall the "feinfaserige Gliose" of granular ependymitis [1277] and can cause aqueductal stenosis [2412]. Already described in NF2 [2387], they have since been described in NF1 after examination of a large series [1195]. Apart from the lesion described above, there are other forms of gliosis, found in various locations and sometimes not easily distinguished from astrocytoma; also, micronodules of proliferating blood vessels in the cerebral parenchyma have been found [2420].

22.3 Von Hippel–Lindau Disease

In this condition, there is an association between cystic cerebellar hemangioblastoma [1656], retinal angiomatosis, or von Hippel's disease and congenital cysts of the pancreas, kidney, liver, and lung, with renal and adrenal, solitary or multiple tumors.

Cerebellar hemangioblastomas are usually solitary, and in less than 20% of cases do they form part of von Hippel–Lindau disease. Some 58 cases had been collected in the literature up to 1958 [1504], and up to 1964 there were 66 reported [248]. Recently, the proportion of hemangioblastomas encompassed in the von Hippel–Lindau syndrome was calculated to be 23% [2012]. In the personal series of 67 cases there were 3, recognized by strict criteria [1864]. In one there was an associated retinal angiomatosis and in the remainder the hemangioblastoma was solitary but familial [802]. However, it has been found that the association is more frequent than originally thought [1231], especially when there are multiple hemangioblastomas, confirming previous observations [2271]. The uncertainties in identifying associations may be due to an incomplete expression of the disease, and besides familial cases with more or less complete association, there are rarer cases of familial solitary hemangioblastoma [248].

The wide range of clinicopathological observations can be summarized today as follows: There are single or multiple hemangioblastomas at the three sites, retina, spinal cord, and cerebellum, in various combinations; inconstantly, lesions in other organs develop; there is often a familial incidence [2420]. To underline the multiplicity of hemangioblastomas, the term "hemangioblastomatosis" was coined [734]. In its nosographic definition, therefore, von Hippel–Lindau disease excludes solitary, sporadic hemangioblastomas [1864].

The syndrome is transmitted in an autosomal dominant fashion. From the clinical point of view, cerebellar hemangioblastomas and renal carcinomas are the most important lesions, because they are frequently the cause of death, the other lesions often being asymptomatic.

22.4 Sturge–Weber Syndrome

Also called encephalotrigeminal angiomatosis [508] or meningo-facial angiomatosis [3067], Sturge–Weber syndrome is characterized by a hemispheric capillary-venous malformation, with radiologically visible calcification, and a cutaneous nevus or a homolateral port wine nevus in the trigeminal region. Contralateral hemiparesis and partial motor seizures are often present. Homolateral buphthalmus and glaucoma may coexist, and mental handicap may be present as well.

Macroscopically, the lesion appears as a mass of small blood vessels in the leptomeninges and cortex, with foci of calcification.

Microscopically, it features large quantities of capillaries and veins situated in the pia and cortex, with hyaline degeneration of their walls. Calcification develops as fine granules in the capillaries, and calcospherites of various dimensions are formed by confluence. Calcification involves the external layers of the cortex, sparing the pia. There is a reactive gliosis and neuronal loss.

The supposedly incomplete forms have been much discussed, while various associations with ganglionic ectopia, hemangiomas, and tumors have been reported.

22.5 Other Dysgenetic Syndromes

The Wyburn–Mason syndrome [3081], a sporadic disease, has many affinities with Sturge–Weber syndrome. It consists of an arteriovenous mesencephalic malformation associated with a cutaneous vascular nevus in the trigeminal territory and retinal angiomatosis.

Hereditary hemorrhagic teleangectasia (Rendu–Osler–Weber disease) has an autosomal dominant inheritance and may involve the CNS, with multiple blood vessel malformations of the teleangectatic type [2349].

There are also "multiple angiomatosis" and the familial retinal cavernous angiomatosis.

Lastly, there is ataxia teleangectasia or Louis–Bar syndrome, an autosomal recessive disease which affects children. This is characterized by progressive cerebellar ataxia, conjunctival and facial teleangectasia, immune deficiencies with immunoglobulin anomalies (especially of IgA), hypersensitivity to the effects of irradiation, and a tendency to develop lymphoid tumors or other malignancies. The main neuropathological lesions are cerebellar atrophy due to maturation defects in the Purkinje and granule cells [890, 2940], degeneration of the posterior columns of the spinal cord, and nucleocytoplasmic abnormalities of the satellite cells in the ganglia and in Schwann cells. Numerous other lesions, of both vascular and cellular type, have been described.

23 Lymphomas

Primary lymphomas of the CNS are tumors whose nosography has only been worked out in relatively recent times, but not all the problems have been resolved.

In the past, they were labeled with different names such as microgliomatosis, reticulum cell, perivascular, periadvential, adventitial, perithelial or reticuloendothelial sarcomas, malignant lymphomas, malignant reticuloendotheliosis, reticulohistiocytic encephalitis, granulomatous encephalitis and lymphoproliferative diseases. At the base of the old conception was the so-called reticulum cell, which is an undifferentiated element capable of evolving toward both macrophage and lymphocyte lines and, in the CNS, into microglia.

The resemblance of these tumors to the extraneural lymphomas had already been commented upon in 1943 by Kinney and Adams [1427].

The reticulum cell is not normally positive to silver carbonate staining [1781]. It becomes positive only after macrophage differentiation and, in the CNS, after microglia differentiation. Microglia cells were considered the cells of origin of the tumors [3109, 164]. However, as these tumors show both positive and negative cells, they were separated into reticulum cell sarcomas (negative) and microgliomas (positive).

A series of objections to this concept were raised. First of all, argyrophilia could not be considered a basis for separating the two entities, given the similarity of the histological aspects and of their clinical features [345]. Furthermore, argyrophilia is not enough to establish the microgliomatous nature of the cell. Lastly, the perivascular arrangement of tumor cells suggests that the tumor may originate from the perivascular histiocytes of the brain, rather than from microglia which lie free in the nervous tissue. It was, therefore, proposed to unify these tumors under the term "reticuloendothelial cell sarcoma," which emphasized the histiocytic nature and left aside the relationship with microglia [345].

The abundance of "lymphocytes" admixed with tumor cells had been stressed [345]. Only later [1106] was a clearly lymphocytic variant identified in this group of tumors, with two subclasses: pure lymphocytic and lymphoplasmacytoid, depending on the presence of lymphocytes or immature (lymphoplasmacytoid) plasma cells, on the basis of Rappaport's classification of extraneural lymphomas [1966]. The lymphocytic variant was the most frequent in the group, the histiocytic variant (reticuloendothelial cell sarcoma) being much less common. Furthermore, argyrophilic cells were few compared with the exuberant proliferation of lymphoid cells and undistinguishable from reactive microglia, without any transitional forms. On this basis, the cell of origin of these tumors (from now on called lymphomas like their extracerebral counterpart), was considered to be an undifferentiated mesenchymal cell, capable of lymphoid and stromal differentiation, ubiquitously distributed and favoring the adventitial space.

From 1960 on, malignant lymphomas were reclassified according to an immunologically based scheme [1710, 1614]. The tumors were supposed to be the product of altered hematopoiesis, associated with a defect in the mechanisms of regulation, maturation, and/or differentiation of cells of the immune system. The majority of lymphomas are formed by a predominant cell population, analogous to a cell type of the normal pathway of differentiation. Therefore, they are classifiable according to the properties of lymphocytes expressed during normal development and differentiation. The demonstration of intracytoplasmic immunoglobulins and membrane antigens, employing methods commonly used to characterize B and T lymphocytes, led to the discovery that the majority of the so-called extracerebral "reticulum cell sarcomas" have features of B cells and, hence, have been classified as B-cell lymphomas [2726]. A similar study of cerebral reticulosarcomas demonstrated that these tumors are B-cell lymphomas of immunocytic, immunoblastic, and lymphoblastic type, containing intracytoplasmic immunoglobulins. The argyrophilia seen in cerebral tumors is similar to that of extracerebral lymphomas and indicates the reactive histiocytic component associated with lymphomas [1212]. It does not depend on the tumor location but on the occurrence of cells producing immunoglobulins, which are thought to stimulate a histiocytic reaction and the production of reticulin fibers [1613]. The term "microglioma" has, therefore, been abandoned. These tumors are today considered fully fledged lymphomas.

Primary cerebral lymphomas must be kept separate from a secondary involvement of the CNS by systemic lymphomas. Primary cerebral lymphomas are intraparenchymal tumors and may either present as a single or, frequently, as multicentric foci. They affect subjects who do not have systemic disease. For a long time, the tumor remains localized to the encephalon. Secondary lymphomatous involvement of the CNS is generally a neoplastic infiltration of the subarachnoid (lymphomatous leptomeningitis) or the subdural or epidural spaces, which may lead to compression of the spinal cord. Cerebral involvement is clinically manifested in 5%–10% of patients with a systemic lymphoma [1630] and in 20%–30% at autopsy [1302]. However, lymphomatous intraparenchymal deposits have also been described during the course of systemic disease [1300, 1630]. The evolution of a primary cerebral lymphoma into a systemic disease occurs in 7%–11% of cases in large series [1099, 1683], demonstrating that the distinction between primary cerebral lymphoma and systemic lymphoma is not so clear cut. The term "primary" has predominantly chronologic and clinical meanings. A median survival of 1 year has been noted with primary cerebral tumors and of 2 months only, for cerebral involvements by extracerebral lymphoma [1729].

Ocular involvement has been frequently reported in association with cerebral lymphomas [598]. It may be either a direct extension of the brain lymphoma or another site of a multifocal disease.

23.1 Frequency, Age

Primary cerebral lymphomas represent 0.3%–1.5% of all intracranial tumors and 0.9%–2% of all malignant lymphomas [822, 1106, 1306, 182, 3076, 1313, 2516]. In the

personal series they represent 2.2% of all intracranial tumors. There is an increased incidence in immunosuppressed patients, after renal [429, 2173] and cardiac [195] transplantation, in systemic lupus erythematosus [1665], during Epstein-Barr virus infection [2147, 1163], and in the Wiskott-Aldrich syndrome [1097] and other hereditary [836] or acquired [2680] immunodeficiency syndromes. A dysfunction of T suppressor lymphocytes with a consequent proliferation of a clone of B lymphocytes is thought to occur.

An increased incidence has been reported since the beginning of the century [2020, 656]; it cannot be adequately explained by the increased frequency of immunodepressive syndromes [1161] and seems to be unrelated both to AIDS and organ transplantation.

Two cases of lymphoma associated with meningioma have been reported [2666]. Cerebral lymphomas occur at all ages (from 16 months to 90 years), with a peak between the fourth and sixth decade. The incidence is 1.5–2.5 times greater in men than in women [250].

23.2 Macroscopic Appearance

CNS lymphomas occur mostly in the cerebral hemispheres, especially in the frontal lobes and less frequently in the posterior fossa.

Spinal cord lymphomas are very unusual [2662]. A primary meningeal localization has only rarely been described [1780].

Primary cerebral lymphomas present as single lesions; multiple lesions (Fig.23.1) occur in 22%–45% of cases [1106, 1099, 3076, 1877]. Sometimes they appear as a diffuse and symmetrical infiltration of the basal ganglia, brain stem, and ventricular walls, with involvement of the corpus callosum and "butterfly" growth in the white matter of the hemispheres.

23.3 Microscopic Appearance

The tumor is composed of roundish cells, with a mosaiclike pattern and a preferentially perivascular distribution. The nuclei have different, categorized forms, and the number of mitoses is variable (Fig.23.2). The tumor is more widespread than it appears macroscopically. At a distance from the tumor center, foci of proliferation may be found, characterized at their periphery by cell proliferation in the perivascular spaces (Fig.23.3a,b). Sometimes, the latter are accompanied by an inflammatory picture, simulating encephalitis, with perivascular sleeves, composed of small mature-looking lymphocytes and rare plasma cells (Fig.23.4a). They have been considered to be part of an immune cellular reaction against the tumor, as in other cerebral tumors [1391]. Howev

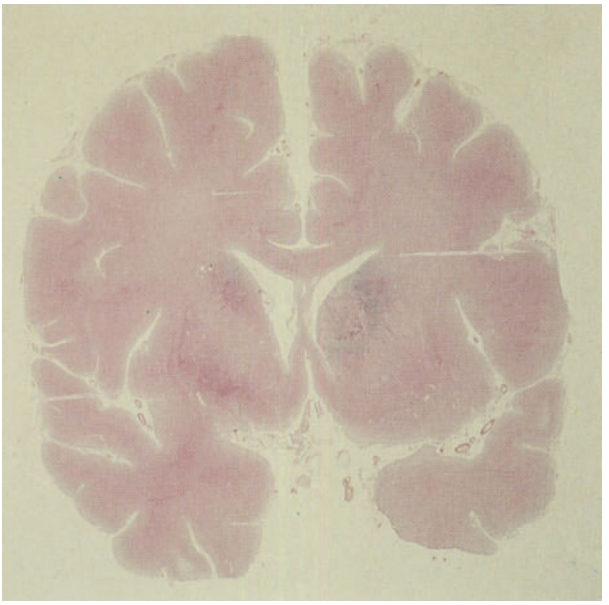


Fig.23.1. Lymphoma affecting basal ganglia and temporal lobe

er, the monoclonality of the plasma cells [1212] and the abundance of these perivascular sleeves suggest that they can be preneoplastic lymphatic stages.

The perivascular arrangement of the tumor cells, evident also in the main tumor, is a characteristic feature. The rims of the perivascular cells are separated by concentric rings of reticulin (Fig.23.3c,d), corresponding to basement membrane containing laminin (Fig.23.5) [927], collagen types III, IV, and V, and fibronectin [1340, 1471]. In the intervascular areas, reticulin is much less abundant, even though it appears in relation to the perivascular network (Fig.23.4b). It is not produced by tumor cells, as originally thought when they were considered as cells of the "reticulum," but it derives from the thickening and fragmentation of the basement membranes consequent to the growth of tumor cells in the perivascular space [927]. Cells of a histiocytic nature and containing fibronectin have been seen both around the blood vessels and in the tumor. They could have a role in reticulin deposition, as hypothesized in extracerebral lymphomas [1613]. An alternative hypothesis is that cerebral pericytes or astrocytes may produce reticulin in an attempt to arrest the diffusion of foreign cells [1340].

Cerebral lymphoma, therefore, originates in the perivascular spaces, to which it initially remains confined and from which it subsequently infiltrates and destroys the cerebral parenchyma.

Monoclonal and polyclonal cytoplasmic immunoglobulins have been demonstrated by immunohistochemical techniques applied to paraffin sections in a proportion of cases [1212, 2819, 1622, 33, 1877, 2645, 656]. This is in agreement with a B-cell origin of these tumors, confirmed by the expression of other B-cell surface [1524, 885, 144] and intracytoplasmic [2516, 656] antigens. In general, cerebral lymphomas ex-

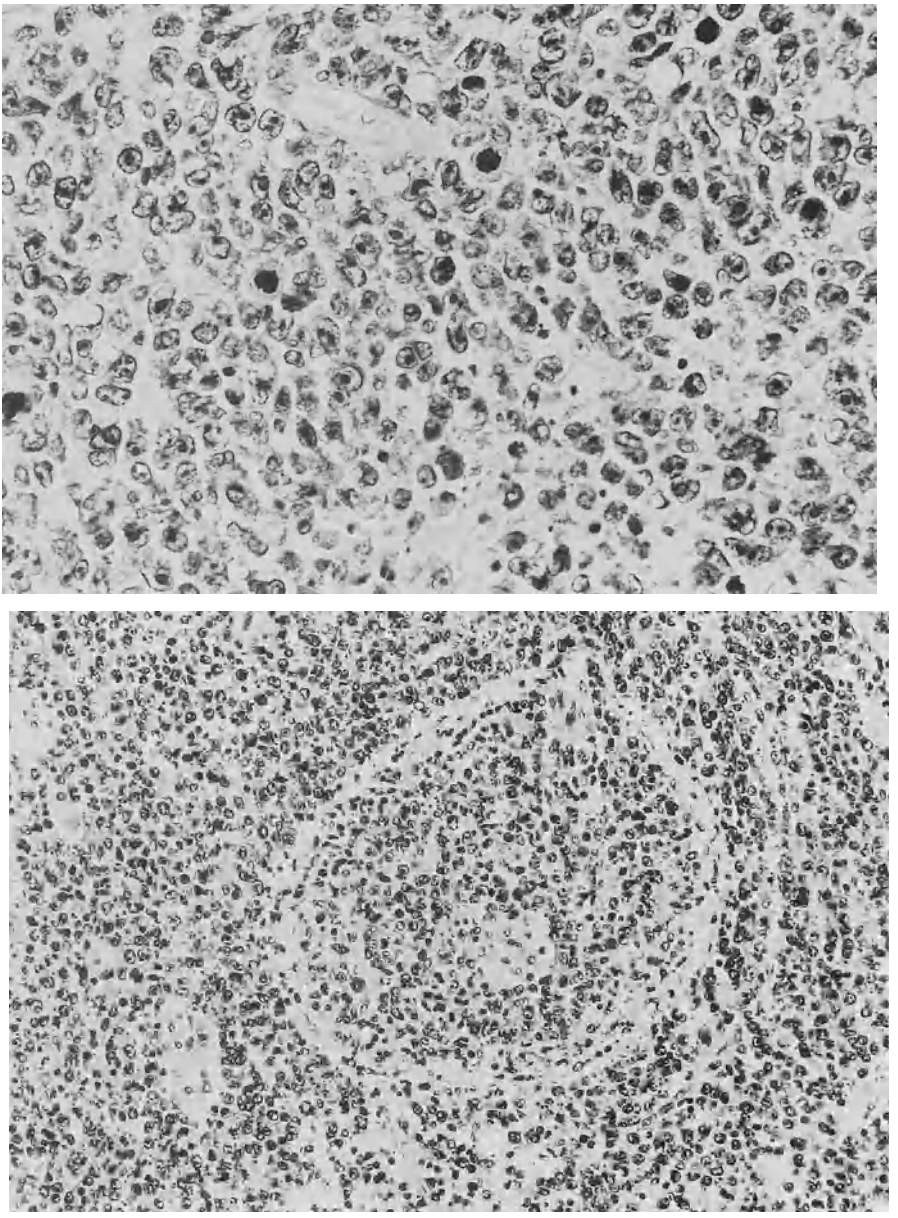


Fig.23.2a,b. Brain lymphoma: **a** typical aspect with frequent mitoses, H&E, ×400; **b** perivascular growth of the tumor, H&E, ×200

