

# Central Nervous System Neoplasms in the Rat

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## INTRODUCTION

The need for a histological classification of rat brain neoplasms became apparent in the early fifties when research began to focus on chemical induction of brain tumors in this species (Jänisch & Schreiber, 1977). Unfortunately, different classification schemes were introduced by various research groups, making the comparison of experimental results difficult. Some investigators simply designated all neuroepithelial tumors in the rat as gliomas, whereas others used a histogenetic classification. At present, the situation is not much different, since the classification of rat brain tumors is almost entirely based on the light microscopic cytomorphologic features. Additional techniques, such as electron microscopy and cytology, are only rarely applied. This is certainly the case with spontaneous tumors which are often not recognized grossly. In addition, the results of immunohistochemistry, a powerful technique in cases of human brain tumors and in selected experimentally induced tumors, are disappointing so far in spontaneously occurring tumors in the rat. Despite these limitations, there is a need for a more uniformly used classification scheme for rat brain tumors. Table 1 outlines such a classification. The classification is based on H & E stained sections, which is certainly an advantage for the toxicologic pathologist as time and resources often do not allow the application of additional techniques.

## TUMORS OF NEUROEPITHELIAL TISSUE

### *ASTROCYTOMA (Figures 1, 2)*

Astrocytomas in the F344 rat occur throughout the brain without showing a preferential anatomical site (Ward and Rice, 1982). The cerebrum is the most common site in the Sprague-Dawley rat (Newman and Mawdesley-Thomas, 1974; Gopinath, 1986). Roughly one-third of the neoplasms are detected macroscopically (Gopinath, 1986). They appear as swollen areas, grayish masses or areas of discoloration. Light microscopically, astrocytomas do not show discrete borders and are moderately to densely cellular. The cells have moderate amounts of eosinophilic cytoplasm and rounded to elongated, hyper- to euchromatic nuclei and indistinct cell borders. Based on their cytologic features, astrocytomas can be subclassified as protoplasmic or fibrillary. The latter is the most common type in the rat. However, such a subclassification is not recommended for routine use in long-term rat studies. Common features of astrocytomas are the spread of neoplastic astrocytes along perivascular spaces (perivascular cuffing), arrangement of tumor cells around neurons (neuronal satellitosis), and tumor cell infiltration of the meninges. Necrosis with pseudopalisading of tumor cells and cystic changes are only rare findings. Mitotic figures range from rare to frequent. Immunohistochemical demonstration of glial fibrillary acidic protein (GFAP) has failed so far in all naturally occurring astrocytomas, whereas normal and reactive astrocytes reacted positively in these cases. This suggests dedifferentiation which is consistent with electron microscopic observations of no distinctive intermediate filaments or junctions in rat neoplastic astrocytes (Bigner et al., 1986; Solleveld et al., 1990). In contrast, positive staining with

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GFAP has been observed in a number of experimentally induced tumors, among which were avian sarcoma virus- and ethylnitrosourea-induced astrocytomas.

Small focal accumulations of glial cells, (gliosis) are sometimes observed in the brain and/or spinal cord. In the absence of apparent inciting factors, gliosis must be considered a potential preneoplastic lesion of neuroglial origin. It is important to indicate whether a lesion diagnosed as gliosis is a secondary or reactive response or a proliferative lesion that may be within a biological continuum from hyperplasia to neoplasia (Solleveld & Boorman, 1990).

#### *OLIGODENDROGLIOMA (Figure 3)*

The most common anatomical locations of oligodendrogliomas in the F344 and Sprague-Dawley rat strains were found to be cerebral hemispheres, basal ganglia and corpus callosum (Krinke et al., 1985; Ward and Rice, 1982). Large tumors often show cystic or hemorrhagic changes, features which increase gross detectability. Light microscopically, the typical oligodendroglioma is characterized by uniform cells with small, round, dark-staining nuclei, clear cytoplasm and delicate cell membranes. Vascular hypertrophy and hyperplasia are common and are characteristic of an oligodendroglial component in rat brain tumors. Various other patterns can be recognized, particularly in large, often less differentiated tumors, such as row-like nuclear arrangement and pseudorosette formation. Hemorrhage, hemosiderosis and necrosis are also common features in the larger neoplasms. Application of immunohistochemistry using antibodies to the major myelin proteins, particularly 2', 3'-cyclic nucleotide 3'-phosphodiesterase may be a useful diagnostic aid in cases of less differentiated tumors. In addition, the larger tumors often show mixtures of different cell types and a diagnosis descriptive of a mixed glioma should sometimes be considered, e.g., oligo-astrocytoma. In such cases, one should determine whether the astrocytes are reactive or neoplastic by using GFAP as a marker.

#### *MIXED GLIOMA (Figure 4)*

Most common in the rat is the oligo-astrocytoma. The tumors may show an admixture of the two cell types or areas of oligodendrocytes present alongside those composed of astrocytes. This tumor type exhibits all features of both tumor types, including vascular endothelial proliferation. One should realize, however, that tumors diagnosed as astrocytoma or oligodendroglioma almost never consist of pure cell populations but are diagnosed according to their predominant cell type. Therefore, the diagnosis "mixed glioma" should only be applied to those cases in which there is a seemingly equal distribution of the 2 cell types.

#### *ANAPLASTIC GLIOMA*

Naturally occurring brain tumors, but more often chemically induced ones, may be anaplastic and may show a variety of cellular morphology and growth patterns. An astrocytic or oligodendrocytic differentiation is often not apparent. Cellular atypia is common and an occasional multinucleated giant cell may be present. The latter features were sometimes used to diagnose the neoplasm as glioblastoma multiforme. However, this is a pre-committed term in human neuro-oncology and should not be used in cases of rat astrocytomas. It is more appropriate to diagnose such neoplasms as anaplastic gliomas in the rat.

#### *EPENDYMOMA (FIGURE 5)*

Spontaneous occurrence of this tumor type is extremely rare in the rat. However, they are readily inducible in offspring of dams inoculated with ethylnitrosourea during late gestation (Koestner et al., 1972). The induced tumors are very anaplastic and occur predominantly in the spinal cord. Spontaneous intracranial ependymomas are characterized by round to oval, hyperchromatic nuclei, and an indistinct cytoplasm and cell border. Rosette and pseudorosette formations are present. Demonstration of filaments, such as vimentin and cytokeratin 18, and/or blepharoplasts and microvilli is necessary before definitively diagnosing a neoplasm as an ependymoma.