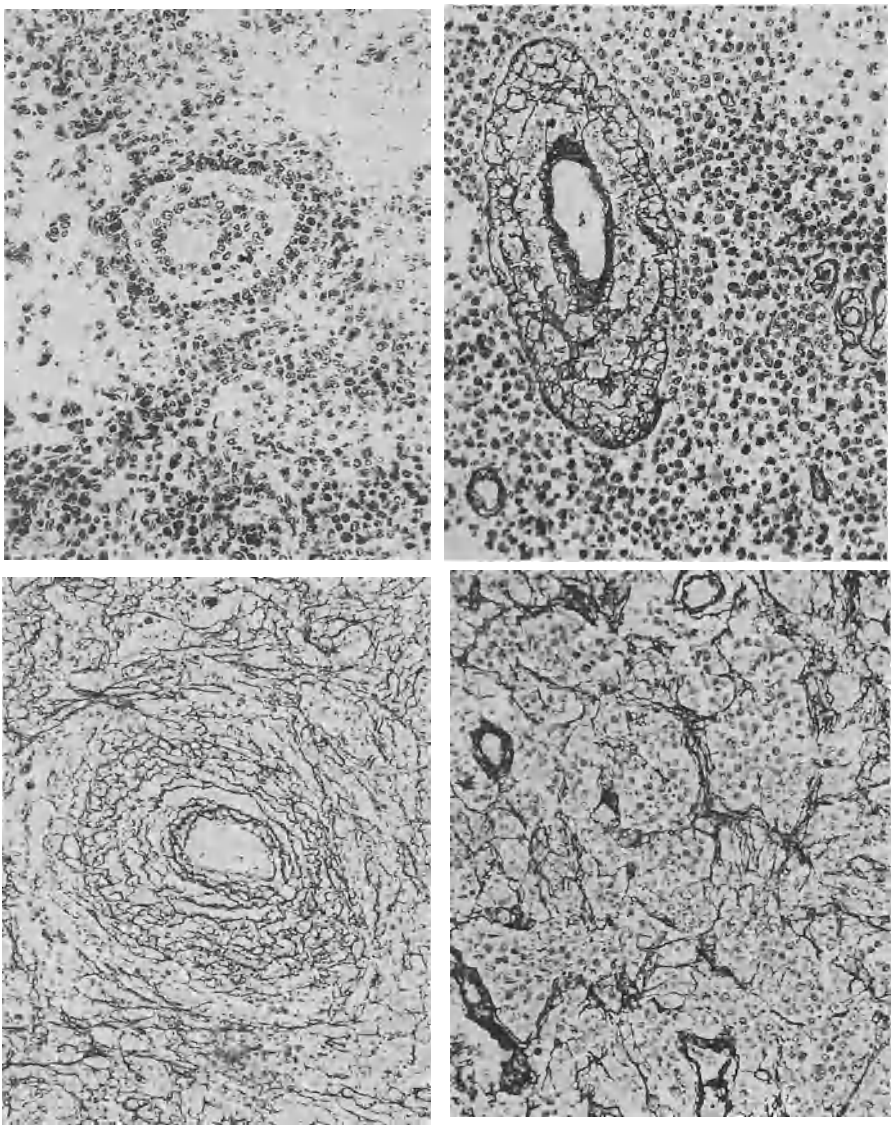


Fig.23.3a–d. Brain lymphoma: **a** perivascular sleeve of tumor cell, H&E, ×300; **b** id, with concentric reticulin rings, Gomori, ×300; **c,d** perivascular rings of reticulin in the tumor, Gomori, ×200 [2486]

press B-cell differentiation [9] antigens corresponding to a more mature phenotype than extracranial lymphomas [885]. A rearrangement of the immunoglobulin genes has also been demonstrated in four cases, which confirms the nature of the B-cell lymphomas [1525].

Antigens of the T-lymphocyte series (UCHL1, OKT-11, and Leu 1) have been demonstrated either in sparse cells and in cells of probable reactive nature [1524, 2516, 755]

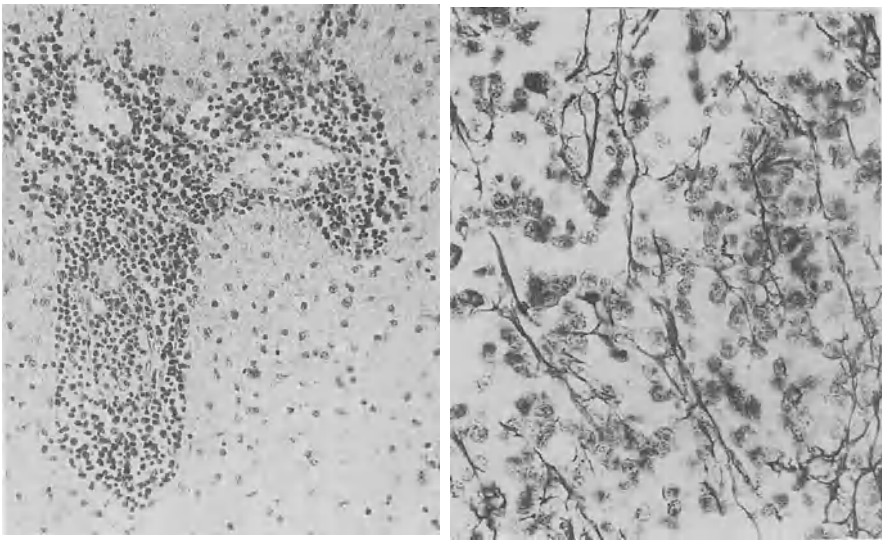


Fig.23.4a,b. Brain lymphoma: **a** perivascular sleeve of lymphocytes and plasma cells, H&E, ×200; **b** distribution of reticulin fibers among tumor cells, Gomori, ×300 [2486]

or in the majority of the cell population in a tumor, considered as a T lymphoblastic lymphoma [2516].

Other T-cell lymphomas have been reported [1780, 241, 1931].

Cells bearing histiocytic markers (lysozyme, α_1-antitrypsin, α_1-antichymotripsin) that are present in some cases have been considered to be reactive histiocytes [1877, 656, 2645], as in extracerebral lymphomas [519]. There are also cells of reactive microglia (Fig.23.6).

Further confirmation of the lymphomatous nature of the tumor cells does not help with the problem of the origin of the tumor cells in primary cerebral lymphomas, the brain being an organ devoid of lymphoid tissue. The development of cerebral lymphomas in the perivascular space is in agreement with the hypothesis of their origin from a mesenchymal pluripotent perivascular cell [1106]. Hematopoietic pluripotential stem cells have, in fact, been demonstrated in the brain of adult rats [140]. An origin from lymphocytes of the choroid plexuses and arachnoid membrane has also been suggested [2622]. The antigenic resemblance of glia to normal and tumor lymphocytes [3032] and the cross-reactivity of lymphoma cells with specific glial antigens seem to suggest that glia also have a role in the pathogenesis of cerebral lymphomas [241]. However, the perivascular multicentric origin is also compatible with an origin of tumor cells from the blood.

Two theories as to the origin of cerebral lymphomas have been proposed, both supported by clinical and pathological findings [1161]. Reactive lymphocytes are attracted to the brain by an infective process, probably viral, and a second local event then transforms a reactive population into a neoplastic clone, with a superficial molecule specifically binding to the neural tissue and its endothelium. This could explain the high frequency of cerebral lymphoma in patients with AIDS, undergoing chronic immune stim-

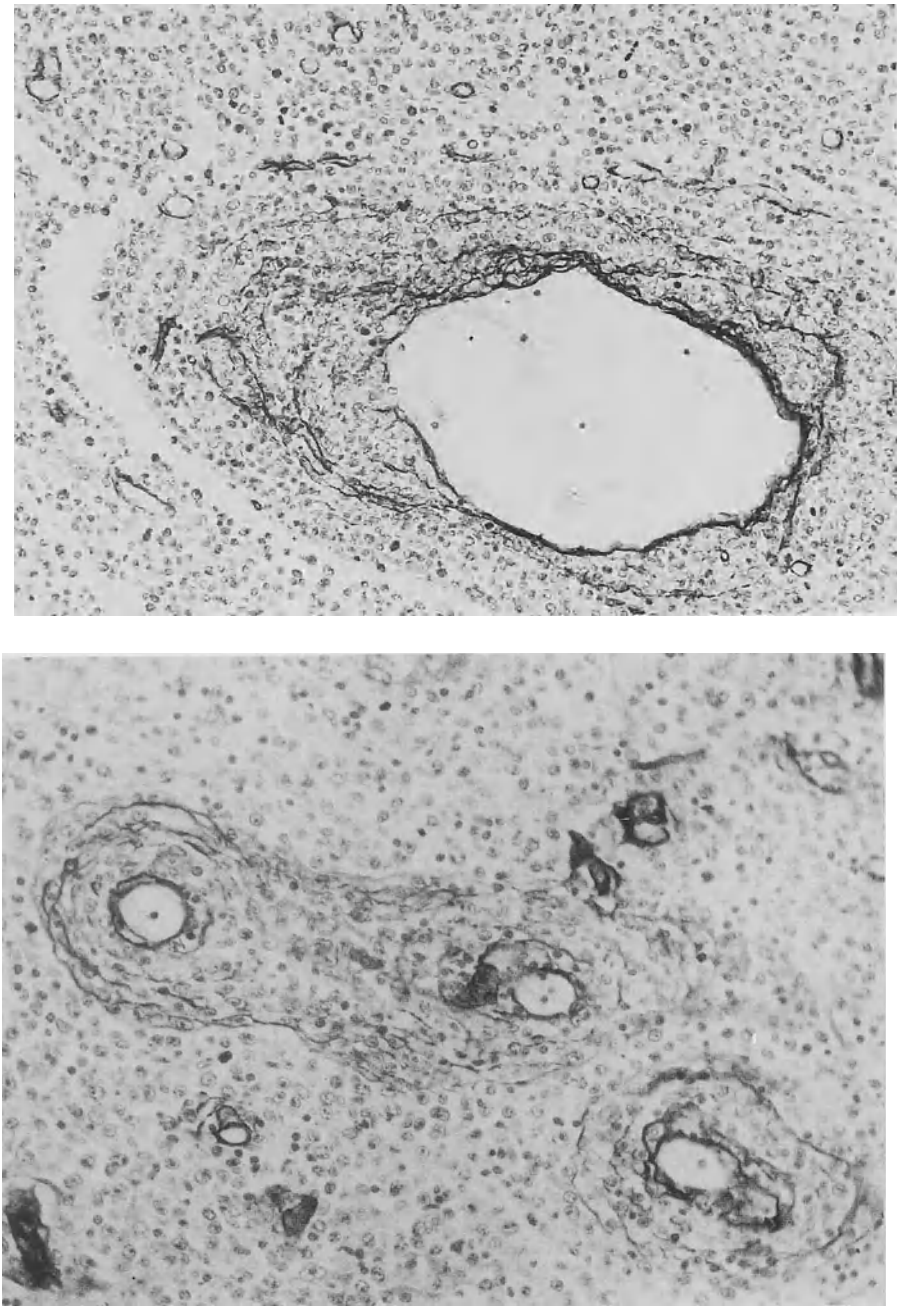


Fig.23.5a,b. Brain lymphoma, perivascular rings of laminin, PAP-DAB, ×200

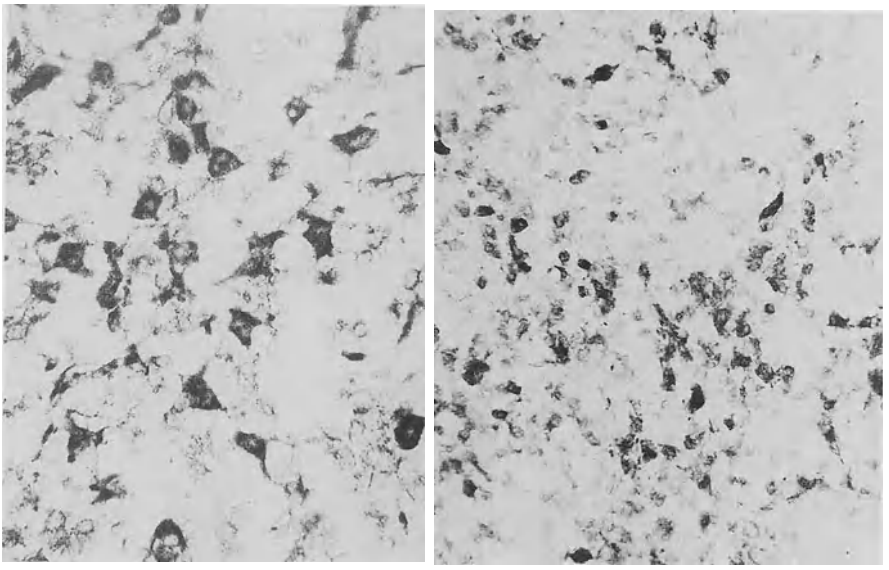


Fig.23.6a,b. Reactive microglia cells: **a** Hortega silver carbonate, ×400; **b** α-naphthylesterase, ×300

ulation due to repeated infections [2645]. Alternatively, the neoplastic transformation of B lymphocytes could occur in a lymph node or in an extranodal lymphatic site.

The neoplastic clone is supposed to reach the encephalon through the blood stream and settle only there, because it bears surface molecules specifically binding to the neural tissue. Both these hypotheses could explain the cerebral "primary onset," and the second theory would account for the extracerebral localization of a cerebral lymphoma in 10% of cases. The existence of molecules specifically binding to an organ or tissue, called "homing molecules," have been demonstrated on the surface of lymphocytes circulating in the lymph nodes [866] and in subclones of malignant melanoma [2026]. Direct evidence for cerebral lymphomas does not exist at present, although it is known that some surface antigens are shared by hematopoietic and neural cells, in particular, HLA-DR [1084] and Leu-7/HNK-1 antigens [2180].

If the distribution of various types of lymphoma is compared in the published series, evident discrepancies are noted, especially when the classification of Lukes and Collins [1710] is followed. The prevalence of immunoblastoma [1306, 2819, 1290, 588, 1877], lymphoplasmacytoid lymphoma [1212, 33, 2645], centrocytic-centroblastic [656], centroblastic [2699, 2516], lymphoblastic [1077], and highly malignant unclassifiable lymphoma [241] has been reported. Authors who have followed Rappaport's classification agree on the prevalence of the histiocytic diffuse type [2819, 1622, 1099, 3076, 823]. According to the International Working Formulation system [657], the predominant histological classes are immunoblastic (Fig.23.7a), small noncleaved (Fig.23.7b), and large noncleaved lymphoma [1099] or large immunoblastic lymphoma [1161], that is high-grade malignancy tumors. Also low grade tumors, for example, plasmacytoma (Fig.23.7c), are included.