#### *CHOROID PLEXUS NEOPLASMS (Figure 6)*

Choroid plexus tumors are infrequently encountered in the rat. These intraventricular tumors are subclassified as papillomas and carcinomas. Choroid plexus papillomas are characterized by papillary fronds lined by one or more layers of cuboidal to columnar cells. The cells are characterized by round, regular-sized nuclei and an abundant cytoplasm. These tumors may react positively with cytokeratin and neurofilament antibodies. Choroid plexus carcinomas show invasion of adjacent neural tissue, loss of papillary architecture and/or cellular pleomorphism.

#### *PINEAL GLAND NEOPLASMS (Figures 7, 8)*

Pineal gland tumors are extremely rare. They appear grossly as pale masses between the occipital pole of the telencephalon and the cerebellum. Descriptions vary from well-differentiated pinealomas to undifferentiated pineal gland carcinomas. The well-differentiated tumors are composed of two cell types, viz., large, pale-staining parenchymal cells and smaller, dark-staining interstitial cells. Pseudorosette formation may be present. The undifferentiated tumors lack any pattern and show pleomorphic cell features. In these cases, the diagnosis of pineal gland carcinoma is often based on its anatomical location. Mitoses are common in pineal neoplasms.

## TUMORS OF NEURONAL CELLS AND OF PRIMITIVE BIPOTENTIAL PRECURSORS (Figures 9, 10)

Gangliogliomas have been described in the cerebral hemispheres of the rat (Ward & Rice, 1982). They consisted of admixed astrocytic and neuronal components, the latter not infrequently undergoing mitosis. They grow expansively, the astrocytic component behaving in a benign fashion.

Ganglioneuromas have been described by Bullock & Curtis (1930) and Fitzgerald et al. (1974). The tumors were observed in the optic nerve and in a cranial ganglion. The neoplasms consisted of nests or strands of large ganglion-like cells embedded in a cellular stroma. The latter were thought to represent satellite cells or Schwann cells. However, it cannot be entirely excluded that the stromal component in these tumors was glial in origin and therefore not different from the above described gangliogliomas.

Medulloblastomas are highly cellular cerebellar tumors in the rat. The cells are characterized by round to elongated, very hyperchromatic nuclei, and indistinct cytoplasm and cell borders (Figures 9, 10). Whorl formation is a common feature. Neuronal differentiation has been observed. Classic Homer-Wright rosettes as found in man are not seen in the rat. Specific immunohistochemical markers for this tumor type have not yet been identified in the rat.

## TUMORS OF NERVE SHEATH CELLS

### SCHWANNOMA, BENIGN OR MALIGNANT (Figures 11, 12)

Naturally occurring intracranial schwannomas are extremely rare in the rat, but are readily inducible by chemical carcinogens (Rice and Ward, 1988). In the rat, most schwannomas are composed entirely of Antoni type B tissue often showing cystic and hemorrhagic changes. This tissue is characterized by stellate or ill-defined cells with hyperchromatic nuclei embedded in a myxoid stroma. Antoni type A tissue is characterized by interlacing bundles of plump spindle cells with indistinct boundaries. Although Verocay bodies occur, they are a rare observation in the rat. Tumor cells, particularly the nuclei, stain positively with S-100 protein. Most tumors show infiltrative growth and should be classified as malignant. Induced schwannomas are often anaplastic.

## TUMORS OF MENINGEAL AND RELATED TISSUES

These can be subclassified as meningiomas, meningial sarcomas, granular cell tumors and melanomas. Although meningiomas and granular cell tumors are described as being part of the same histological spectrum

with the meningotheial arachnoid cell as a progenitor (Mitsumori et al., 1988), the evidence is not considered yet conclusively established. Therefore, it seems appropriate to regard the granular cell tumor as a separate entity but of meningeal origin. Supportive evidence for this consideration is that this tumor type has not been induced experimentally to date.

### MENINGIOMA/MENINGEAL SARCOMA (Figures 13, 14)

Meningiomas are detected grossly. They are clearly defined from surrounding brain structure and appear as meningeal thickenings or as plaque-like lesions. Compression of underlying brain tissue may occur. Meningeal sarcomas are poorly defined, diffuse or circumscribed, masses and usually not clearly demarcated from surrounding brain tissue. Different types of meningeal neoplasms can be distinguished but subclassification is often not used in long-term toxicity and carcinogenicity studies. However, for the sake of clarity, the different histological types will be discussed separately. Two types of meningiomas are recognized, viz., fibroblastic and meningotheial. Fibroblastic meningiomas are characterized by elongated cells having a pale eosinophilic cytoplasm. The nuclei are also elongated and show a reticular chromatin pattern. The cells often form interwoven bundles with varying amounts of collagen separating individual cells. Meningotheial meningiomas are characterized by a lobulated arrangement of cells; the lobules are separated from each other by a fibrous stroma. The cells have abundant homogeneous eosinophilic cytoplasm and a vesicular nucleus. Psammoma bodies are not a feature of rat meningiomas.

Although meningeal sarcomas are often subclassified as fibrous, spindloid and undifferentiated, they probably represent a single type showing different grades of differentiation. The sarcomas consist of a cellular arrangement in bundles with interlacing or irregular patterns. The amount of collagen varies; it is most abundant in the fibrous type. The fibrous and spindloid types have elongated cells with elongated nuclei. The cytoplasm in the fibrous type is eosinophilic, whereas it is more basophilic and less abundant in the spindle cell type. Undifferentiated sarcomas contain pleomorphic cells with sometimes bizarre nuclei and an occasional multinucleated giant cell.

### GRANULAR CELL NEOPLASMS (Figures 15, 16)

Granular cell tumors are often recognized grossly as solitary friable growths, light-pink to pale yellow or gray and sharply demarcated from surrounding brain tissue. They occur in the cerebrum and cerebellum at the dorsal, lateral or ventral surfaces. Microscopically, they appear well delineated, and almost all show contact with

the meninges. They begin as a focal area of hyperplasia of granular cells within the meninges and grow by expansion causing compression and atrophy of adjacent brain tissue. Invasion of Virchow-Robin spaces is not uncommon. The large-bodied, round to oval cells are characterized by a granular eosinophilic cytoplasm which reacts positively with periodic acid Schiff reagent and negatively with GFAP, S-100 protein and desmin. Two types of nuclei can be observed: large vesicular and small, round to elongated, hyperchromatic ones. An occasional mitotic figure may be present.