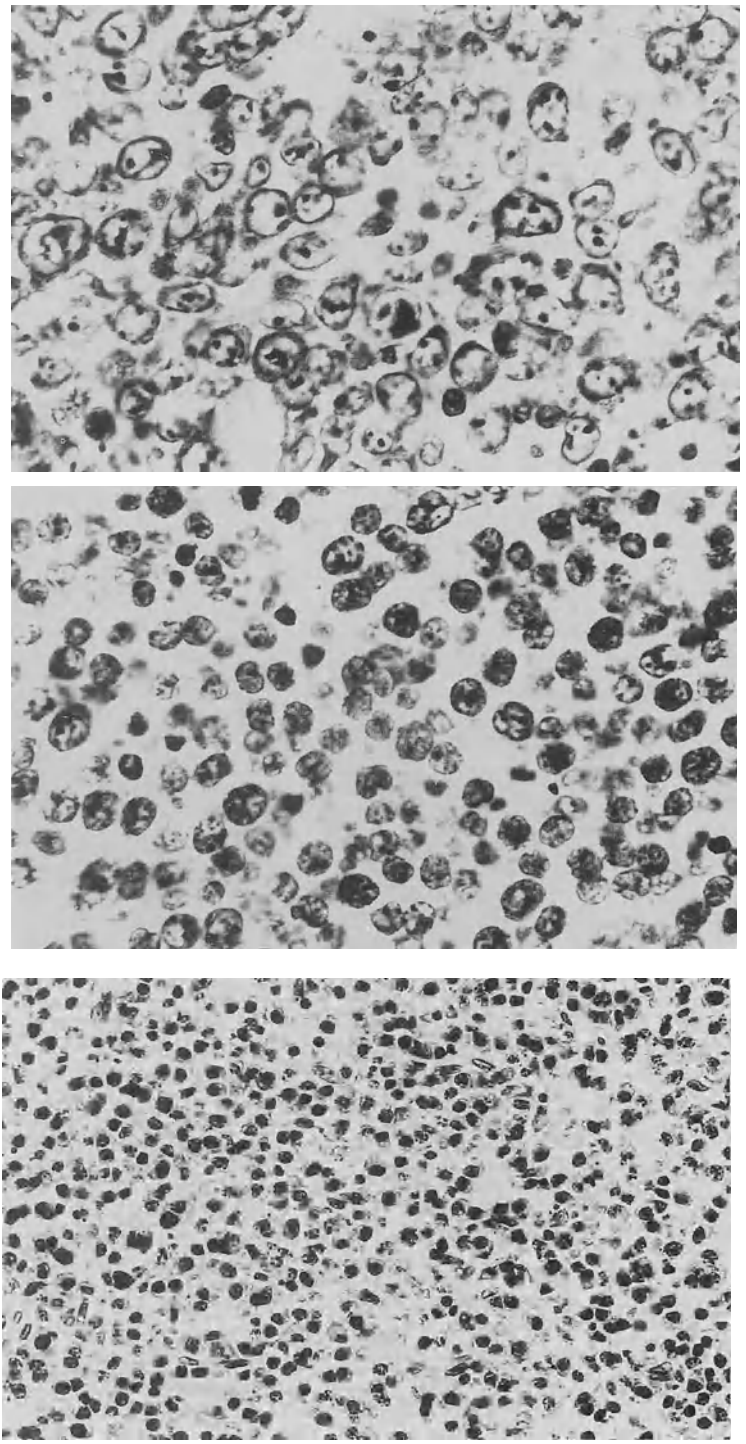


Fig.23.7. **a** Immunoblastic lymphoma, H&E, ×400: **b** small noncleaved cell lymphoma, H&E, ×400; **c** plasmocytoma, H&E, ×200

These discrepancies derive from the uncertainties of the classification of lymphomas and from the great variability of aspects within the cerebral lymphomas. This variability depends on the evolution of the process: The morphologically predominant cell type changes from the appearance of a follicular center or lymphoplasmacytoid cell to that of a cell closer to the immunoblast [2819]. This fits in with the concept of the progression of noncerebral lymphomas from a follicular center cell lymphoma or lymphoplasmacytoid lymphoma to an immunoblastic sarcoma [1710]. While in extraneural lymphomas, the majority of cells are in the same phase of maturation, the opposite is the case in cerebral lymphomas. The presence in the latter of follicular center elements, reported in almost all series, may be explained only by this hypothesis of progressive maturation.

23.4 Epidural Lymphomas

Epidural spinal primary lymphomas have to be considered. They present at a site which is typical of systemic lymphoma, but they are mostly isolated, both at the onset and during their course [318, 1035, 992]. Histologically, they are well or poorly differentiated, small cell, lymphocytic lymphomas and have a good prognosis, because of the low degree of malignancy and their radiosensitivity. These lymphomas originate either from preexisting lymphoid tissue in the epidural space, by diffusion in the paravertebral space, or via the blood in the peridural adipose tissue [1110].

23.5 Lymphomas in AIDS

Primary cerebral lymphomas are common in the acquired immunodeficiency syndrome (AIDS) [626]. In some series, they rank second after toxoplasmosis as a cause of focal neurological lesions, representing 5% of neurological complications [2677, 1634]. Except for the age of onset, which is obviously the same as that of the AIDS population, they do not differ in clinical characteristics from other primary cerebral lymphomas. Pathologically however, they have unusual features, and it is difficult to subclassify them as to type, due to the very marked pleomorphism and small "noncleaved" cells coexisting with large immunoblasts [2680]. These cases are all thought to be multicentric [2680]. The prognosis is clearly worse, survival being less than 2 months [2677, 920]. It improves after radiotherapy, even though it remains shorter than that of non AIDS patients [149, 964]. The radiological diagnosis is difficult because the CT scan appearance is similar to that of a *Toxoplasma* abscess.

23.6 Prognosis, Treatment

Some authors have reported a lack of correlation between the histological type and prognosis [1306, 588, 1362], but others found a longer survival to be related to certain histological types, such as the plasmacytoid lymphoma and centrocytic-centroblastic lymphoma [241], the low grade lymphomas according to the classification of Kiel [1290], and the "small cleaved cell" lymphoma [1161]. Overall, however, the prognosis is worse than in systemic nodal or extranodal lymphomas of the corresponding type. The prognosis is, however, better than for secondary cerebral lymphomas.

Surgical intervention is mandatory, also because in the majority of cases the diagnosis is only reached by histological examination. However, surgical procedures do not influence the prognosis. The use of corticosteroids is advantageous per se and sometimes causes a reduction in the tumor mass, with prolonged survival [2652, 3004, 2913]. Survival after surgery alone is about a month, independent of the type of operation [1975].

Postoperative radiotherapy gives good results as primary cerebral lymphomas are highly radiosensitive, although the control of the disease obtained by radiotherapy is transient and not comparable with that of extracerebral lymphomas. Postoperative radiotherapy produces lengthening of the median survival from 4 to 15 months [182, 972, 2428, 1362, 1975, 3098], with a median survival of 55% at 1 year and 32% at 2 years.

There is no direct demonstration of a relationship between the radiation dose and survival [972]. Doses of 35–45 Gy have been demonstrated to be efficacious [2428], but generally 50–55 Gy are given. Doses above 50 Gy have been effective [1975]. Whole brain irradiation and local radiation do not seem to affect survival differentially [972, 2215], even if theoretical considerations seem to advise whole brain irradiation, for example, the tumor's diffuse spread, its frequent multicentricity, and its recurrence in areas distant from the original tumor [823].

Chemotherapy for these tumors was given after it was noted that some patients responded very favorably, even though transiently, to corticosteroids [10]. These may be lympholytic, apart from reducing the edema [3047, 2652, 2913]. Not many patients have undergone chemotherapy alone or in association with radiotherapy. The drugs used include methotrexate, cytosine arabinoside-C, BCNU, ACNU, CCNU, CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone), BCOP (BCNU + cyclophosphamide + vincristine + prednisone), VENP (vincristine + cyclophosphamide + procarbazine + prednisone), dacarbazide, and procarbazine [1670, 1111, 4, 1622, 1867, 811, 241, 1975, 601].

Methotrexate has been administered intraarterially with prior alteration of the BBB through intravenous and/or intrathecal osmotic agents [2018]. Modest improvements in survival have been obtained in various series. The global evaluation of treated cases gives a median survival of 13 months with 68% of patients surviving at 1 year and 27% at 2 years [860]. The best results have been obtained with high dose methotrexate therapy [1111, 2207, 730, 860]. Overall, patients treated with methotrexate have a median survival of 19 months, 100% surviving at 1 year and 40% at 2 years [860]. The results of chemotherapy have been inferior to those obtained in extracerebral lymphomas up to the present. The therapeutic problem is today considered in view of a different treatment for AIDS and non-AIDS patients.

24 Metastases

24.1 Frequency

The exact figure of the frequency of cerebral metastases is unknown since the data from epidemiological, clinical, and autopsy series are inconsistent. In epidemiological studies, the average incidence varies from 2.8 to 11.1/100,000 and could be very close to that of primitive CNS tumors [2969]. That derived from clinical, neurological, and neurosurgical series increases from 3.5%–4.2% in the period 1930–1950, to 10%–13% in the 1960s [2486]. Autopsy series have recently yielded a figure of 15%–20% [2229, 2794].

Autopsy series give percentage values on average higher than those of clinical series, mainly because asymptomatic lesions are found. In the large series from the Memorial Sloan-Kettering Cancer Center of New York relating to the period 1970–1976 [2227], intracranial metastases were present in 24% of patients who died because of tumor. Nine percent of these were intracerebral only, without any involvement of the meninges. It has been estimated that from 20% to 50% of bearers of a malignant neoplasm develop cerebral metastases, which are the cause of death in 50% of cases [2315].

Tumors of the lung, breast, skin (melanomas), kidney, digestive tract, and choriocarcinoma are responsible for 95% of cerebral metastases. Metastases from lung cancer are the most frequent, representing more than 50% of cases. At the time of diagnosis, however, the primitive tumor site is unknown in a significant percentage of cases [1876].

The tendency to metastasize to the CNS is not the same for all types of tumor [343]. It is marked for melanoma and choriocarcinoma (which is a rare tumor), with a variable frequency from 39% to 92%. Lung tumors come second (26%–46%), in the following order: adenocarcinoma, microcytoma, large cell carcinoma, and epidermoid carcinoma [505]. Breast tumors metastasize with a variable frequency from 15% to 20%. The risk is greater for stage 3 and 4 adenocarcinomas [2698] and tumors with few estrogen receptors [2740]. Hypernephromas metastasize to the CNS in 10%–25% of cases, while carcinomas of the gastrointestinal tract more rarely metastasize to the brain. There are, however, rarer tumors which have a relatively high frequency of craniospinal metastases, such as Ewing's sarcoma [1412, 2649].

The interval between the diagnosis of the primitive tumor and the development of cerebral metastases is variable, being on average 4 months for lung and 3 years for breast carcinomas, while hypernephromas and gastrointestinal carcinomas metastasize in later stages of the disease. It is controversial whether the incidence of metastases has been increasing in the recent past. It seems to have increased for tumors which, following radio- and chemotherapy, are associated with a long survival, such as lung microcytomas [2054], soft tissue sarcomas, and sarcomas of bone [736].

Various types of primitive tumors may have preferential metastatic sites within the cranial cavity. Prostatic carcinomas, extending from bony lesions, involve the dura more frequently than the cerebral tissue. Lung carcinomas and melanomas, instead, metastasize more frequently to the brain. Adenocarcinomas of the breast first develop leptomeningeal metastases, followed by lung tumors and melanomas. It has to be noted that the meninges are more affected than the brain by noncarcinomatous metastases (melanoblastomatosis and meningeal sarcomatosis). Supratentorial localizations predominate (80%–86%), preferentially in frontal, temporal, and parietal locations. Regarding specific anatomic locations, the hemispheres rank first, while basal ganglia and brain stem (only 11% of cases) rank second. The posterior fossa is significantly overrepresented in pelvic (prostate or uterus) and gastrointestinal primary tumors [616]. Unusual sites include the pituitary, optic nerve, choroid plexus, and pineal gland. At the last site 35 cases have been reported [2995]. In more than 60% of cases, metastases are multiple, with a greater incidence in autopsy than clinical material.

24.2 Sex

In relation to sex, there is a prevalence in males, probably related to the higher incidence of lung tumors. The incidence was 9.7/100,000 for males and 7.1/100,000 for females in the USA [2969].

24.3 Age

The incidence rate of cerebral metastases increases with age: 0.6 between 0 and 24 years, 5.3 between 25 and 44 years, 31.1 between 45 and 64 years, and 42.7 above 65 years [2176]. The average age lies in the sixth decade of life. The low incidence in the young is due both to the relatively lower frequency of solid tumors and their lesser tendency to metastasize to the CNS.

24.4 Metastatic Pathways

Neoplastic cells reach the CNS mostly via the bloodstream; however, the incidence of brain metastases in clinical series does not correspond to that of neoplastic cells found at autopsy in patients bearing a malignant tumor, which is 100% for liver and brain [2045]. Malignant cells have to cross the capillary wall, i.e., the basement membrane. Populations of cells are not preselected on the basis of their adhesion properties to endothelial cells or any other features [773]. The preferential site of metastases is at the border between the white and gray matter; the hypothesis is that malignant cells embo-

lize in clusters of 100 and 200 μm in size, which stop there [1110]. Metastases, which may also reach the CNS through bony and dura infiltration, are more frequently multiple. Single metastases represent up to 40% of cases involving primary lung tumors [2229]. Breast tumors have a high percentage of single metastases, over 40% [2874], more often in younger subjects, but in more advanced stages of the disease. Renal tumors usually metastasize after a long interval and are responsible of 10% of single metastases. However, these are unfortunately associated with metastases in other organs [891]. Melanoma also may give rise to single cerebral metastases.

Usually, the prognosis even for single metastases is very poor, with a 2-year survival rate no greater than 15% [3031].

There are reported cases of extracerebral malignant tumors metastasizing to intracranial tumors, usually meningiomas or acoustic neurinomas. Metastases to neuroepithelial tumors are extremely rare [1941, 812].

24.5 Macroscopic Appearance

Metastases may be solitary, multiple, or diffuse (Fig.24.1). Multiple or single metastases prevail in the neural parenchyma, while the widespread ones are more common in the meninges. The former have a nodular, roundish appearance with clear-cut borders. The cut surface is uneven, sometimes smooth; the color is usually grayish-red, but sometimes it is variegated because of regressive events, such as necroses, cysts, and hemorrhages. The consistency is soft, and in the unfixed state the tumor tends to disintegrate. The neural tissue is often edematous, both in proximity and at some distance from the metastasis. Sometimes, a single tumor nodule causes edema of the whole hemisphere [2469]. In relation to meningeal locations, it has to be remembered that in diffuse metastases, the macroscopic appearance is similar to that of meningitis. On the other hand, small metastases located in the dura mater may have a macroscopic appearance similar to that of meningiomas. In these cases, only the histological examination allows the underlying pathology to be ascertained.

24.6 Microscopic Appearance

Even though in a certain number of carcinoma metastases the histological appearance recalls that of the primary tumor, frequently the recognition of the latter is impossible. This happened in 11.8% [2643], 25.5% [286], 35% [548], and 25% [2742] of cases. In general, from the various series, the order of frequency of tumor types is: lung carcinoma, breast carcinoma, carcinoma of unknown origin, melanoma, sarcoma, other tumors. In some series [2596], the proportion of metastases from the lung (55.2%) was followed by those from breast (14.3%); in others [809], lung and breast tumors are followed by renal carcinomas; in still other series, 95% of metastases [3049] were due to carcinoma of the lung, breast, kidney, gastrointestinal tract, melanoma, and choriocarcinoma.

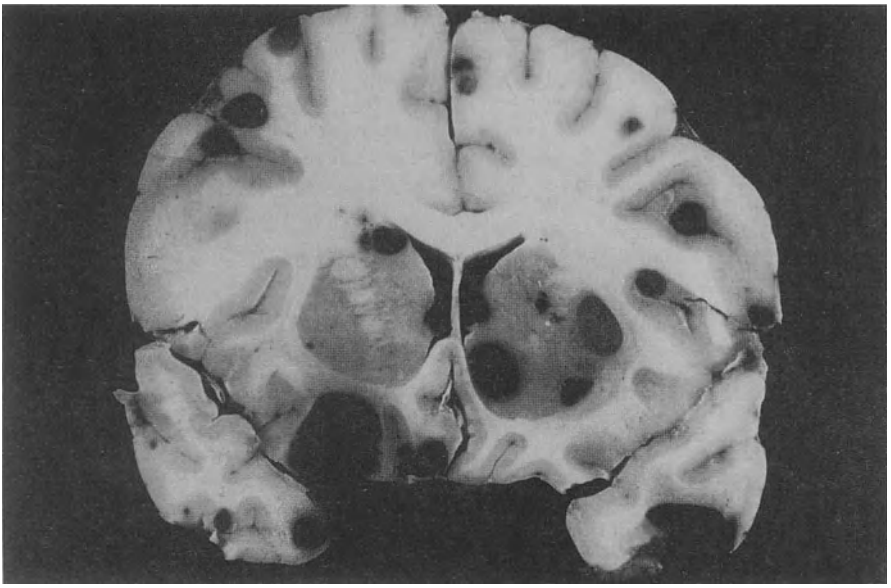


Fig.24.1. Multiple metastases of melanoma

The border with the surrounding nervous tissue may be clear-cut, but it usually is characterized by the presence of neoplastic infiltration, such as prongs and perivascular sleeves of tumor cells clearly demarcated from the neural parenchyma. In the nervous tissue, apart from edema, reactive gliosis may be marked and is represented predominantly by large hypertrophic astrocytes, clustered particularly in proximity to the metastatic tissue. Similar to what is observed in glioblastoma, endothelial proliferation is almost constantly present, and sometimes a rich network of sinusoidal-type vessels develops around the metastasis. The collagen stroma is usually scanty, contrary to what is observed in metastatic nodules located in organs rich in mesenchyma.

Amongst the more frequent regressive events, necrosis, processes of softening and liquefaction, cyst formation, and hemorrhages must be listed. Metastases are more or less rich in mitoses and have a variable growth rate from one tumor to another, very often differing from that of the primitive tumor. Useful data have been obtained from the calculation of the LI after the administration of BrdU: It may be higher than in the primitive tumor, indicating that the metastasis is growing more rapidly than the primary tumor itself [431].

24.7 Differential Diagnosis

In some cases the differential diagnosis includes glioblastoma, lymphoma, or medulloblastoma and may be very difficult, except if one can identify the origin of the metastasis. The immunohistochemical demonstration of different antigens may be very useful

(Fig.26.2). Carcinomatous cells may have particular modalities of spread throughout the CNS and may, through direct subarachnoid diffusion or via the ventricles, give rise to carcinomatous meningitis.

24.8 Prognosis and Therapy

The average survival of patients with cerebral metastases is around 1 month without therapeutic intervention. It increases to 2 months with corticosteroid treatment and to 3–6 months with radiotherapy to the whole brain: About 40% of patients die not because of brain metastases but because of the systemic disease [2226, 358].