#### *MALIGNANT MELANOMA (Figures 17 - 19)*

Malignant melanomas have been observed in pigmented rats and are easily recognizable grossly as dark brown or black masses not sharply demarcated from surrounding brain tissue. Microscopically, most tumors are heavily pigmented, although amelanotic areas may be present. The latter areas have a bandlike or whorling pattern and the cells are composed of an eosinophilic cytoplasm with centrally located, spherical nuclei. The amelanotic areas may resemble granular cell tumors. S-100 protein positive staining differentiates this tumor type from granular cell tumors which are negative for S-100 protein.

### **PRIMARY LYMPHOMA**

#### *MALIGNANT RETICULOSIS (Figure 20)*

This tumor type is also known as lymphoreticulosis, reticulum cell sarcoma, microglioma and microgliomatosis. It is currently a controversial diagnostic entity and a more appropriate diagnosis is hampered by the lack of reliable markers (Garman, 1988, Krinke et al., 1985; Solleveld et al., 1986, 1990). The tumors are rarely detected grossly. Histologically, this tumor type is characterized by a densely mixed cellular central region and a more dispersed peripheral area and prominent perivascular, ventricular and leptomeningeal mixed cell infiltrates. The cell mixture may comprise rod-like cells (microglia?), lymphocytes, histiocytes and fibroblasts. Collagen and reticulum fibers are present in varying amounts. Malignant reticulosis should be differentiated from an inflammatory response, glial neoplasm or generalized lymphoma. Marked infiltration of the neuropil and the presence of mitoses are more characteristic for a neoplastic response than for an inflammatory one; the mixed cell population and nodular growth pattern are important criteria for distinguishing malignant reticulosis from a glial tumor, and generalized lymphoma can be excluded by performing a thorough microscopic examination of other tissues. It is currently thought that

malignant reticulosis may represent primary brain lymphomas, but they have yet to be evaluated for the presence of cell-associated immunoglobulins.

### **SECONDARY NEOPLASMS**

The most common secondary growths are pituitary carcinomas, malignant nasal neoplasms, Zymbal gland (auditory sebaceous gland) carcinomas and those of the hemopoietic system.

Pituitary carcinomas may invade the base of the brain, but must be clearly differentiated from expansive growth of pituitary adenomas. Nasal tumors (squamous cell carcinomas, adenocarcinomas and esthesioneuroepitheliomas) may invade through the cribriform plate into the olfactory lobes of the brain. Zymbal gland carcinomas, often appearing as squamous cell carcinomas, may invade the temporal bone and the temporal lobes of the cerebrum. In cases of mononuclear cell leukemia, leukemic nodules can be seen throughout the brain and are often associated with vascular damage and necrosis. Generalized malignant lymphomas may manifest themselves as meningeal and perivascular lymphoid infiltrates.

### **DISCUSSION**

The spontaneous rate of naturally occurring brain tumors in the rat is highly variable and higher than often thought. This is best illustrated by a study of FD&C Blue no. 2 (Swenberg, 1986). The high dose animals in that particular study showed an apparent treatment-related increase in the incidence of gliomas, viz., 12% versus 3% in controls. However, when the incidence of gliomas in control rats from 18 color studies conducted in 4 laboratories was considered, 2 control groups had similar incidences, namely 10 and 11%, respectively. The high incidence in untreated control rats, and the occurrence of tumors of different histogenetic origin in the brain of rats, make an accurate histopathological diagnosis of utmost importance for safety assessment purposes. In addition, the variation in incidences of naturally occurring brain tumors in rats and the high chances of haphazard distribution among the randomly grouped animals should also be taken into account in this regard since they may lead to erroneous decisions (Koestner, 1986).

As described by Azzopardi (1979) any histopathological classification should be reasonably simple, easy to understand, reproducible in the hands of different workers and as comprehensive as is compatible with simplicity. All classifications depend on our knowledge of the pathology and histogenesis of the tumors being classified and, since this knowledge is far from perfect or complete, no classification can be other than a reason-

able working compromise. This is what we have tried to accomplish by proposing the current classification scheme for brain tumors in the rat. The classification is based mainly on the light microscopic cytomorphologic features of the tumors. Although the descriptions of the various tumor types are entirely based on naturally occurring tumors of the central nervous system in the rat, they also apply to chemically induced ones. Over 40 compounds have been demonstrated to induce such tumors in rodents by various routes of exposure other than the intracranial inoculation (Koestner, 1990). The most potent, with a success rate of 90% to 100%, are methylnitrosourea, ethylnitrosourea, azoethane, 1,2 diethylhydrazine, and 1-phenyl-3,3-diethyltriazine.

Two tumor types are still controversial diagnostic entities: the granular cell tumor and malignant reticulosis. The cell(s) of origin of both tumor types have not yet been conclusively established. Therefore, they should be regarded as separate entities in the evaluation of tumor data.

## CHARACTERISTICS OF CENTRAL NERVOUS SYSTEM TUMORS IN THE RAT

### *Astrocytoma*

1. Densely cellular and poorly demarcated
  2. Uniform cells with round or oval nuclei, moderate amount of pink cytoplasm, and indistinct cell borders
  3. Perivascular cuffing (neoplastic astrocytes)
  4. Arrangement of neoplastic astrocytes around neurons (satellitosis)
  5. Necrosis with pseudopalisading
  6. "Spontaneous" tumors: GFAP negative
- N. B. Multinucleated giant cells and vascular endothelial proliferation are not features of naturally occurring astrocytomas in the rat.