Whole brain radiotherapy (WBRT) is indicated and is carried out with different modalities, depending on whether the metastases are single or multiple and on whether the primary tumor is advancing or stable. A single metastasis localized to an accessible site, with controlled systemic disease, has to be resected before radiotherapy [2228]: In fact, it has been recently demonstrated in a randomized study that the median survival after combined surgery and WBRT is significantly longer (40 weeks) than after WBRT alone (15 weeks) [2141]. In long-term survivors, WBRT with unconventional fractionation (single fractions >200 cGy) increases the risk of radiation-induced dementia [599]. For recurrent brain metastases, results after brachytherapy with ^{125}I [2231] or radiosurgery [1684] seem encouraging. Studies are in progress concerning brachytherapy, employed as a supplementary boost after external radiotherapy, in cases of a single brain metastasis with a stable primary tumor. Chemotherapy may be used in chemosensitive tumors such as small cell lung cancer and breast cancer [1127].

24.9 Carcinomatous Meningitis

This is being described more and more frequently, and in general it represents a late event in the course of the disease. However, with the improvement of treatment modalities, it has also been described in patients in full remission.

Setting aside the description of meningeal involvement in leukemia and in non-Hodgkin's lymphomas, carcinomatous meningitis has been described in lung and breast tumors [1669, 2084, 974, 2830, 1477, 257]. The risk with small cell lung carcinoma has been calculated to be 25% at 3 years [2054, 2358]. This complication has been described in a series of other malignant tumors [1232].

The invaded meninges are thickened and whitened, masking the blood vessels at the base of the brain. The cranial nerves may be involved, and nodules of different size may be found. Areas of thickening and nodules may also be found on the ependyma. Microscopically, the subarachnoid space is filled with neoplastic cells both at the cranial and spinal levels. Tumor cells ensheathing blood vessels penetrate the parenchyma and

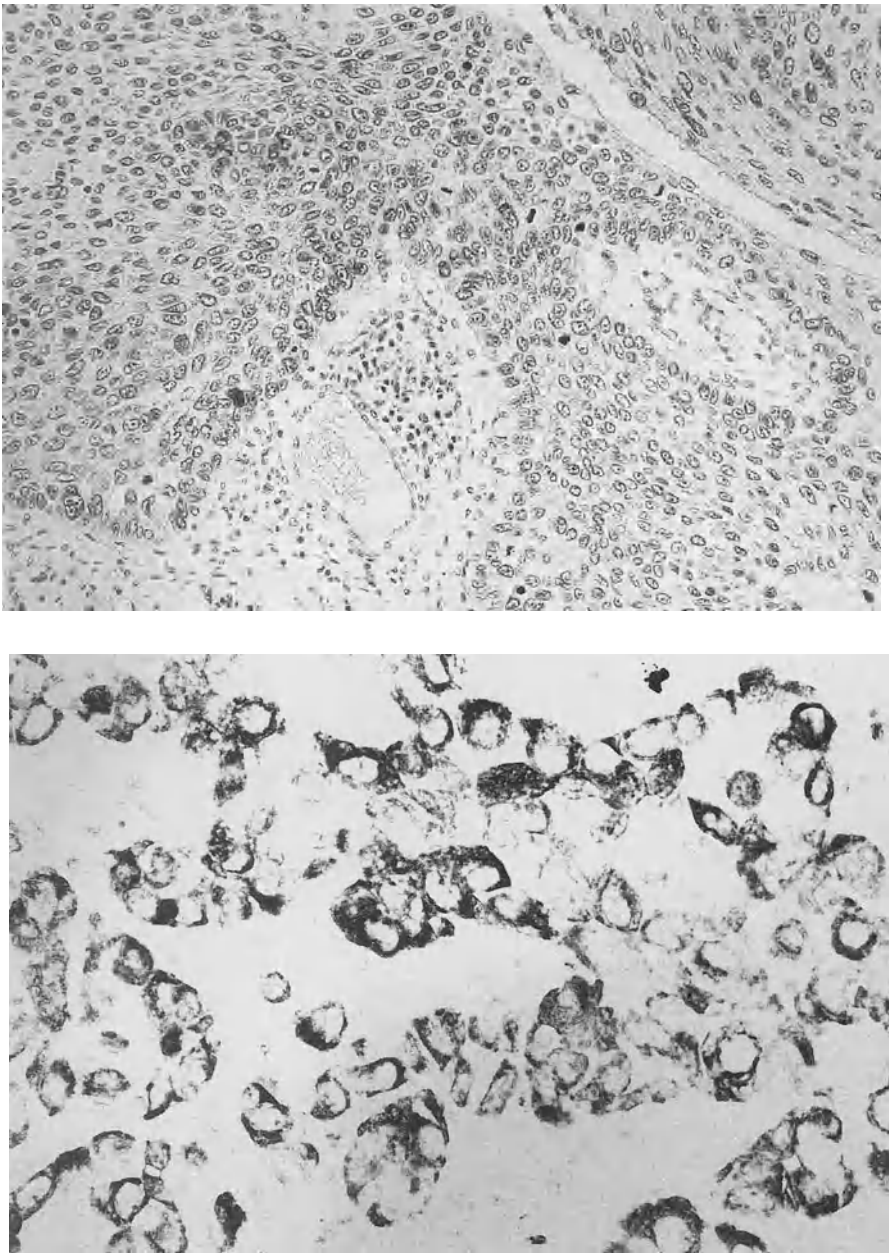


Fig.24.2. a Carcinomatous metastasis with many mitoses and hyperplastic stroma, H&E, ×300; **b** carcinomatous metastasis: positivity for cytokeratin, PAP-DAB, ×400

sometimes give rise to small deposits in the white matter, following the penetrating meningeal vessels. Neoplastic cells may cover the choroid plexuses [1110].

The pathogenesis of carcinomatous meningitis has not been completely elucidated. The tumor may reach the meninges by contiguous spread from the brain or spinal cord from the retroperitoneum through the intervertebral foramina, or via the hematogenous route [1477]. Ependymal nodules and perivascular sheets may be interpreted both in a causal role and as a consequence. The treatment of choice is combined chemo- and radiotherapy.

24.10 Spinal Metastases

Spinal metastases are less frequent than intracranial ones, but not as rare as one would imagine. Metastases to the spinal cord are often missed, because less attention is focused on the spinal cord in comparison with the brain. The metastasizing tumor is usually a bronchogenic carcinoma. The spinal cord may be involved via the hematogenous route or secondarily from the leptomeninges.

More rarely, metastases may involve the choroid plexus, the optic nerve, the pineal body, etc.

25 Biological Basis of Therapies

25.1 Radiotherapy

25.1.1 Cellular Response to Ionizing Radiation

The primary target of ionizing radiations is the DNA, damage to which may occur as a result of either indirect and direct actions. The former is typical of low LET (linear energy transfer) radiations, such as X- and gamma rays, that yield relatively little energy along their path (0.3–2 keV/μm). The interaction with water molecules induces, through the release of fast electrons, the formation of free radicals ($OH \cdot$, $H \cdot$) which damage the DNA by extracting hydrogen atoms. Oxygen, if present at an adequate concentration, fixes the damage; under hypoxic conditions, the action of the so-called endogenous radioprotectors (i.e., sulfhydryl compounds), which are reducing agents, prevails. The direct action is typical of high LET radiations and charged particles (fast neutrons, protons, pions, etc.), with fast electrons directly damaging the DNA.

Lesions in the DNA can be classified into four types: (1) double-strand breaks, (2) single-strand breasks, (3) cross-linking of DNA to DNA or to other molecules, and (4) base damage. The repair is accomplished by different enzyme systems, such as ligases [1033] and nucleases. There is still uncertainty about the mechanisms by which ionizing radiation has varying lethal effects on the different cell types. As the intrinsic susceptibility of the DNA to radiation damage is similar for all cell types (viruses, bacterial, mammalian cells) [27], the DNA cannot be regarded as the sole target involved in the development of the radiation-induced lethality. The "DNA-membrane complex", essential for the beginning of cell replication and rich in lipids, which are particulary sensitive to radiation damage in the presence of oxygen, might be an important target in the induction of cell death [38, 1047].

From a radiobiological point of view, two types of radiation- induced cell death are known: interphase death and mitotic (reproductive) death. The former consists of a direct killing of cells, obtainable generally with doses in excess of 10,000 cGy in non-dividing cells (e.g., neurons), with the only exceptions of lymphocytes and oocytes, which are more radiosensitive. The latter is the cell death contingent upon the process of division (not necessarily the first division after irradiation) and, therefore, consists of a loss of the capacity to divide: It is obtainable with the lower doses employed in clinical radiotherapy both on neoplastic and most normal cells (e.g., bone marrow stem cells, endothelial cells, oligodendrocytes).

In culture, a cell which has retained its ability to divide indefinitely and produce a colony (clone) is defined as a clonogenic cell. The response of mammalian cells to various doses of ionizing radiation is graphically represented by a curve, with the dose plotted on a linear scale and the surviving fraction of cells on a logarithmic scale. With low LET radiation the dose-response curve is characterized by an initial shoulder, followed by a straight exponential part. The shoulder represents the fraction of cells whose damage has not been lethal and is repaired in few hours: It there

fore expresses the ability to accumulate and repair the sublethal damage. By increasing the doses, the fraction of cells only sublethally damaged diminishes until a level is reached after which every dose increment induces a mitotic death in a constant number of cells, and the dose-response curves assumes an exponential slope. When a given dose of radiation is split into smaller doses ("fractionation") separated by an interval of time, a reappearance of a shoulder after every split dose is observed: This means that the number of cells able to repair the sublethal damage and to survive with fractionation is greater than the number of cells which would survive a same total dose delivered in one fraction. This phenomenon is exploited in clinical pratice to minimize the late effects on normal tissues.

The exponential part of the curve is described by the value of D_0, which represents the dose required to reduce the number of clonogenic cells to 37% (1/e) of their initial number, whereas the shoulder may be described by different parameters (n, α, D, survival at 200 cGy). The in vitro radiosensitivity of cells from different human tumors seems to predict the clinical radioresponsiveness better if evaluated by means of parameters describing the shoulder other than those of the exponential slope [3001, 771, 1741]. Tumors with varying radioresponsiveness, such as medulloblastoma and glioblastoma, have similar values of D_0 (135 against 143), whereas the differences are more significant when comparing the values of survival at 200 cGy (0.28 against 0.72).

The sensitivity of cells to low LET radiation varies according to the oxygen status and the cell cycle phase. Hypoxic cells are more radioresistant than fully oxygenated ones: This "oxygen effect" is measured by the "oxyigen enhancement ratio" (OER), which is the ratio of the dose of radiation under hypoxic conditions to that under oxygenated conditions to produce the same biologic effect. OER values are usually 2.5–3; all normal tissues are considered as fully oxygenated. Cells are generally most sensitive in mitosis and most resistant in late S phase, whereas intermediate sensitivities are found in the G_1 and early S phases [620, 1380, 1420].

Different studies [135, 1857, 903, 1741] have shown that most glioma cells in vitro are quite radioresistant, similar to melanoma, and even more resistant than the normal glial cells [2030]. Dose-response curves are chraracterized by a large shoulder, reflecting an elevated capacity for the accumulation of sublethal damage [1763, 2247]. A certain variability has been found among different cell lines from the same tumors: some glioblastoma cells have displayed radiosensitivity values more like those of medulloblastoma cells than of melanoma [903, 771]. Also, xenografts from glioblastoma into nude mice were not always radioresistant [2763]. Similar in vitro characteristics have been reported for cells of the 9L gliosarcoma of rat [1380].

Fractionated irradiation, which is commonly employed in clinical practice, is influenced by four factors: redistribution of the normal and tumor cells, repair of the sublethal damage, repopulation, and reoxygenation. The rationale of radiation treatment is to exploit and, eventually, maximize the differences between tumors and normal tissues in relation to these factors.

The redistribution along the cell cycle consists in the fact that, after the first radiation dose, surviving cells, partially synchronized by their greater susceptibility in the more radiosensitive phases (i.e., M phase), tend to accumulate in G_2 ("premitotic G_2 block"). A precise timing of the second radiation dose in a radiosensitive phase would permit the killing of a greater number of cells. Anyway, during standard daily radiotherapy it is unlikely that any significant synchronization, resulting in a preferential depletion of tumor cells, will occur due to a redistribution in the cell cycle.

The repair of sublethal damage is generally completed within 1 h: It might be slower in tumor cells than in normal ones due to a reduced adhesion between cells or to a reduced ability of repair in hypoxic cells. Another type of radiation-induced damage is the "potentially lethal damage" (PLD), whose repair may occur more easily in noncycling and in starved cells.

Reoxygenation is of therapeutic relevance in neoplasias containing a high fraction of hypoxic cells (generally rapidly growing), which are more radioresistant. The first radiation dose kills a certain number of fully oxygenated tumor cells, which are removed, and as a result, a higher oxygen diffusion to the hypoxic cells will occur. This phenomenon may be the basis both for an increase in radiosensitivity and for regrowth.

25.1.2 Therapeutic Studies with low LET Radiations on Experimental Brain Tumors

Both transplantable and autochthonous experimental brain tumors have been employed. The site of transplantation influences the response to radiation. The 9L gliosarcoma of rat is less responsive when transplanted subcutaneously than intracerebrally (D_0 332 cGy vs. 180 cGy). This may be due to differences in the perfusion and/or oxygenation of the tumor or to the number of cells repairing the PLD [2972, 3026]. Furthermore, dead cell removal is quicker subcutaneously [1526]. When employing intracerebral tumors in rats, the length of survival is the only parameter evaluable, as one cannot measure the size of the tumor before and after treatment or define the time of regrowth after radiation. Both with single and fractionated treatments a certain degree of dose-response relationship has been found: Total doses of 3000, 4600 and 5750 cGy were more efficacious than doses of 2000 or 2300 cGy, whereas an increase of the dose per fraction did not ameliorate the results [895, 2731, 1103, 3027].

The transfer to clinical practice of data coming fron experimental studies is limited by several factors, such as the frequent employment of single high doses, the different brain radiosensitivity and the short survival periods of animals, which does not permit an adequate evaluation of late effects.

25.1.3 Methods of Improving the Therapeutic Ratio in the Radiotherapy of Brain Tumors

Most malignant gliomas, both clinically and experimentally, have been shown to be quite radioresistant [575], and therefore, various methods of improving the therapeutic ratio in their treatment have been explored.

25.1.3.1 Altered Fractionation

Compared with a conventional treatment with daily fractionation, "accelerated fractionation" delivers the same total dose with more than one fraction per day, shortening the total treatment time. This technique might reduce tumor repopulation [2828], even though a too short interval between fractions might increase the risk of late damage [59, 273]. Hyperfractionation, i.e., the use of multiple small daily fractions in the same total treatment time, may permit the delivery of a higher total dose with an increase of the cell kill of the tumor. Nevertheless, it must be taken into account that the increase in tolerance of the nervous tissue (spinal cord of rat), by reducing the dose per fraction (from 200 to 100 cGy), is lower than expected theoretically [2904].

25.1.3.2 Brachytherapy

Brachytherapy consists of a continuous low dose irradiation delivered by an interstitial implant of radioactive isotopes in the tumor. The potential advantages over the teletherapy are a continuous reoxygenation, which makes the neoplastic cells more susceptible to radiation injury; a modification of the distribution in the cell cycle with a tendency of cells to accumulate in G_2 (more radiosensitive); a more effective repair of sublethal damage by normal tissues. Brachytherapy delivers doses higher than those of teletherapy to the tumor, provided it is relatively small, and the normal nervous tissue is better spared as the amount of radiation reaching it varies inversely with the square of the distance from the radioactive source. Some characteristics of gliomas render brachytherapy attractive: Most gliomas recur locally [1162], with only 5%–9% developing multiple lesions [441, 130], and slowly growing tumors (e.g., astrocytomas, oligodendrogliomas) seem radioresistant to low doses of external radiotherapy. Brachytherapy may be associated with teletherapy to increase the cell kill [2783, 180].

^{125}I brachytherapy has been shown to be efficacious in different experimental brain tumors, such as the 9L gliosarcoma [1034], ASV gliomas [2096, 701], and xenografts of human gliomas in nude mice [1664]. Another method of delivering a high radiation dose on a small target by external beams is radiosurgery, which is well known in clinical practice [1031], but experimental models are lacking.

25.1.3.3 Association with Chemotherapeutic Agents

A cytotoxic drug may enhance the activity of radiotherapeutic by a number of mechanisms. It may interfere with the repair of the radiation-induced damage, permits a reoxygenation of hypoxic cells by inducing a tumor shrinkage, and synchronizes the cell population by killing a certain number of tumor cells. Nitrosoureas are the best known chemotherapy agents in the field of brain tumors. In vitro, both with human glioma cells [1857] and cells from the 9L gliosarcoma [3024, 608, 607] BCNU, and to a lesser extent CCNU, has been shown to potentiate the activity of radiation in a dose-dependent fashion, probably by means of an inhibition of the repair of sublethal damage. There was a certain variability among different cell lines, with some of them responsive only to combined treatments and not to single treatments. In vivo, the combination of BCNU to radiotherapy has been demostrated in a dose-dependent fashion to be superior to single treatments in improving both median and long-term survival; in these latter, as in humans, a pulmonary fibrosis was evident [128, 2730, 3025, 2703, 3028]. Brachytherapy has been reported to be potentiated by BCNU [1034].

Radiosensitive properties have been attributed to bleomycin [1421].