### *Oligodendroglioma*

1. Moderately cellular and well demarcated
2. Uniform cells with round to oval nuclei, clear cytoplasm, and delicate cell membranes
3. Vascular endothelial hypertrophy and hyperplasia
4. Hemorrhage and necrosis
5. Calcification (extremely rare)

### *Mixed glioma*

1. Admixture of neoplastic oligodendrocytes and astrocytes or areas of neoplastic oligodendrocytes

- and astrocytes present alongside each other
2. Vascular endothelial hypertrophy and hyperplasia
3. All other characteristics of astrocytomas and oligodendrogliomas

### *Anaplastic glioma*

1. Astrocytic or oligodendrocytic differentiation not apparent
2. Cellular atypia is common
3. Occasional multinucleated giant cell

### *Ependymoma*

1. Densely cellular
2. Uniform cells with round to oval nuclei, and indistinct cytoplasmic boundaries
3. Rosette and pseudorosette formation
4. Projects from an ependymal surface

### *Choroid plexus neoplasms*

1. Papillary aspect of intraventricular growth
2. Large cells with cuboidal to rounded outlines, round to oval nuclei, and abundant light eosinophilic cytoplasm
3. Vascular core not prominent

### *Pineal gland neoplasms*

1. Composed of 2 cell types, viz., large pale-staining parenchymal cells and smaller dark-staining interstitial cells
2. Pseudorosette formation
3. Cellular arrangement around blood vessels
4. Sometimes very pleomorphic

### *Ganglioglioma*

1. Admixture of neuronal and astrocytic components
2. Astrocytes behaving in a benign fashion
3. Mitoses not uncommon in neuronal component

### *Ganglioneuroma*

1. Nests or strands of ganglion-like cells
2. Stromal component (satellite or Schwann cells or glia?)

### *Medulloblastoma*

1. Highly cellular
2. Round to elongated, very hyperchromatic nuclei and indistinct cell borders
3. Neuronal differentiation may be present
4. Lack of classic Homer-Wright rosettes

### *Schwannoma (benign or malignant)*

1. Herringbone to storiform pattern, nuclear palisading and Verocay bodies (Antoni type A tissue)

2. Loosely textured, edematous areas, foci of degeneration which progress to the formation of small cysts (Antoni type B tissue)
3. Transition from residual nerve fiber
4. S-100 positive

#### *Meningioma*

1. Fibroblastic: Spindled cells having pale eosinophilic cytoplasm and elongated nuclei with a reticular chromatin pattern. The cells form interwoven bundles with varying amounts of collagen separating individual cells
2. Meningothelial: Cells with abundant eosinophilic cytoplasm and vesicular nuclei are arranged in lobules which are separated by a fibrous stroma. N. B.: Psammoma bodies are not a feature of rat meningiomas.

#### *Meningeal sarcoma*

1. Cellular arrangement in bundles with interlacing or irregular patterns
2. Elongated cells and nuclei and amount of cytoplasm varies dependent on degree of differentiation
3. Sometimes pleomorphic cells with bizarre nuclei and an occasional multinucleated giant cell

#### *Granular cell neoplasms*

1. Moderately cellular and well demarcated
2. Cells with granular cytoplasm reacting positive with PAS and diastase-resistant and large vesicular and small, round to elongated hyperchromatic nuclei
3. Contact with the meninges
4. Negative for GFAP, S-100 protein and desmin

#### *Malignant melanoma*

1. Heavily pigmented for larger part
2. Bandlike or whorling pattern
3. Cells with eosinophilic cytoplasm with centrally located, spherical nuclei
4. Positive for S-100 protein

#### *Malignant reticulosis*

1. Densely mixed cellular central core and a more dispersed peripheral area
2. Prominent perivascular, ventricular and leptomeningeal infiltrates
3. Mixture of cells consists of rod-like cells, lymphocytes, histiocytes and fibroblasts

TABLE 1.

### ***CLASSIFICATION SCHEME FOR CENTRAL NERVOUS SYSTEM NEOPLASMS IN THE RAT***

#### ***I. TUMORS OF NEUROEPITHELIAL TISSUE***

##### *A. Astrocytic and oligodendroglial tumors*

Astrocytoma  
Oligodendroglioma  
Mixed glioma (oligo-astrocytoma)  
Anaplastic glioma

##### *B. Ependymal and choroid plexus tumors*

Ependymoma  
Choroid plexus papilloma  
Choroid plexus carcinoma

##### *C. Pineal gland neoplasms*

Pinealoma  
Pineal gland carcinoma

##### *D. Neuronal and primitive bipotential precursor cell neoplasms*

Ganglioglioma  
Ganglioneuroma  
Medulloblastoma

#### ***II. TUMORS OF NERVE SHEATH CELLS***

Schwannoma (benign or malignant)

#### ***III. TUMORS OF MENINGES AND RELATED TISSUES***

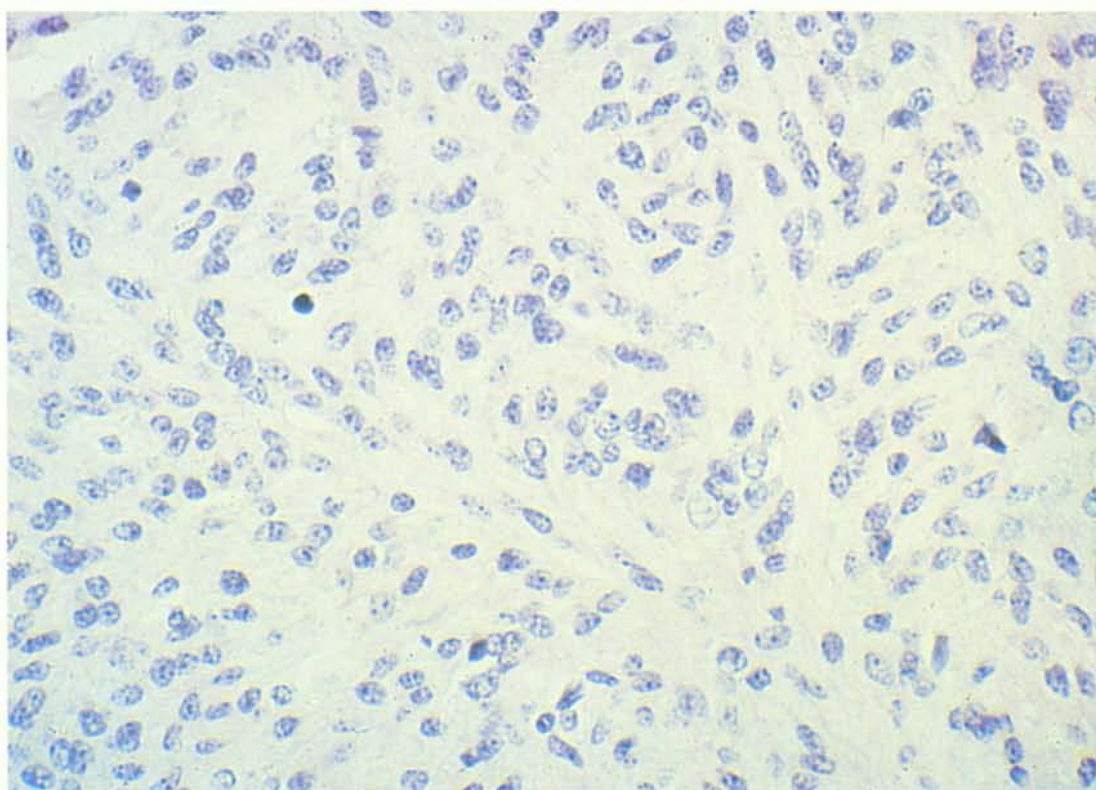
Meningioma  
Meningeal sarcoma  
Granular cell tumor  
Malignant melanoma

#### ***IV. PRIMARY LYMPHOMAS***

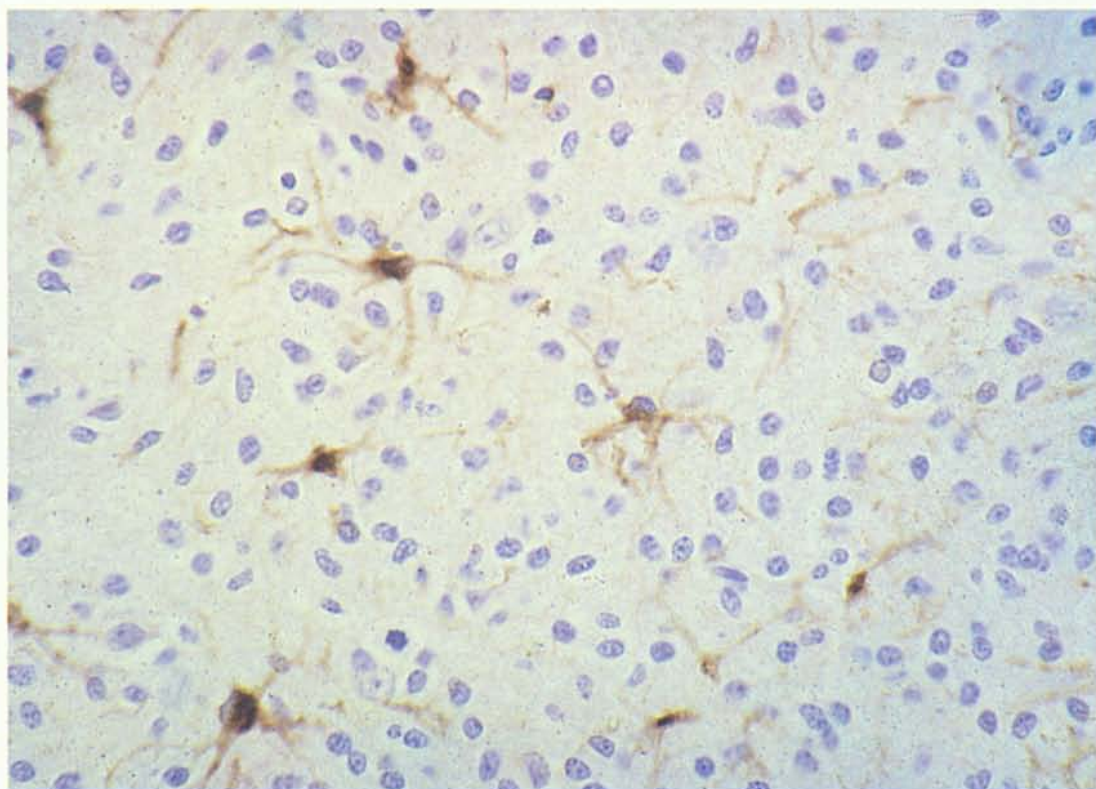
Malignant Reticulosis

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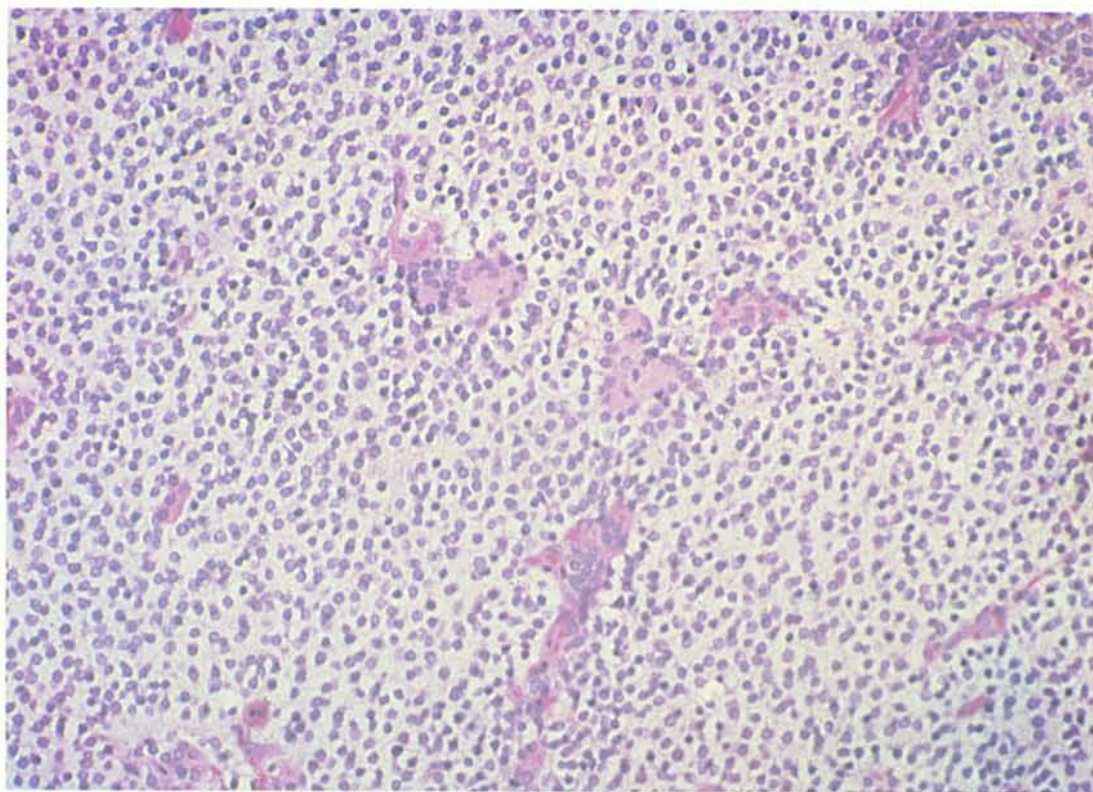
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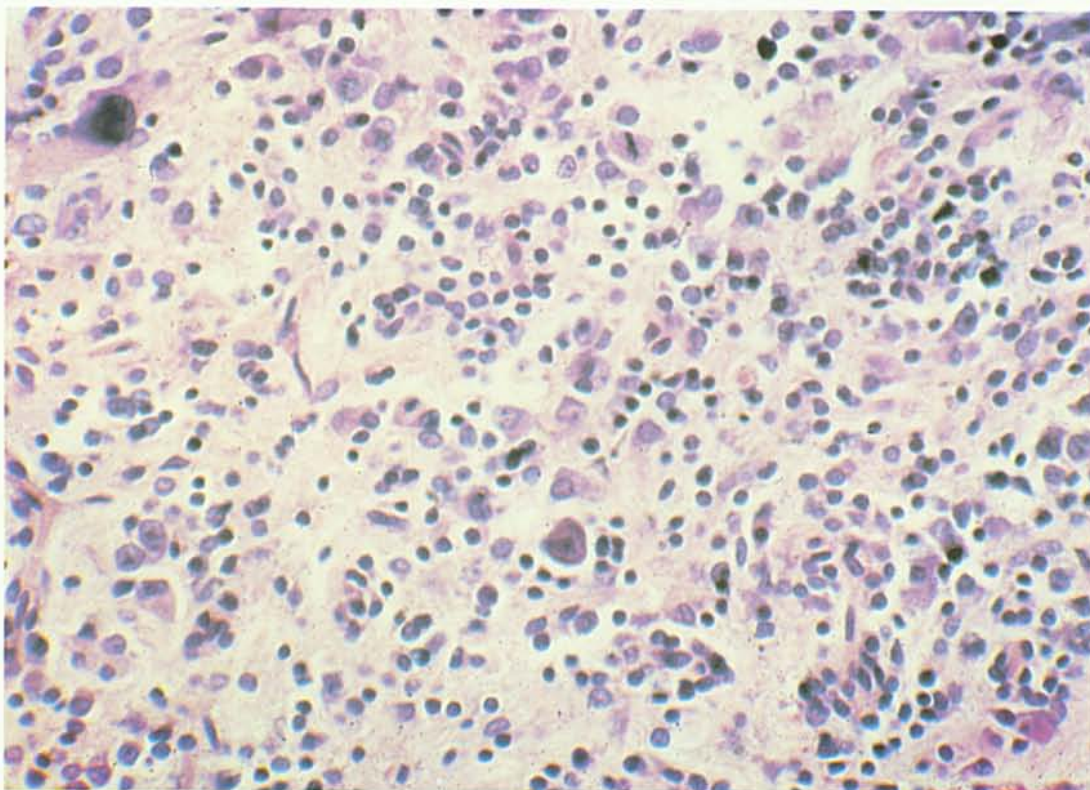