25.1.3.4 Radiosensitizers

Malignant tumors, including brain tumors, are thought to contain a variable percentage of hypoxic cells responsible, at least in part, for the regrowth after conventional radiotherapy [1360]. A radiosensitization of hypoxic cells may be obtained through several mechanisms: an increase of oxygen diffusion by increasing the blood flow (triiodothyronine) or of oxygen pressure in the blood (hyperbaric oxygen); a direct cytotoxic effect (hyperthermia, nitroimidazoles); an oxygen-mimetic action in the presence of a low

oxygen concentration due to a high electron affinity (nitroimidazoles). Among nitroimidazoles, metronidazole and misonidazole are the best studied: Being liposoluble compounds, they reach high concentrations in both tumors and normal nervous tissue. Studies in vitro and in vivo regarding the radiosensitizing action of misonidazole have yielded conflicting results [2285]. In recent years, new compounds were being investigated, either with greater radiosensitizing properties (pimonidazole, RO 03-8799) or with better pharmacokinetic characteristics (etanidazole, SR 2508) [2024]. Nonetheless, a limiting factor of this therapeutic approach might be the limited size of the hypoxic fraction, reported both in some experimental [1611] and human [2057] gliomas.

Thiol-depleting agents reduce the cellular availability of sulfhydryl compounds, which favor the repair of damage from radiation-induced free radicals. The best known among these endogenous radioprotectors is glutathione (GSH), whose concentration in human brain tumors has been related to the degree of radiosensitivity [1520]. The intracellular level of GSH may be lowered by the *l*-buthionine-sulfoximine (BSO) which inhibits GSH synthetase, thus inducing a low to moderate enhancement of radiosensitivity [1909]. The depleting action of BSO has been demonstrated in D-54MG human glioma xenografts in nude mice, with a selective depletion of tumor and not of normal nervous tissue [2657, 764]. In the same model BSO potentiates the effects of brachytherapy [1664], provided that GSH depletion is almost complete. Furthermore, in vitro studies have suggested that BSO might potentiate the efficacy of nitroimidazoles [1909].

Another category of radiosensitizers is represented by halogenate analogues of pyrimidine, such as BrdU or IrdU, which are incorporated into the DNA of rapidly proliferating neoplastic cells to a much greater extent than in normal glial cells or neurons, because of their low mitotic index. Due to the high rate of hepatic degradation, an intraarterial (intracarotid) or intraventricular administration is required to achieve adequate cerebral concentrations [950, 999, 623].

Compounds able to reduce the energetic capabilities of neoplastic cells may interfere with the repair of radiation-induced potentially lethal damage, which requires energy. A certain efficacy has been reported in vitro on glioma cells for drugs interfering with glycolysis, such as 2-deoxy-2-d-glucose [690] and lonidamine [2115].

25.1.3.5 Hyperthermia

The potential advantages of hyperthermia are several [625]. Radioresistant hypoxic, S phase, and G_0 cells are heat-sensitive; hyperthermia inhibits the repair of sublethal and potentially lethal damage induced by radiation. Higher temperatures might be obtained in the tumor than in the normal nervous tissue due to the differences in blood flow.

Studies on the nervous tissue's tolerance to heat (generated by ultrasound, radiofrequencies, and microwaves) have shown that the cerebellum is quite heat-sensitive, and the threshold for neuronal damage is about 43°C [289, 2435].

The heat sensitivity of cells from experimental brain tumors (9L, BT4C) was variable [2370, 556, 1104]; in vitro, the hyperthermia response for glioma cell lines has been shown to be similar to the responses of other cell lines with no correlations between radioresistance and heat resistance [2247].

A synergistic effect has resulted from the combination of hyperthermia (42.5°C) and radiation on 9L cells [2370, 1104]. Hyperthermia, both alone and associated with

radiotherapy or chemotherapy or biologic modifiers, has shown a certain efficacy in several experimental brain tumor models in vivo [289, 1863, 1541, 1862].

25.1.3.6 Photoradiation Therapy

This mode of therapy consists in the systemic administration of certain compounds known as photosensitizers, which accumulate preferentially in neoplastic cells; when the photosensitizers are activated by light of an appropriate wavelength and intensity, they are able to destroy the cells [1371]. The primary damage might be to the vessel wall, with ischemic consequences. The best known photosensitizer is the hematoporphyrin derivative, whose efficacy was demonstrated in the 9L gliosarcoma [243], but it was limited by its inhomogeneous distribution and by the capability to penetrate into normal nervous tissue, thus inducing ischemic damage [3022].

New photosensitizers and more sophisticated systems of light delivery to deep tumors are currently being investigated [3023].

25.1.3.7 High LET Radiations

High LET radiation, compared with the low LET one, releases higher ionizing energy at the end of their path (so-called "Bragg peak"). The dose-response curve is characterized by a smaller shoulder (i.e., fewer cells able to repair the sublethal damage), and fractionation of the dose does not reduce its efficacy too much. In general, high LET radiations have a greater relative biological effectiveness (RBE), i.e., the ratio of the dose of a standard radiation such as X-rays of 250 keV, to the dose of a radiation of another type to produce the same biologic effect in the same biologic system. High LET radiations are less dependent for their efficacy upon the presence of oxygen (OER of 1–1.7) and cell cycle phases. Experimentally, fast neutrons have been shown to be equal, but not superior, to conventional radiation in prolonging the survival of rats bearing brain tumors [895, 2703].

Encouraging results, both in vitro and in vivo, have been obtained with the boron neutron capture therapy (BNCT) [747, 459]. It consists of the systemic administration of ^{10}B which preferentially accumulates in neoplastic cells, followed by irradiation with fast neutrons: From the reaction, highly ionizing α-particles are yielded.

25.1.3.8 Radioprotectors

An alternative method to improve the therapeutic ratio is that of selectively decreasing the sensitivity of normal tissue to the effects of radiation, without modifying the tumor sensitivity. The best known radioprotectors are the sulfhydryl compounds (cysteine, cysteamine and its derivatives), which act as free radical scavengers competing with oxygen in binding to the free radicals created by radiation. They protect fully oxygenated cells (such as normal cells) to a much greater degree than the hypoxic ones [2196]. WR-2721, a thiophosphate derivative of cysteamine, has been extensively studied: It is active in vitro on brain tissue [3108], but being highly hydrosoluble, it does not cross the BBB [2890]. Higher concentrations of WR-2721 in the brain of animals seems to be obtainable by a direct injection into the CSF [2706] and by an intracarotid injection with previous opening of the BBB with hyperosmolar mannitol [1562].

In recent years, the possibility that barbiturates (pentobarbital) may reduce cerebral radiation toxicity [2075, 2083] by a mechanism still unknown has been suggested.

25.2 Chemotherapy

25.2.1 General Concepts

A drug is effective against a tumor if neoplastic cells are sensitive to it and if the drug reaches the site of action at a cytotoxic concentration for an adequate period of time. Several factors may therefore influence the response to chemotherapy: the mechanism of action of the drugs and their timing, correlated to the kinetic parameters of the tumor; the intrinsic chemosensitivity of neoplastic cells; and the drug delivery, which, for brain tumors, is strongly influenced by the existence of the BBB [2608, 821]. Chemotherapy agents are either cycle-specific, i.e., effective only in some phases of the cell cycle, or non-cycle-specific, i.e., effective whatever the phase. Some drugs, e.g., BCNU, are non-cycle-specific, but they are more effective during DNA synthesis. A single agent may seldom be effective against all neoplastic cells, for several reasons: Tumors may be composed of cells with varying chemosensitivity; a tumor cell line, initially sensitive to a drug, may become resistant after several exposures (e.g., methotrexate); the volume reduction obtained either with a non-cycle-specific agent or with surgery or radiotherapy induces a shift of tumor cells from the nonproliferating (G_0) to the proliferating compartment, thus increasing the growth fraction. Polychemotherapy, i.e., the association of drugs with different mechanisms of action, relies on these premises. For instance, if a non-cycle-specific agent is used first, a cycle-specific agent (e.g., 5-fluorouracil, methotrexate) should be used during the following phase of regrowth. Some drugs (e.g., vincristine, VM26) may be used to synchronize the cell cycle to accumulate the greatest number of cells in a phase sensitive to a cycle-specific agent administered subsequently. With polychemotherapy, it is also possible to associate drugs with different toxicities (e.g., nitrosoureas, which are myelotoxic, and vincristine or VM26, whose myelotoxicity is much lower), so that every agent may be administered at a full dose.

25.2.2 Chemosensitivity and Chemoresistance in Brain Tumors

The existence of a heterogeneity in the sensitivity to various chemotherapeutic agents (BCNU, cisplatin, procarbazine, vincristine, doxorubicin, α-difluoromethylornithine, etc.) for clones deriving from both human malignant gliomas [1486, 827, 2603, 3111, 136] and experimental brain tumors [2360, 3102, 2956] is well established. There are differences in the chemosensitivity among tumors and among different regions of the same tumor [2608]. BCNU-sensitive cells are usually hyperdiploid, whereas BCNU-resistant ones show diploid karyotypes [2602] and might be the dominant cell type in the recurrent tumors [2601]. The exposure to low drug doses of BCNU might facilitate the development of highly resistant clones [2608]. Different mechanisms may underlie the drug resistance, being different in different tumors and for different drugs, and some of them might act simultaneously. A reduced uptake is known for methotrexate [363], whereas an increased active efflux has been shown in lines from human gliomas for vincristine [1331] and in C rat glioma for doxorubicin and ACNU [2956, 3104]. The existence of an increased active efflux mechanism in cell lines from 9L gliosarcoma is un

certain [2608, 3104]. The drug resistance to vincristine and doxorubicin is a "multidrug resistance" (MDR) [2559, 1806]: In cells deriving from both noncerebral and cerebral tumors, the MDR seems correlated with high levels of a membrane P-glycoprotein [2559, 1807], which could bind to antineoplastic agents and thrust them out of the cell. The development of an MDR seems correlated with an increased expression and amplification of either a gene (MDR.1 gene) or a family of genes which codify this P-glycoprotein [1355, 2579]. An increased expression of MDR-dependent mRNA has been detected in vincristine-resistant cell lines from human gliomas [1806]. The MDR.1 gene has been detected in normal brain and benign and malignant tumors, while P-glycoprotein can be present in tumor blood vessels even though it is not demonstrable in tumor cells [1981A]. Calcium blocking agents, e.g., verapamil, which specifically compete with some cytostatic drugs for binding with P-glycoprotein, may prevent the efflux of the drugs from the cell in vincristine- and ACNU-resistant cell lines from glioma [3104, 1806].

Other mechanisms involved in the resistance to chemotherapy agents are either an alteration of the intracellular distribution and/or a transformation of the drug [2559] or an activation of compensatory metabolic pathways, e.g., an increase of dihydrofolate reductase synthesis for methotrexate [363].

In recent years studies have been devoted to cellular mechanisms of repair of damage from alkylating agents, particularly chloroethylnitrosoureas (CENUs). One of the reaction sites between these compounds and DNA is the O6-position of guanine. Repair from this damage is based on the action of the enzyme *O*-alkylguanine DNA alkyltransferase (GATase), which moves the alkyl group formed in the DNA to a cysteine residue contained in its sequence. This reaction restores the guanine in DNA and inactivates the alkyltransferase: Thus, a "de novo" synthesis of the enzyme will be necessary. GATase is present in cell lines and xenografts from human gliomas, in surgical specimens from several brain tumors (especially meningiomas and neurinomas), and in normal nervous tissue [3035, 2555]: The amount of this enzyme is variable but generally lower in cell lines than in xenografts or in resected tumors, and the same is true for normal nervous tissue compared with brain tumors. It has been hypothesized that the GATase activity level might influence the cell chemosensitivity to alkylnitrosoureas, including chloroethylnitrosoureas [1980]. Recent data seem to confirm this hypothesis: a BCNU-resistant cell line from the 9L gliosarcoma (BTRC-19) has shown high levels of GATase [1659], and an inverse ratio between the GATase level and the chemosensitivity to BCNU has been found in xenografts from human gliomas [2555]. An increase of O-alkyltransferase activity in cell cultures and xenografts from brain tumors after radiotherapy has been reported [2359]. If a radiation-induced increase of BCNU resistance is confirmed, the administration of CENUs would be more effective before, and not after, radiotherapy.

Glutathione (GSH) binds to intermediate products of CENU catabolism, thus reducing their alkylating activity, and may prevent damage from several chemotherapeutic agents. A mild correlation between GSH content, GSH synthetase activity, and BCNU resistance has been shown in cell lines from human gliomas [31]. BSO, which depletes the intracellular glutathione content, seems to increase the cytotoxicity of BCNU in resistant cell lines from human gliomas [30] and of melphalan in xenografts from medulloblastoma [833].

Several assays have been developed to test the chemosensitivity of brain tumors in vitro [1422].

The colony forming assay (CFA) measures the effect of a drug upon stem cells, i.e., cells that maintain their ability to divide. It has several limitations: Noncycling cells, which may potentially enter the cycle, are sometimes not measured, and a high percentage of stem cells in gliomas may actually be in a resting state (G_0); a low cell density does not occur in vivo; many neoplastic cells do not form colonies, whereas a growth of normal tissue is possible. Radiolabeled precursor inhibition assays measure the drug-induced inhibition of labeled precursors of DNA, RNA, and protein synthesis (e.g., thymidine, uridine, or amino acids). The main limitation of these assays is the possibility of measuring only an inhibition of synthesis, which may be a temporary effect, and not the extent of cell death. Microcytotoxicity and growth inhibition assays measure chemosensitivity by counting viable cells, one or several passages after drug exposure. The advantage of the short time needed for the test is hindered by a lack of sensitivity due to the large amount of drug required. Organ culture and multicellular tumor spheroid assays are based on the morphologic evaluation of tumor growth. They more closely reproduce in vivo conditions (e.g., problems of drug penetration), but they are considered less reliable. The sister chromatid exchange (SCE) assay measures the drug-induced metaphasis SCE. For detecting the effects of low drug concentrations, it is rather sensitive, but it does not directly measure cell kill.

Several authors, employing in vitro assays, have retrospectively correlated the chemosensitivity with clinical outcome [1489, 240, 2361, 2360, 2833]. In vitro resistance to BCNU generally predicts clinical resistance, whereas in vitro sensitivity is associated with a clinical response in only 65% of patients. A sensitivity to BCNU has been reported as more frequent in young patients with longer survival expectations. Studies in which chemotherapy is prospectively selected on the basis of in vitro results are in progress, while the true clinical impact of drug testing remains to be defined.

The regional heterogeneity of malignant gliomas remains a limiting factor for all in vitro assays; however, more problems are to be solved before they are considered reliable in planning an adequate chemotherapy for individual patients: the use of a drug concentration reproducing tumor concentrations in vivo; the use of a time exposure adequate for both cycle and non-cycle-specific drugs; the possibility of testing single agents which require metabolization before they are effective and multiple agents.

25.2.3 Drug Delivery to Brain Tumors

Several factors determine the concentration in the nervous tissue and in brain tumors of a systemically administered drug [1002]. These are the plasma level of the free drug in relation to time, the BBB permeability, and the local brain flow rate. After the systemic administration of a drug, the time needed to achieve a peak in the serum depends on the modalities of administration; the concentration thereafter diminishes because of redistribution, elimination, and catabolism. The amount of drug reaching the nervous tissue depends on the plasma concentration peak and its duration: A high steady-state concentration may optimize drug uptake, whereas a rapid clearance makes it minimal. The BBB permeability to the drug is directly correlated with its lipophilicity, as determined by its octanol/water partition coefficient, p. Highly lipid-soluble compounds (e.g., nitrosoureas) may rapidly diffuse through the BBB, and the only limitation to their distribution in the nervous tissue is the local flow rate, whereas water-soluble compounds have a very limited penetration in the nervous tissue. Recent studies utilizing quantita-

tive autoradiography in experimental brain tumors [224] and PET in human brain tumors [1289, 298] have shown that the breakdown of the BBB may be variable within large metastatic lesions and malignant gliomas, and in some areas, the BBB is almost intact. Most often, there is a breakdown in the BBB with a reduction of blood flow, but in peripheral areas, the breakdown is minimal, and the blood flow is nearly normal. In the BAT (brain adjacent to tumor) the capillary permeability may sometimes be reduced compared with normal nervous tissue [1626]. In very small tumors and in low grade gliomas, the BBB and flow rate are almost normal [1002].

For drugs which cannot cross an intact BBB (e.g., water-soluble compounds), the only possibility of access to a brain tumor is that of a passive diffusion from areas with a breakdown of the BBB, but this mechanism seems to have a limited cytocidal effect [1624]. Problems of drug distribution may exist even in the presence of a breakdown of the BBB [1002]. The distance between capillaries is often increased in brain tumors, thus reducing drug and oxygen diffusion, with many cells remaining in G_0, and thus not sensitive to cycle-specific agents; both normal tissue around the tumor and the CSF act as a diffusion sink, reducing the cytocidal concentration of the drug inside the tumor; and the perivascular drainage is effective in brain tumors. Except for the nitrosoureas, most antineoplastic drugs do not have the physicochemical characteristics required to diffuse through the BBB; therefore, they do not reach an adequate concentration in the nervous tissue after intravenous administration, and this fact has led to the search for new modalities of drug delivery and for new drugs.