*Fig. 1. Well-differentiated astrocytoma showing moderate cellularity, indistinct cell borders and round to spheroidal, euchromatic nuclei.*



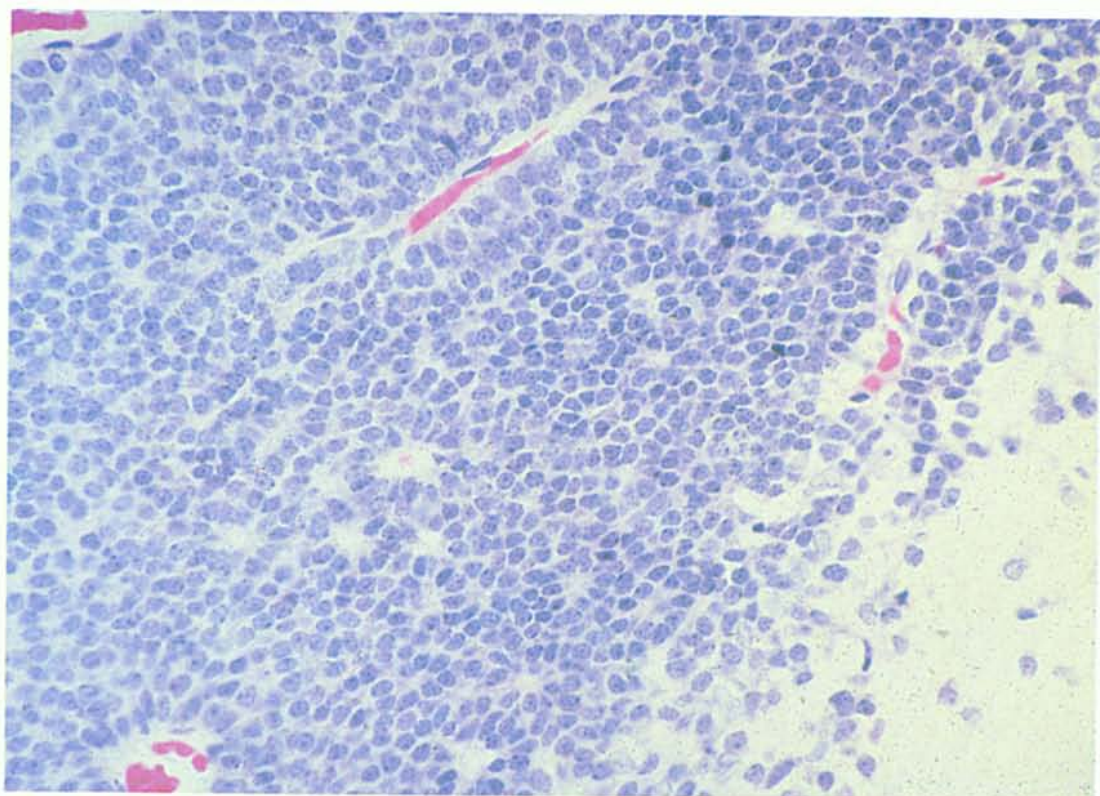
*Fig. 2. Immunostaining of astrocytoma with glial fibrillary acidic protein. Positive staining of reactive astrocytes and lack of staining of neoplastic astrocytes.*