Among new therapeutic modalities, some are meant to increase the blood concentration of the drug, by administering very high doses or by locoregional, intraarterial administration. Methotrexate, which is water soluble, can scarcely diffuse through the BBB at conventional dosages [2606], but its uptake is significantly increased if it is administered at high continuous doses (over 24 h) [363] (in association with leucovorin rescue to minimize the cytotoxic effects on normal tissue). High doses of drugs with hematologic toxicity (e.g., BCNU) may be administered intravenously in association with autologous bone marrow transplantation [776].

Intraarterial (carotid and vertebrobasilar) administration of a drug [2739] leads to higher concentrations of the drug in the tumor, as confirmed in PET studies [762], with minimal systemic toxicity. Among different drugs (alkylating agents, antimetabolites, plant alkaloids, cisplatin, nitrosoureas, antibiotics), most studies have employed BCNU, because of its liposolubility and its rapid plasma degradation. At present, the risk of delayed neurotoxicity is high, especially with superselective infusions distal to the ophthalmic artery [800, 143]. Neurotoxicity has been related to the drug itself, to the ethanol used as a diluent, to the association with radiotherapy, and to a streaming phenomenon [2449] determining a dyshomogeneous distribution of the drug, with the risk of neurotoxic concentrations in normal areas.

Modalities to circumvent the BBB have also been developed.

25.2.3.1 Intra-CSF and Interstitial Chemotherapy

The administration of drugs directly into the CSF by a lumbar or a ventricular route allows a high concentration of the drug to be reached in the CSF with a lower dosage. The drugs most often used are methotrexate and cytosine arabinoside. Drug diffusion

through the BBB is minimal, except for a few areas [1003], and some risks must be considered, such as erroneous injection into the subdural and extradural space, infections and neurotoxicity. The administration of the drug directly into the tumor (interstitial chemotherapy) is feasible with intraoperative topical application and local injection by catheters and implantable pumps [1057, 279, 2851].

25.2.3.2 Transient and Reversible Blood–Brain Barrier Modification

The so called osmotic opening of the BBB is based on the observation [2273] that the rapid intracarotid administration of a water soluble hyperosmolar agent, e.g., mannitol, determined a transient and reversible opening of the BBB (within 4 h), with a sevenfold increase of the permeability to methotrexate [2274]. The increased capillary permeability seemed to depend on an osmotically induced shrinkage of the endothelial cells with a partial opening of the tight junctions; their progressive rehydration restored the integrity of the BBB. Several antineoplastic drugs (cisplatin, adriamycin, bleomycin, 5-fluorouracil) showed neurotoxicity in dogs and rodents, when administered after osmotic opening of the BBB, and only methotrexate and cyclophosphamide proved to be relatively safe [2015, 2014]. Data deriving from the application of this modality in experimental brain tumors are contradictory: According to some authors [2014], there is an increase of the capillary permeability in the tumor and peritumoral tissue, while according to others [2985, 1009] there is an increase of permeability only in normal nervous tissue (brain cortex, corpus callosum). These discrepancies could be partially ascribed to the different responses of microvessels in different experimental tumors [1098]. Nonetheless, the osmotic opening of the BBB has been recently questioned [786], because it is aspecific and allows the diffusion of many hydrophilic endogenous compounds (bradykinin, peptides, and amino acids) which may be neurotoxic. Because of these incertainties, it seems preferable to conduct more experimental studies before this modality is extensively utilized in man [1009].

Brain irradiation at low doses can transiently increase the vascular permeability in the nervous tissue of rats [1625, 2195, 618], but not in experimental brain tumors, and the same seems true at high doses [2707, 618].

25.2.3.3 Carrier Systems and Liposomes

Experiences with these two modalities are still in an early phase.

The diffusion of some drugs (especially water-soluble ones) through the BBB would be increased if their structural similarities with other compounds normally carried through the BBB by active carrier systems could be exploited. For instance, melphalan has been shown to have some affinity for the large neutral amino-acid carrier system [1002] and sarcosinamide chloroethylnitrosourea has some affinity for the colamine carrier system [2656]. It is possible to develop real carrier drugs, i.e., lipophilic compounds, which could transiently bind a polar agent and diffuse with it through the BBB. Liposomes are artificial lipid vesicles diffusing through the capillar endothelium, and they may incorporate and carry several drugs, enzymes and monoclonal antibodies [281]. An increased cytotoxicity for methotrexate carried by liposomes on human glioma cells has been reported in vitro [1435]. However, in an experimental model of brain

metastasis from melanoma [2465], an accumulation of liposomes in the tumor and in normal nervous tissue with significant toxicity from embolism has been shown.

The search for specific antineoplastic agents to be used in brain tumors continues in two directions [1003]: (1) the synthesis of new lipophilic compounds; (2) an incraese of the liposolubility of already known agents. SHM (spirohydantoin mustard) and AZQ (aridinylbenzoquinone), estramustine, fotoemustine, etc.) are drugs belonging to the first group, whereas drugs derived from the nitrosoureas BCNU and CCNU (MeCCNU, PCNU, ACNU, etc.), from methotrexate (trimetrexate), and from chlorambucyl (prednimustine) belong to the second group.

25.3 Immunotherapy

Two different immunotherapeutic approaches are possible: (a) the utilization of monoclonal antibodies as either cytotoxic agents or carriers of chemotherapeutic agents and radionuclides; (b) the stimulation of the immune response against the tumor.

The possibility of using monoclonal antibodies as cytotoxic agents against tumor cells was experimentally confirmed in vivo and in vitro [1430, 1893, 2332, 377]. These data suggest that adequate monoclonal antibodies against tumor cells may have a therapeutic role for solid tumors in man.

Since 1905 Ehrlich suggested employing antibodies as carriers of chemotherapeutic agents, but this approach became suitable for immunotherapy only with the use of monoclonal antibodies. Highly specific monoclonal antibodies may be used as carriers of radionuclides, toxins or drugs [269, 3029,1047A]. Toxins from both plants and bacteria (ricin, abrin, gelonin, diphtheria toxin and toxin from *Pseudomonas aeruginosa*), drugs, (chlorambucil, methotrexate, daunomycin, and neocarzynostatin), and many radionuclides have been successfully conjugated with antibodies. There is a growing interest in the epidermal growth factor receptor (EGFR) as a target for monoclonal antibodies in human malignant gliomas [2341, 276].

These techniques present, however, many limitations in their use. The first one depends upon the incomplete specificity of monoclonal antibodies against brain tumors, with a cross-reaction with normal tissue. The amount of antibodies reaching the target depends upon several factors, e.g., tumor vascularization, capillary permeability, blood flow rate, and extracellular fluids [327]. Antibodies may easily reach the deep portion of the tumor, because of the breakdown of the BBB, but the same is not true for the periphery of the tumor, which is actively proliferating. Therefore, agents which may modify the BBB permeability to antibodies [2013] might be needed. Another major limitation derives from the antigenic heterogeneity of malignant gliomas [327], so that a monoclonal antibody may only bind to a limited proportion of the tumor cells. This low sensitivity is a consequence of the high specificity of monoclonal antibodies, so that better results might be obtained if different antibodies binding to different tumor antigens were given at the same time. Finally, the possibility of an anaphylactic reaction, due to repeated administrations of immunoglobulins, must not be neglected.

The second approach to immunotherapy is a modification of the cell-mediated immune response against the tumor. Stimulation of the immune response may be obtained with either lymphokines, e.g., χ-interferon and IL2, or activated lymphocytes. In the immune response, χ-interferon may stimulate the expression of class II HLA-DR antigens in macrophages, thus increasing the antigen presentation to T lymphocytes. It has been observed that astrocytes and glioma cells may express HLA-DR antigens and that χ-interferon may increase the expression of these antigens [900, 2201]. Moreover, these cells may present antigens to T lymphocytes in vitro. One may hypothesize that the administration of χ-interferon also stimulate the in vivo immune response to gliomas, increasing the presentation of tumor antigens to T lymphocytes that infiltrate the tumor [593]. IL2 might be used because it stimulates T-cell proliferation, thus increasing the number of activated lymphocytic populations. Another technique involves the administration of specifically activated autologous lymphocytes. T lymphocytes cytotoxic for tumor cells might be administered, as it is now possible to expand in vitro lymphocytic clones activated by tumor cells [3093].

The existence of specific lymphocytic populations has been shown in human gliomas, which are significantly more active than peripheral blood lymphocytes and kill allogenic and autologous tumor cells. The possibility of expanding these populations to a sufficiently high number and injecting them into the tumor seems attractive. Also, the so-called LAK cells, autologous killer cells activated by lymphokines, may be useful in the immunotherapy of gliomas [1271].

A major obstacle to these techniques for immunotherapy is the presence of factors that decrease the immune response against gliomas. Besides the existence of circulating immunoglobulins and antigen-antibody complexes that may inhibit the immune response [2654], a factor that may antagonize the activity of IL1 and IL2 has been isolated in cultures of glioma cells [798]. This factor, which has been recently identified as transforming growth factor β_2 (TGF-β_2) [587], inhibits the IL2-dependent T-lymphocyte proliferation and the production of cytotoxic T lymphocytes in culture and of LAK cells [1537]. Antibodies against this "glioma-derived T-cell suppressor factor" to antagonize its immunosuppressant effect might be tried.

26 Effects of Treatment on Brain Tumors and Normal Nervous Tissue

26.1 Effects of Radiotherapy and/or Chemotherapy on Human Brain Tumors

The effects of radiotherapy and chemotherapy on malignant gliomas have been studied extensively [3050, 902, 1295, 334, 2505, 2506, 2508, 1034A]. Since they are not specific, it is difficult to separate them from those developing spontaneously in the tumor during its natural course. An example is glioblastoma central necrosis. The frequency of the changes depends on the material available for study, biopsy or autopsy, time elapsed between treatment and death, and radiation dose. Macrophagic areas, monstrous and giant cells (Fig.26.1), atypical mitoses and bizarre astrocytes are maximally represented at a short distance from the irradiation and, therefore, might be considered as "short-term effects". Vessel wall changes, e.g., hyalinization and fibrinoid necrosis, increase both with the radiation dose and the distance from treatment. Also, the disappearance of morphologic features typical of active growth such as endothelial proliferations and mitoses, parenchymal mitoses and circumscribed necroses with pseudopalisading can be attributed to radiotherapy. All these features reappear along with the tumor regrowth that most frequently happen for glioblastomas between 6 and 12 months after doses of about 6000 cGy [2508, 336]. Interesting but not specific are the morphologic patterns of regrowth: An overgrowth of a population of small anaplastic cells may take place and tumor repopulation may start again both from cells in the brain adjacent to the tumor (BAT) and from cells close to the central necrosis. The tumor builds up new vessels from those of the normal nervous tissue already damaged by irradiation, as demonstrated by the occurrence of endothelial hyperplasia in vessels with fibrous-hyalin degeneration of the wall. In long term survivors, more commonly after 1 year past the end of radiotherapy, a population of fibroblastic-like cells develops from thickened hyalinized vessel walls [2522]. These cells have been interpreted as an expression of a sarcomatous transformation, even though true fibrosarcomas from irradiated glioblastomas have never been observed, perhaps because of the associated short duration of survival.

Morphologic changes produced by chemotherapy on malignant gliomas are hardly distinguishable from those produced by radiotherapy. An increase of monstrous and giant cells and, less frequently, of nuclear hyperchromasia and nuclear-cytoplasmic inclusions after treatment with different drugs are reported [1297].

In all autopsy series of malignant gliomas treated with radiotherapy after surgery [334, 2505, 2506] or intraarterial chemotherapy [2363], there are patients with no sign of tumor regrowth but with severe damage of the normal nervous tissue.

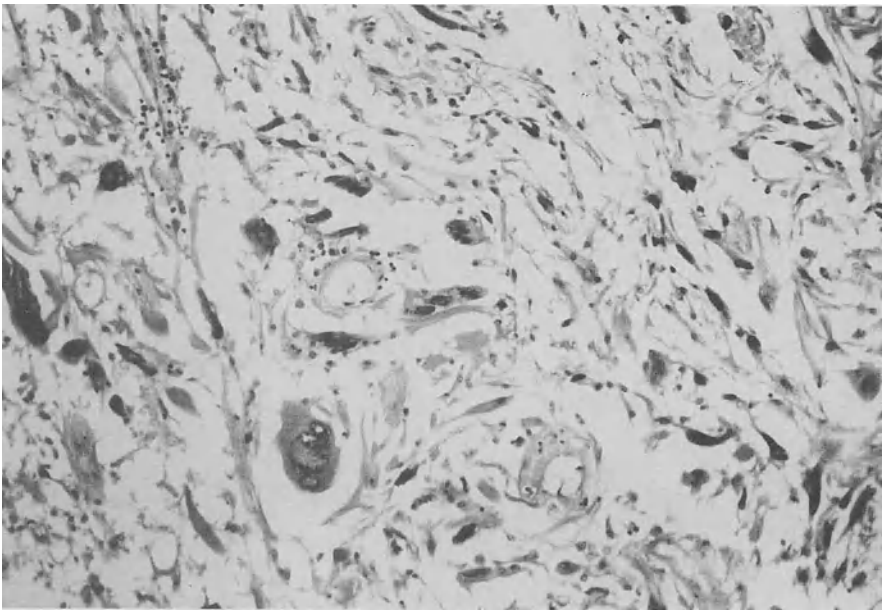


Fig.26.1. Monstrous cells in irradiated glioblastoma, H&E, ×400

Very few data are available on the effects of radiotherapy on well-differentiated astrocytomas. In a personal series [2510], astrocytomatous areas of glioblastomas were studied, and the only change was chronic edema. In one case, small necrotic foci were found, probably representing small anaplastic foci sterilized by radiation. In the case of brain tumors more radiosensitive than gliomas, such as medulloblastomas, germinomas, lymphomas, leukemias, and metastases, an almost complete sterilization of the neoplastic cells may sometimes be observed.

26.2 Effects of External Radiotherapy on the Human Brain

Adverse effects of external radiotherapy on the normal human brain may be divided into three types according to the latency period [2618, 1607A]: acute, early delayed, and late delayed. Acute effects occur during irradiation and clinically are variably characterized by headache, nausea and vomiting, somnolence, temperature elevation and an exacerbation of neurologic symptoms and/or signs, being transitory and reversible with steroids. The acute syndrome is more frequent when the previous neurological status of patients was poor and when treatments with high doses per fraction (>200 cGy) are used. No pathologic data are available on this syndrome.

Early delayed effects appear between 2 weeks and 4 months after irradiation, with a variety of reversible neurologic symptoms, and the incidence may approach 25%

[694]. Autopsy cases are exceptional [1560, 1561, 1916]. The neuropathologic picture consists of multiple, punched-out foci of demyelination, perivascular infiltration of lymphocytes and plasma cells, glial reaction, and absence of degenerative changes of vessel walls.

Among late delayed effects, "cerebral radionecrosis" is the best known pathologic and clinical entity. It may follow the irradiation of extracranial tumors (carcinomas of the nasopharynx, scalp, paranasal sinuses, etc.), intracranial extraparenchymal tumors (pituitary adenomas), and both primary and secondary intraparenchymal tumors [1501, 591, 1786, 2375, 629, 2618, 1772, 2507, 2766, 937, 2456, 2895, 2686, 1170, 22]. The latency period is somewhat dose-dependent and varies from several months to years after exposure, with 70% of cases appearing within 3 years [1501]. An exceptional latency period has been recorded of 32 years [1981].

Radionecrosis develops in brain tissue included in the target volume of radiotherapy, which varies according to the different tumor types. In pituitary tumors, damage occurs in the temporal lobes and/or hypothalamus, seldom in the frontal lobes; with intracerebral tumors treated by whole-brain irradiation (such as malignant gliomas and metastases), the damage frequently occurs in the peritumoral tissue, far from the tumor, contralateral or bilateral, and may coexist with neoplastic tissue, both quiescent and actively growing. It has been hypothesized that structural and/or metabolic changes induced by neoplasia, mainly through edema, make peritumoral areas, which generally receive the highest doses, more prone to radiation-induced damage [334, 2507]. Generally, radionecrosis, like the other minor radiation-induced changes, prevails in the white matter, with the sparing of U-fibers, corpus callosum, internal capsule, and optic pathways (Fig.26.2). Changes may also be found in the cortex and meninges.

Histologically, the most characteristic feature of delayed radionecrosis is represented by fibrinoid necrosis of small and medium-sized vessel walls (Fig.26.3), which frequently coexist with coagulative necrosis of the parenchyma [334, 2507]. Variously associated are hyaline thickening of the vessel walls with endothelial atrophy, thrombosis, hemorrhages, telangectasias, endothelial or adventitial hyperplasias (more rarely), and features attributable to chronic edema, such as demyelination, spongiosis, spongionecrosis, and gliosis. Endothelial cells with bizarre nuclei and bipolar cells with prominent nucleoli (probably fibroblasts altered by radiation) may be present.

The damage to the BBB is best seen at the ultrastructural level [1676, 1809]: Features corresponding to fibrinoid necrosis are represented by vessels with interruption of the endothelial lining and the penetration of fibrin and other blood components into the dilated subendothelial space. Vessels with an uninterrupted endothelial lining but showing surface infoldings and an increase of pinocytotic vescicles and cytoplasmic organelles are visible as well. Basal membranes appear fragmented or laminated ("onion skin effect"), and there is an increase of collagen fibers in the vessel wall.

The common clinicoradiologic picture of delayed radionecrosis is that of an expanding intracranial mass, with focal neurologic symptoms and signs: CT shows a hypodense lesion which often takes up the contrast enhancement (Fig.26.4), especially after the highest radiation doses, and is avascular on angiography study [604]. The diagnosis is difficult when the mass lesion occurs at the site of a previously irradiated tumor, as tumor recurrence and radiation necrosis with little or no persistent tumor cannot be differentiated by CT or MRI [2894]. PET now seems to give more valuable information [2145, 628, 659]: Utilizing as a metabolic tracer ^{18}-F-2-fluoro-2-deoxyglucose, radionecrotic lesions are often hypometabolic in contrast to actively recurrent tumors, which are hypermetabolic. Biopsy remains today the only means to establish a differential diagnosis.

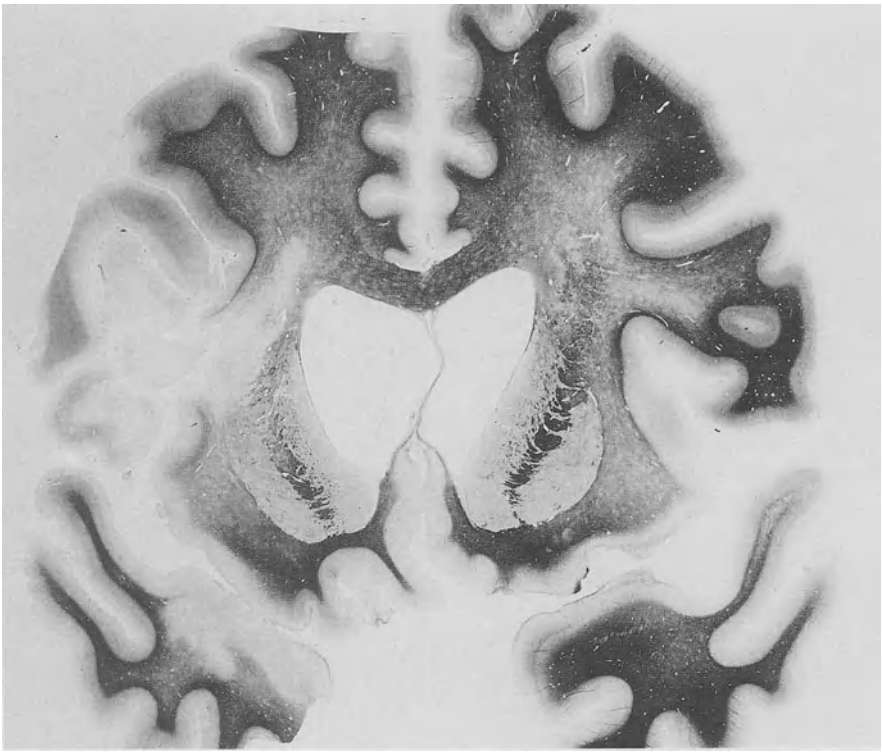


Fig.26.2. Radiation necrosis and chronic edema in the white matter, Luxol Fast Blue B

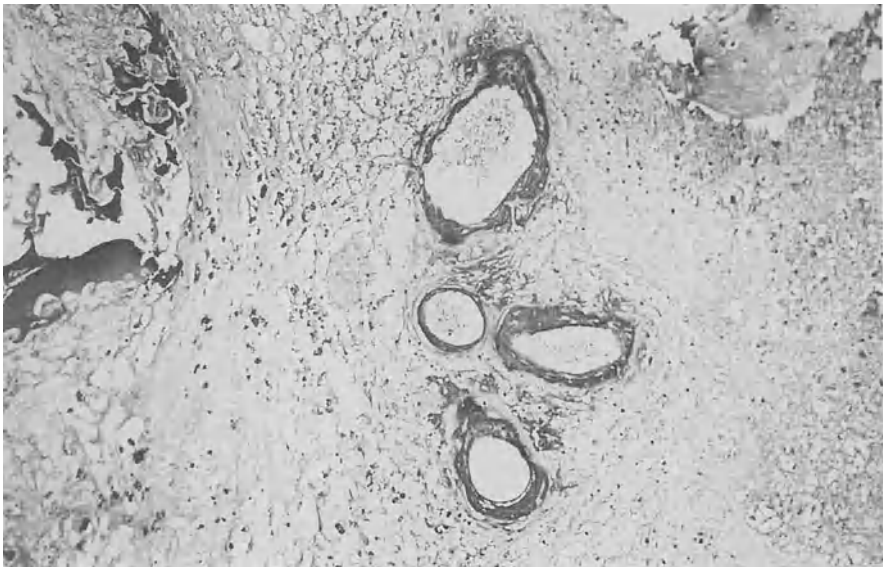


Fig.26.3. Area of coagulative necrosis and fibrinoid degeneration of the vessel walls, H&E, ×200

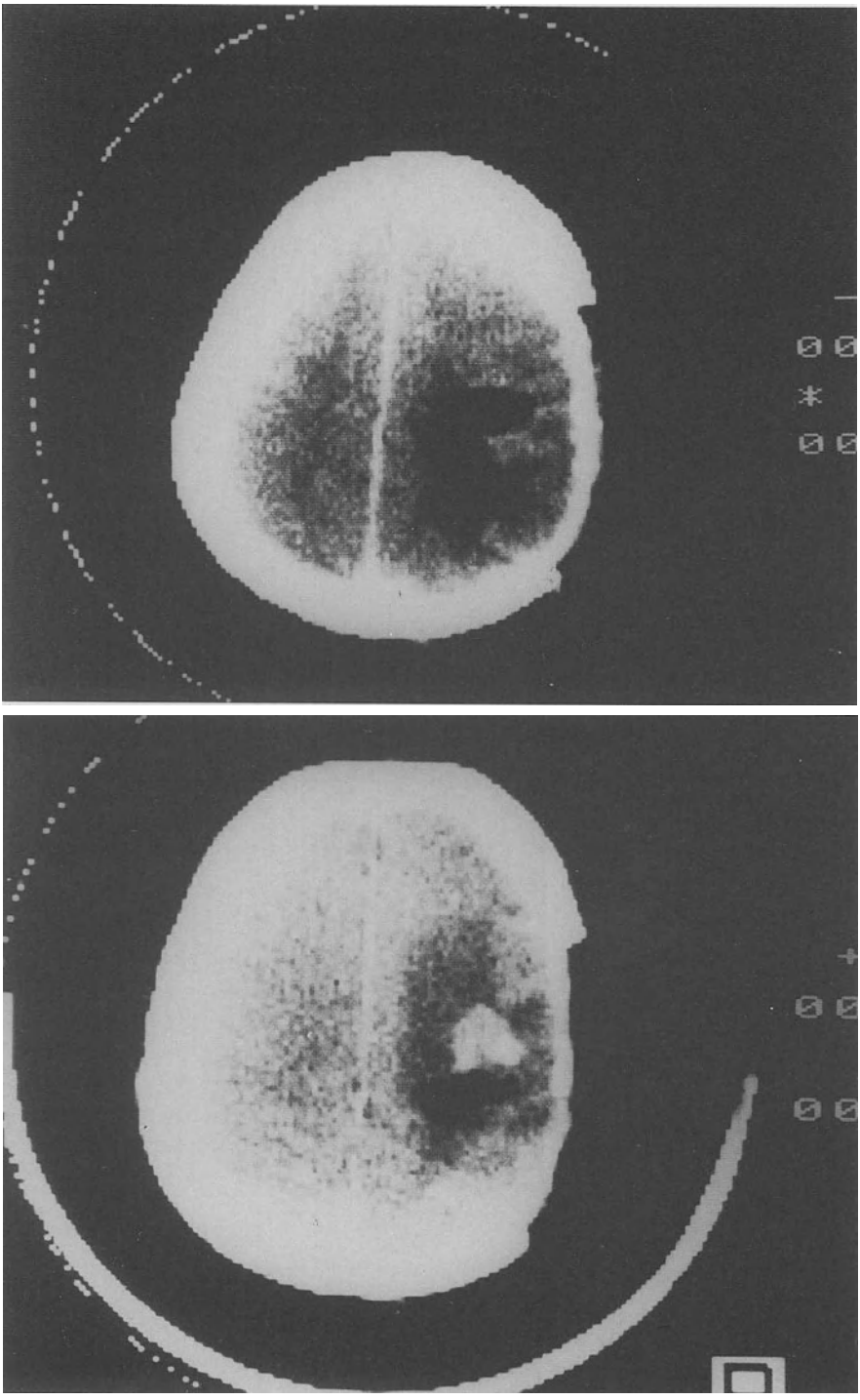


Fig.26.4. a Postoperative CT scan of a right parietal glioblastoma; **b** 18 months after radiotherapy, radionecrosis mimicking a recurrence

When radionecrotic lesions are multiple, the clinical picture is generally that of a progressive dementia, with diffuse hypodensity of white the matter [1888] or multiple enhancing lesions [2424] on CT scan.

The best treatment for radionecrosis presenting as a single intracranial mass is that of surgical removal [694]. Improvement has been obtained with steroids, and recently, the efficacy of anticoagulant drugs has been reported [2334, 935]

The true incidence of pathologically proven delayed radionecrosis with little or no persistent tumor is not entirely known, due to the low percentage of patients (especially with intracerebral tumors) who are biopsied or autopsied at a distance from radiotherapy. It is very rare in extracranial tumors, its incidence ranging from 1.4% to 10.8% in pituitary adenomas [1888, 1006] and from 3% to 5% in malignant gliomas [1778, 1888, 1772, 2686], reaching 12.5% in patients surviving more than 18 months [2686]. The incidence in an autopsy series of malignant gliomas is obviously higher, reaching 10%–22% [1772, 2686].

The factors influencing the risk of radionecrosis are the radiation parameters, the association with chemotherapy agents and individual characteristics. The risk increases with the increase of total radiation dose, being very rare below 5000 cGy and maximum at the highest doses (6000 cGy) [2618, 1888, 1772, 2686]. With the same total dose delivered, the risk increases using doses per fraction higher than 170–180 cGy [1772, 2426], whereas the overall treatment time is not critical. The brain volume included in the target of high doses seems to be important [1773], but no extensive studies are available. Re-irradiation seems to increase the risk of late damage [662].

Hypoxic cell sensitizers do not have central neurotoxicity, whereas no data are available on the association of conventional radiotherapy with brachytherapy or hyperthermia. The use of fast neutrons instead of conventional photons increases the incidence of radionecrosis, while permitting a more efficacious tumor control [2614, 1580, 1761, 394, 687]. Chemotherapy agents such as methotrexate [283] and the nitrosoureas [2609] may increase the toxicity of radiation, expecially when administered in high doses. High steroid doses during radiotherapy have a protective action [334, 2686], whereas preexisting illness such as arterial hypertension [2507], diabetes [1007], some endocrinopathies [71], and, more generally, vascular diseases [3116] may act as predisposing factors.

Independent of the picture of radionecrosis, other changes can be found in the peritumoral white matter of brains of patients autopsied at a distance from radiotherapy, [2507]: hyaline thickening of vessel walls (Fig.26.5a), macrophagic areas (Fig.26.5b), demyelination with loss of oligodendrocytes, spongiosis and spongionecrosis (Fig.26.6), and gliosis. This last sometimes is so strong, with multinucleated and/or monstrous astrocytes, as to be indistinguishable from an astrocytomatous proliferation [1229]. More rarely, amyloid deposits [1750], cortical atrophy [321], and changes in the cerebellar cortex (vacuolization, loss of Purkinje cells and granules) [2420] are observed.

Most patients showing these changes died from tumor progression, but a few, in whom autopsy did not show tumor regrowth suffered a slowly progressive dementia of the subcortical type. Sometimes, the clinical picture is that of a subacute leukoencephalopathy with a relatively short latency (10–24 months), which is being increasingly reported in gliomas, medulloblastomas, and metastases after treatment with unconventional radiation schedules, and with or without aggressive polychemotherapy [1599, 2108, 2679, 600]. The white matter, mainly periventricular, appears diffusely hypodense on CT and hyperintense in T2-weighted images on MRI (Fig.26.7) [839, 2894],

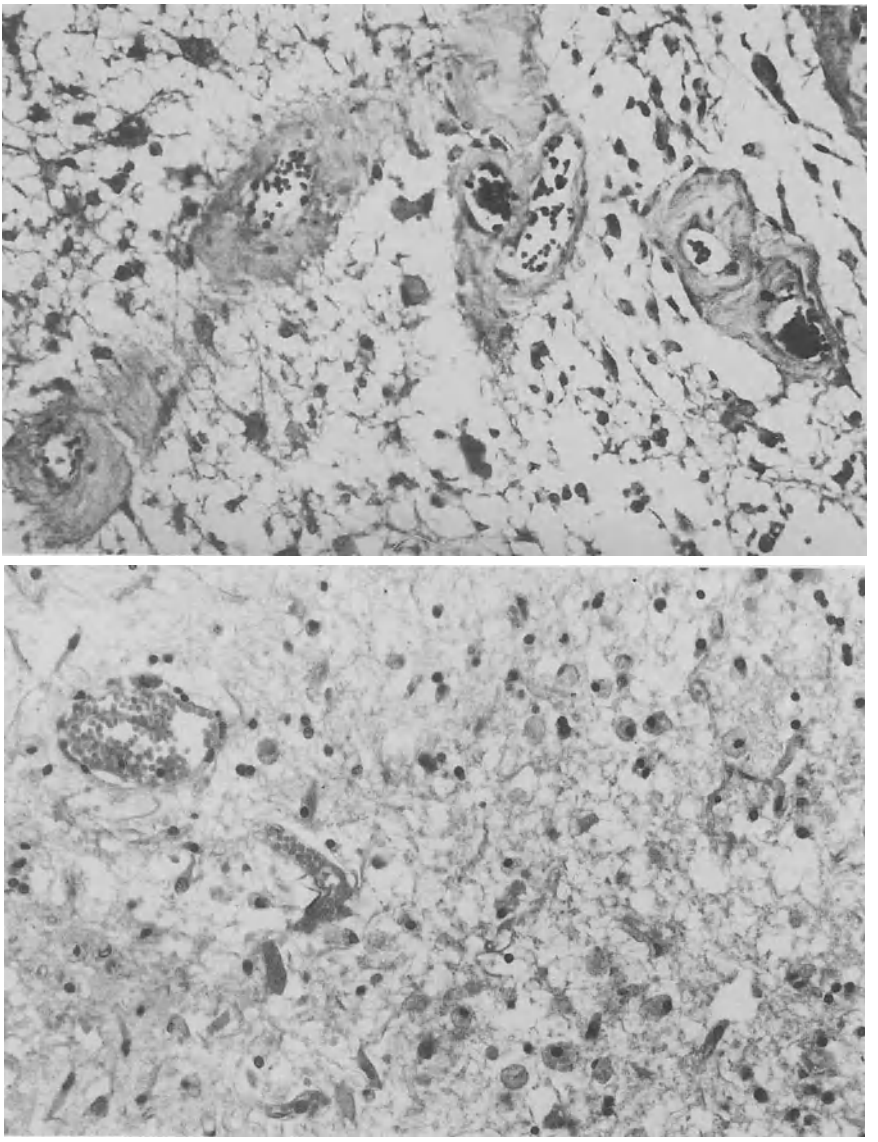


Fig.26.5. a Hyaline degeneration of the vessel walls and **b** macrophagic areas following radiotherapy, H&E, ×300

as seen in atherosclerotic cerebrovascular disease [2875]. Conclusions on the correlation between the pathology and neuroimaging results after treatment are not yet possible, as the number of cases adequately studied is small, and there are many discrepancies. It should be remembered that a very low incidence of cortical atrophy at autopsy in a series of patients showing CT signs of atrophy has been found [2980].

Among late delayed effects are some clinical observations which have not been pathologically substantiated. Besides frank dementia, neuropsychologic sequelae have been reported in a vari-

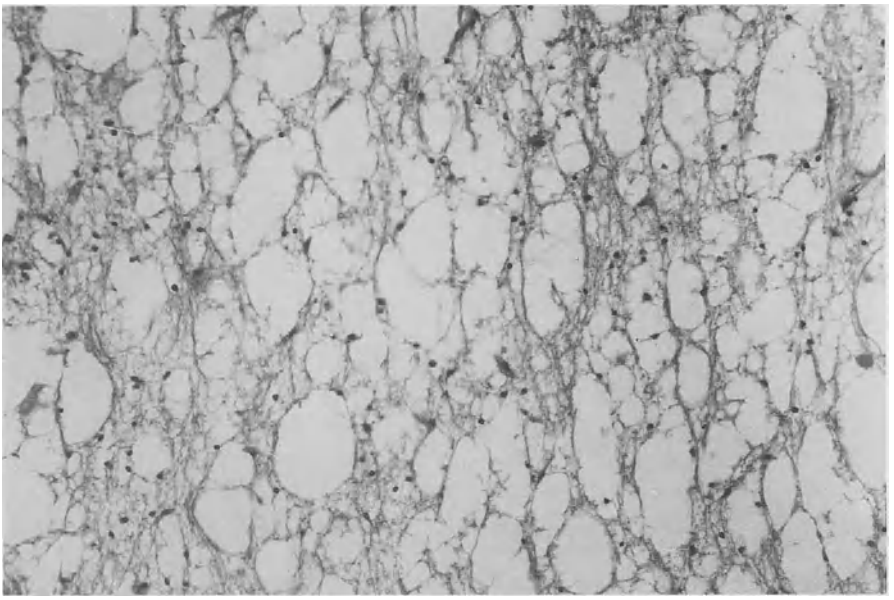


Fig.26.6. Spongionecrosis following radiotherapy, H&E, ×200

able percentage of long-term survivors: 22% of adults with malignant gliomas after high dose, whole-brain radiotherapy [1248] and 20%–100% of children after the treatment of different intracranial tumors, including prophylaxis of the cerebral hemispheres in medulloblastoma [1534, 473, 1287, 938]. They consist of a reduction of IQ with impairment of verbal, visuospatial, and memory functions [2110, 938]. Such disturbances seem to be progressive and are greater in younger children (<3 years of age) and in those also treated with chemotherapy (methotrexate) [677, 2333]. Visual disturbances, due to optic atrophy, fibrosis, and/or necrosis of the optic nerves, chiasm, and pathways, are in the majority described following treatment of pituitary adenomas [1064, 22]. Pituitary dysfunction is a frequent sequel of cranial irradiation. Stunted growth and failure of sexual maturation may develop in patients treated during childhood, whereas in 15%–55% of adults, signs of hypopituitarism are reported [2678, 22]. Hypothalamic dysfunction, following whole-brain irradiation for gliomas, has been reported in 1.25% of patients, with endocrine, behavioral, and cognitive impairment [1858]: In about 50% of patients there was cortical atrophy and enlargement of the third ventricle on CT. Radiation damage to cranial nerves other than the optic one and to peripheral nerves is uncommon [1428]. Cerebral infarctions secondary to a radiation-induced damage of arterial walls (cervical and intracranial arteries) may occur [2166, 790]. It must be stressed that a number of abnormalities on CT and MRI, such as cortical atrophy, enlargement of ventricles, hypodensity, or hyperintensity in T2-weighted images of periventricular white matter, are described at a distance from the radiotherapy site in patients who are clinically normal [536, 484].