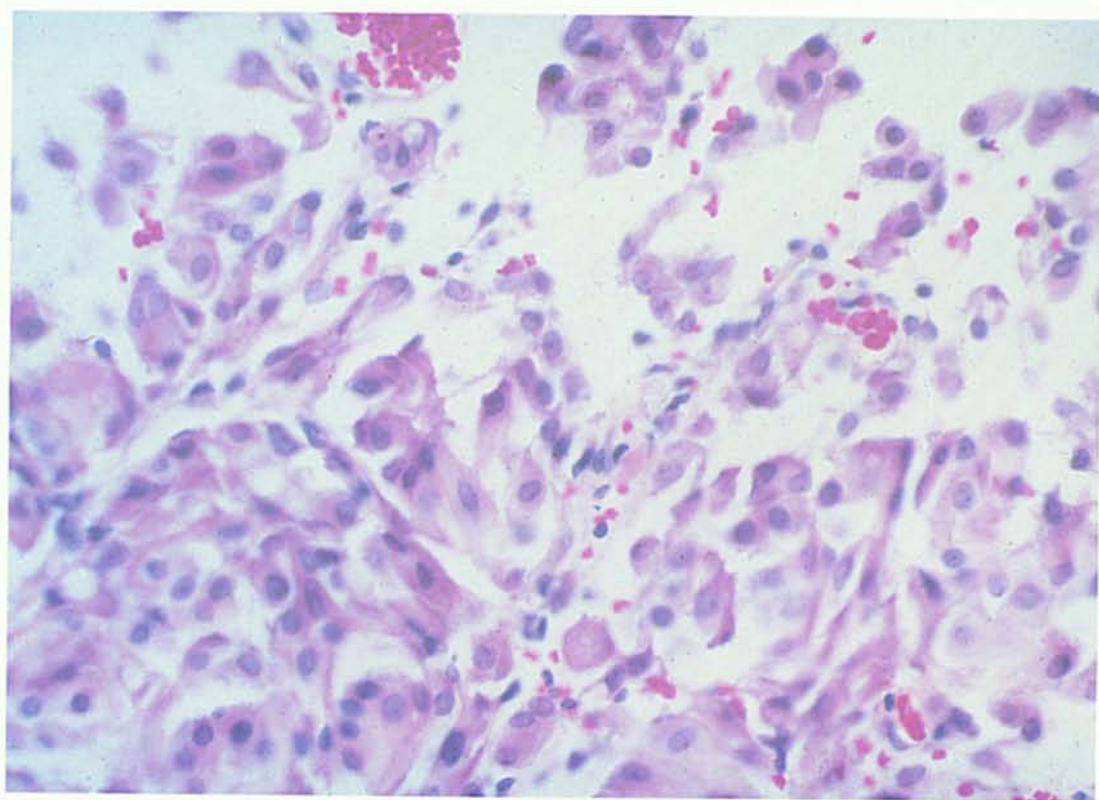
*Fig. 3. Oligodendroglioma showing vascular endothelial hypertrophy.*



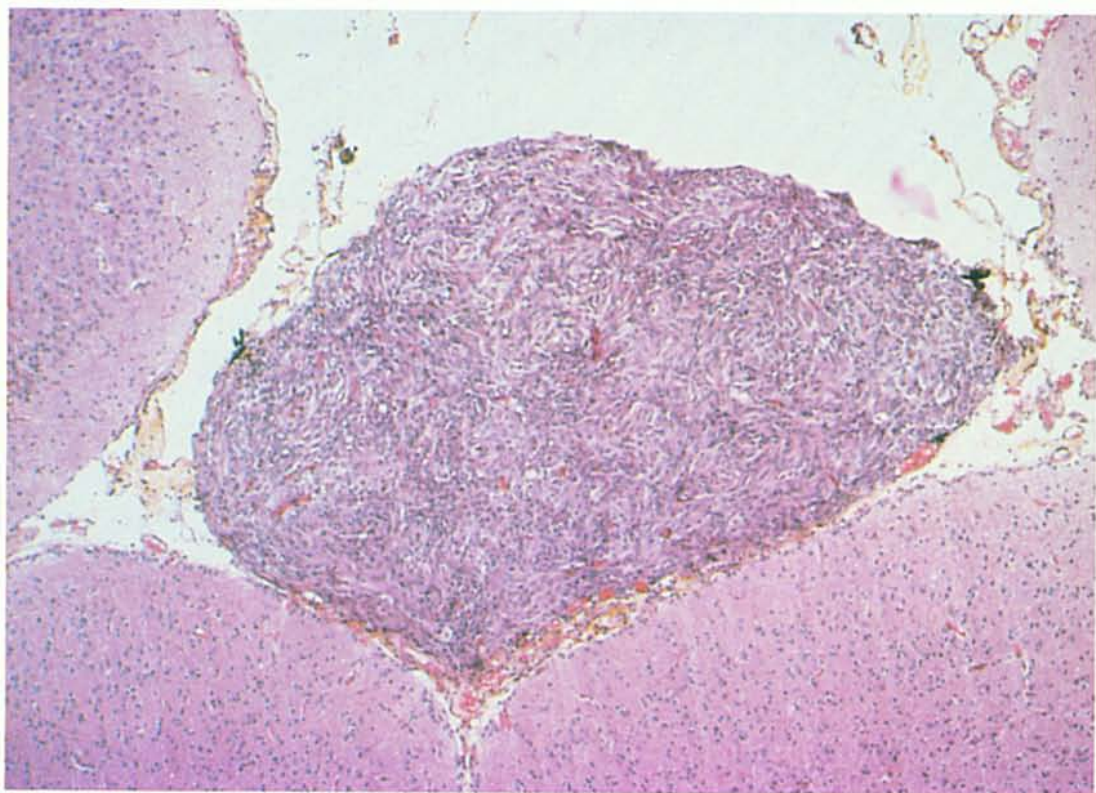
*Fig. 4. Mixed glioma composed of a mixture of astrocytes and oligodendrocytes. Note presence of vascular endothelial hypertrophy and hyperplasia.*