26.3 Effects of Brachytherapy on the Human Brain

In the brain of patients with malignant gliomas who died after receiving 125I brachytherapy, three zones have been described with different expressions of the radiation

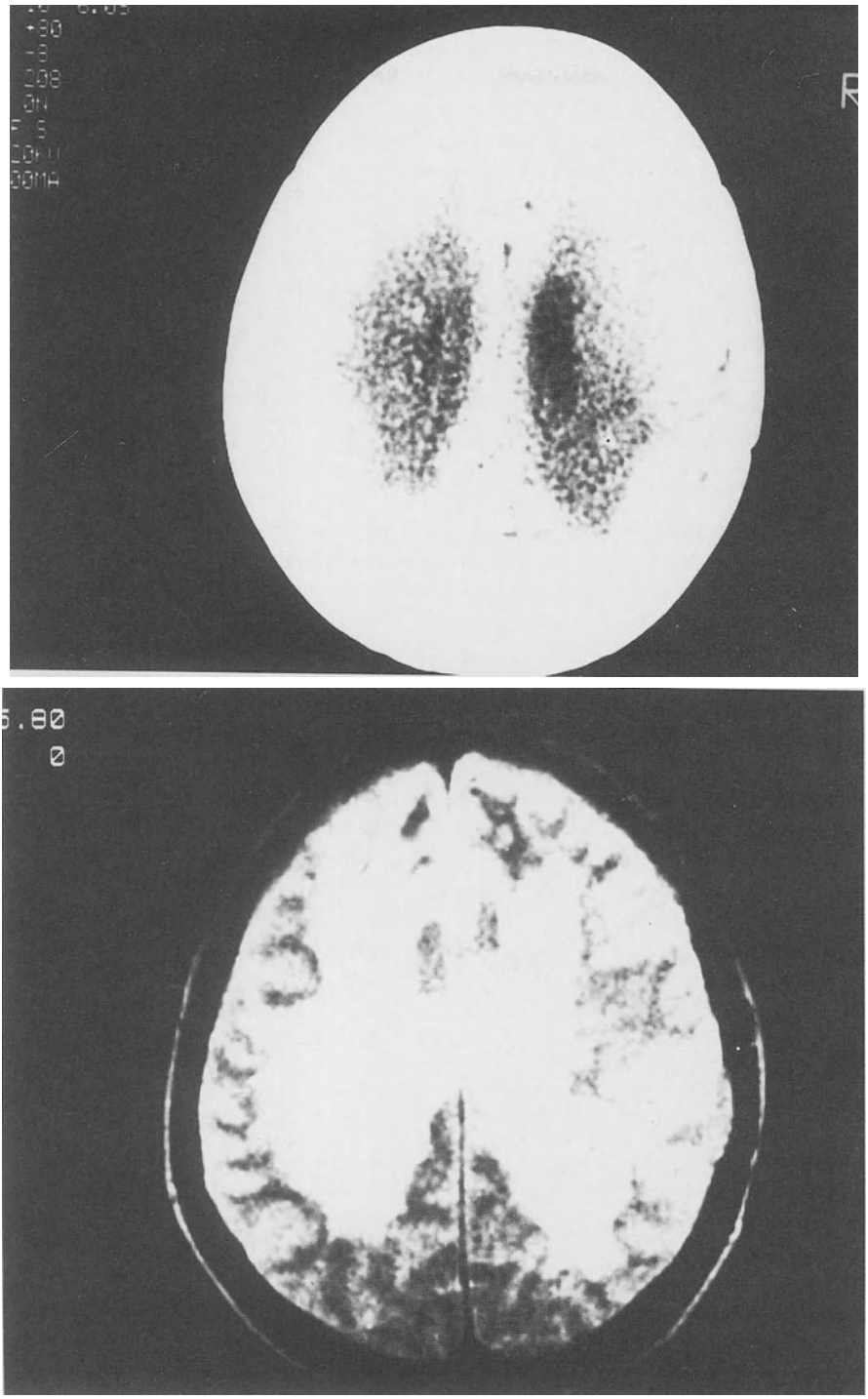


Fig.26.7a,b. Delayed leukoencephalopathy after radiotherapy with unconventional fractionation: **a** CT scan; **b** MR image

damage [578]: a central necrotic zone (doses › 20 000 cGy) involving the tumor and, to some extent, normal white matter; a transitional zone with demyelination, vessel wall changes, and an inflammatory response (doses between 4 000 and 15 000 cGy); a peripheral zone (doses < 4 000 cGy) with chronic edema and gliosis. As already observed after external radiotherapy, coagulative necrosis may involve areas receiving low doses (‹ 2 000 cGy) (individual susceptibility?). The location of the radiation damage depends mainly upon the tumor location: It is predominantly found in the white matter, but the cortex or nuclei of gray matter may be involved [532, 578, 1413]. The association of brachytherapy with external radiotherapy might increase the risk of damage.

26.4 Effects of External Radiotherapy on the Human Spinal Cord and/or Nerve Roots

Chronic progressive radiation myelopathy has been documented from the pathologic point of view. It follows irradiation of the cervical and thoracic spinal cord, with an incidence ranging from 0.5% [234] to 12.5% [1681] and an average value of 3% [2125]. Three fourths of patients develop myelopathy in less than 18 months, more commonly between 9 and 15 months [1559], and in a large series of cases [2565], a bimodal distribution of latency was observed with peaks occurring at 13 months (cases with higher doses) and 26 months (cases with lower doses).

Pathologically, lesions arise predominatly in the white matter, especially in the deeper parts of the posterior and lateral columns [1303, 344], and in some cases may affect the entire transverse section. Based on the latency period and microscopic features, a distinction between an "early delayed" and a "late delayed" reaction has been made [1303]. The former consisted of focal areas of spongy demyelination, axonal swelling, and an absence of vascular changes, whereas the latter was similar to the delayed radionecrosis of the brain. Prominent features were, apart from coagulative necrosis, fibrinoid necrosis and hyaline changes of the vessel wall with the development of teleangiectasias. The spinal arteries and nerve roots were spared.

Clinically, the onset is insidious with paresthesias, disturbances in perceiving pain and temperature, and weakness of the legs. There is a steady progression over 6 months to involve all cord systems. Lesions tend to progress over time, coming to involve some segments of the cord not originally exposed to radiation. Most cases are fatal. Chronic progressive radiation myelopathy is a diagnosis of exclusion [2120], after ruling out other causes of myelopathy. The CSF protein level may be slightly elevated. Myelography, CT, and MRI studies frequently are normal, and only in some instances do they demonstrate swelling or mild cord atrophy.

Detailed knowledge of the radiation tolerance of the cord continues to be elusive, but some facts are well established [966, 1831]. The risk of radiation myelopathy is minimal after doses below 4500 cGy delivered in 180 cGy daily fractions and increases when higher total doses or a higher fraction size or a shorter treatment time is used. The tolerance depends also upon the length of cord treated. Children and patients who have been re-irradiated are at increased risk of radiation myelopathy. Other factors, such as the association of chemotherapy agents or an individual idiosyncracy, have been advocated in some cases.

Apart from chronic progressive myelopathy, other forms of radiation damage to the spinal cord are well known from a clinical point of view: a syndrome characterized by an acute complete

paraplegia-quadriplegia due to an infarction of the spinal cord; a syndrome similar to a lower motor neuron disease; an acute transient radiation myelopathy. Well documented are the "brachial plexopathy" due to radiotherapy following mastectomy and the "lumbosacral radiculopathy" due to irradiation of the lumbosacral area.

26.5 Pathogenesis of Adverse Effects of Radiotherapy on the Normal Nervous Tissue

Generally, the doses utilized in clinical practice induce in the normal nervous tissue of animals only acute functional, and not morphological, changes. It has been demonstrated [1625, 615] that after doses of 200–400 cGy to the rat brain there is an increase of the BBB permeability, more evident in cortical areas, which is less intense in animals treated with dexamethasone. Modifications of the synaptic transmission [3066] and a reduction of glucose consumption [1261] have also been reported.

In the nervous tissue, the most typical effects of radiotherapy are "delayed" because the cells which are the target of the ionizing radiation (oligodendroglia and endothelium) have an extremely low turnover [2294, 1493], and time is required before a critical number of injured cells undergo mitotic death and the damage becomes clinically evident.

As for the "early delayed effects," in addition to the few human pathological data, experimental studies suggest damage to the oligodendrocytes [1795, 2902]. Both in the brain and spinal cord of rats, employing high single doses (3000–4000 cGy) leads to demyelination and necrosis of the white matter, with a paucity or absence of vascular changes [1179, 2900, 1122, 2901]; the latency period (4–7 months) was inversely related to the dose and shorter than after the lower doses (1500–2000 cGy), which induce mainly vascular damage. It has, therefore, been hypothesized for the spinal cord [2901] that the radiation-induced depletion of oligodendrocytes persists with no regeneration only above a critical dose level (2000 cGy). In the brain, apart from the "in situ" depletion of oligodendroglia, the possibility of damage to the cells of the subependymal plate must also be considered. In fact, after irradiation, a reduction of both the mitotic activity [397] and the total number of cells [419] has been described, while only after the highest doses (3000–4000 cGy) was a persistent depletion obtained. When fractionated doses closer to those used in clinical practice were employed in animals, the morphologic changes in the white matter were milder [1795], and some authors reported a transitory increase of the capillary permeability [401, 2195]. Therefore, the possibility of indirect damage to the myelin and oligodendrocytes due to vasogenic edema has been suggested [617].

Three main hypotheses regarding the pathogenesis of delayed radionecrosis have been proposed, a vascular [2557, 2421, 169, 1303], a glial [1252, 3115, 344], and an immunological one [521]. The last one considers the radionecrosis as a result of a hypersensitivity reaction secondary to changes induced in the nervous tissue by the radiation and has not been further advocated. According to Russell and Rubinstein [2420], this interpretation is more in agreement with the character of the "early delayed reaction" described by Lampert and Davis [1561], which displayed some morphological similarities to a primary demyelinating process of an autoimmune character. On the basis of experimental data, the hypothesis of primary damage to the oligodendroglia (the basis of the glial hypothesis) seems to explain better the features of the "early delayed" demyelination and necrosis seen in animals after doses higher than those used in humans, whereas the damage to the endothelium (the basis of the vascular hypothesis) is almost generally recognized as "the primum movens" of the delayed radionecrosis both in animals and in man [1846, 1177, 1787, 401, 3129, 1178, 774, 617]. The experimental models of delayed damage are, in fact, generally characterized by vascular lesions, and especially those induced in monkeys [1787, 401] and dogs [3129, 774] are similar to human material according to both neuropathologic and radiobiologic aspects (type of radiation treatment, latency period, CT aspects, etc.). In the rat, the late delayed damage is characterized mainly by teleangectasias in the brain, and teleangectasias associated with hemorrhages and

endothelial hyperplasias in the spinal cord. Such damage develops after relatively low, single doses (1500–2000 cGy), radiobiologically equivalent to those used in humans, and after long latency periods (8–18 months) [1177, 2901, 2295, 1178]. Arterial hypertension accelerates the development of the lesions [1179].

It has been hypothesized that the endothelium of the brain vessels (especially capillaries) is particularly susceptible to damage from radiation-induced free radicals [2578, 412]. The radiation damages the DNA of the endothelial cells, and death occurs when the cells attempt to divide (mitotic death). The cell loss stimulates the compensatory proliferation of other endothelial cells, and when a critical number of these cells dies, a breakdown of the BBB develops, leading to an increase of permeability and penetration of blood components into the vessel wall and into the parenchyma. Vessel changes, edema with demyelination, and necrosis follow. The stimulation of the proliferative capacity of an endothelium already injured by radiation subsequent to implantation of a tumor has been demonstrated to lead to an acceleration of the development of vascular changes [2705].

It has recently been suggested for both humans [2066] and animals [615] that conventionally fractionated treatment induces alterations of the glucose metabolism in the cortex, (more pronounced in associative areas) in the absence of clear pathologic changes.

26.6 Effects of Chemotherapy on the Human Brain and Spinal Cord

The neurotoxic effects of cancer chemotherapy are numerous and have been extensively reviewed [321], [1297], and [2609]. Here, only some types of normal nervous tissue damage related to the peculiar treatment modalities for brain tumors are described.

There are reports of central delayed neurotoxicity after high dose intravenous [335] or intraarterial (intracarotid) administration of BCNU [1353, 1735, 1454, 2363] in patients who did not undergo cranial irradiation. The changes involved mainly the white matter, consisting of lesions similar to those of delayed radionecrosis (fibrinoid necrosis, thrombosis, hyalinization and perithelial proliferations, coagulative necrosis, edema) along with the presence, in most cases, of axonal swelling in the areas of coagulative necrosis. After the intracarotid injection of BCNU, changes were generally confined to the arterial territories infused, with a clustering of lesions in the superficial gyri and deep periventricular white matter [2363] or deep gray matter [628] in some patients. It has been suggested [335, 2363] that cumulative doses of BCNU primarily injure the blood vessels, leading to secondary tissue edema and necrosis.

In patients who had given the drug intra-arterially, other factors have been advocated to explain the neurotoxicity [800, 1735, 143, 2449]: ethanol as a diluent, an incomplete mixing of the drug and blood leading to a streaming phenomenon, and the association with radiotherapy. The clinical picture of this neurotoxicity is that of a leukoencephalopathy with more pronounced changes visible on CT and MR scans in the territories infused and sometimes a gyral enhancement with calcifications.

A leukoencephalopathy consisting of bilateral demyelinating and necrotizing lesions involving the juxtaventricular white matter has been described following the intraventricular infusion of methotrexate [2611], especially in the presence of ventricular obstruction.

Several forms of transient or permanent neurotoxicity are not uncommon after intrathecally administred chemotherapy (methotrexate, cytarabine, thiotepa), e.g., acute meningeal and/or encephalic reactions, chronic encephalopathies, myeloradiculopathies.

26.7 Effects of Treatment on Normal Nervous Tissue in the Acute Lymphocytic Leukemia of Childhood

Disseminated necrotizing leukoencephalopathy (DNL) is a neurologic syndrome described mainly in children with acute lymphocytic leukemia who received prophylactic treatment of whole-brain radiotherapy (2 400 cGy) before or along with the intrathecal administration of methotrexate and/or cytarabine and/or high dose methotrexate given intravenously. The incidence ranges from 2% to 15%, rising with the increase of radiation and chemotherapeutic doses [227]. In recent years after modification of the treatment modalities, such a syndrome has developed more rarely.

Pathologically, lesions were found in the cerebral white matter (with frequent involvement of the corpus callosum), midbrain, pons, and medulla. The microscopic appearances were quite distinctive with disseminated foci of coagulative necrosis unrelated to the blood vessels, loss of myelin and oligodendroglia, severe axonal damage, and often calcifications. Fibrinoid necrosis of the vessel walls was neither constant nor extensive. As for the pathogenesis, it has been suggested [2420] that the neurotoxicity is of systemic origin, strongly potentiated by the cranial radiation and, probably, by the intrathecal administration of drugs. Clinically, the syndrome developed 4–12 months after treatments, with the typical symptoms and signs of a leukoencephalopathy, progressing in a few months to death. High levels of myelin basic protein in the CSF have been found [873].

Mineralizing microangiopathy is a less well defined entity as pathological data are scarce and most patients are asymptomatic or present with minimal and nonspecific symptoms. In 25%–30% of patients with acute lymphocytic leukemia who are long-term survivors after prophylaxis of the CNS (radiotherapy alone or associated with methotrexate or cytarabine therapy), CT study has shown calcification in the basal ganglia and cortex. From the pathological point of view, predominant involvement of the gray matter (cortical sulci, putamen, cerebellum) with deposition of calcium in the lumen and in the walls of small vessels and sometimes accompanied by perivascular necrosis has been observed [2239]. The pathogenesis is unknown.

Also, after prophylactic treatment of the whole brain in children with lymphocytic leukemia, a high percentage of cognitive deficits have been reported [700, 1856].

26.8 Second Malignancies

See Chap. 2

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