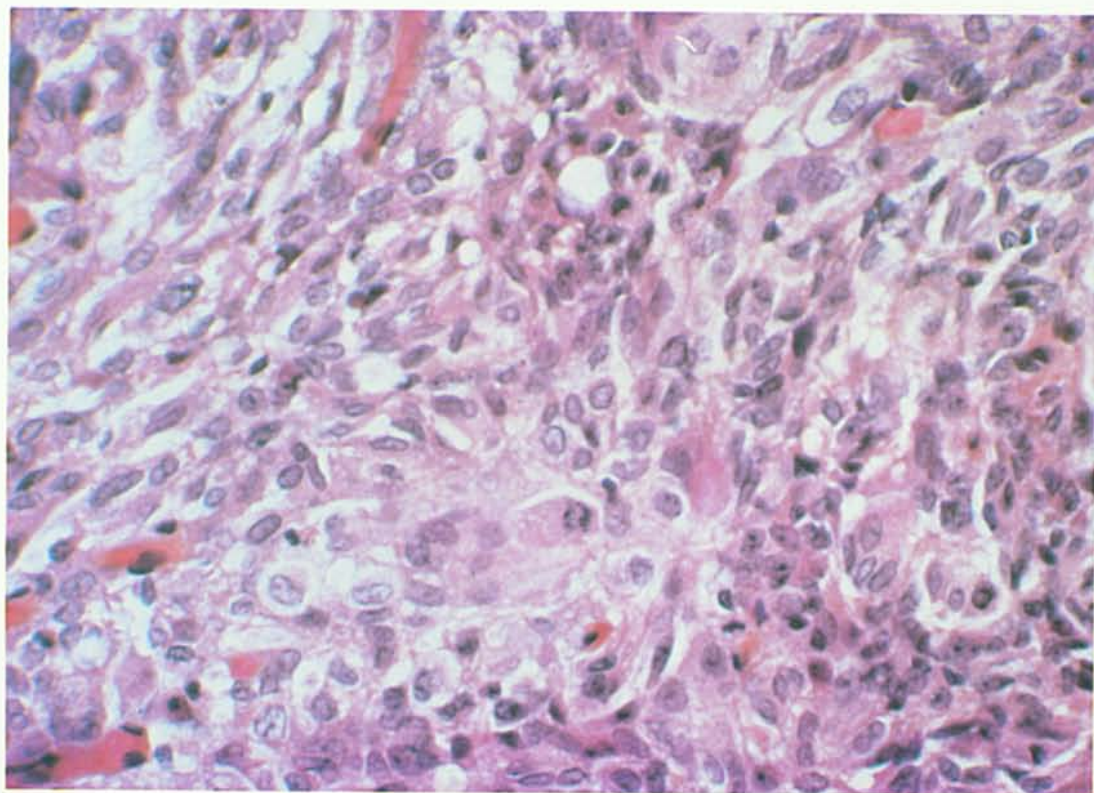
*Fig. 5. Ependymoma showing rosette and pseudorosette formations.*



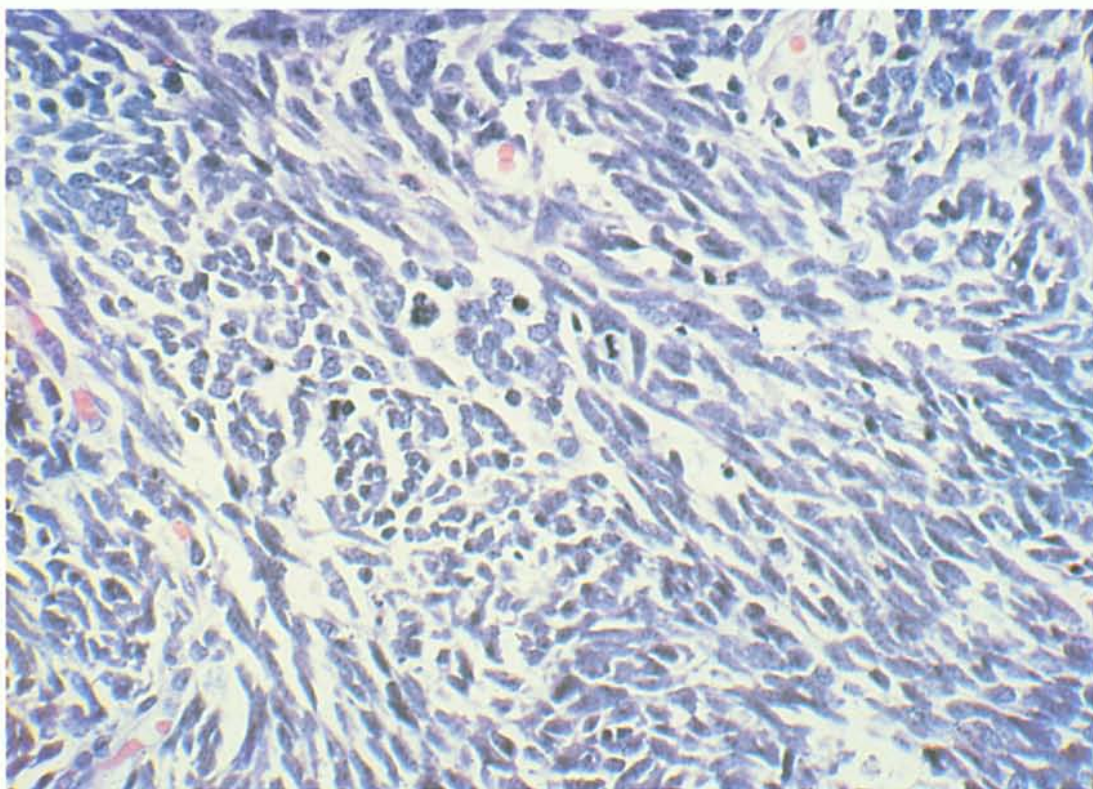
*Fig. 6. Choroid plexus papilloma characterized by round to oval nuclei and an abundant light-pink cytoplasm.*



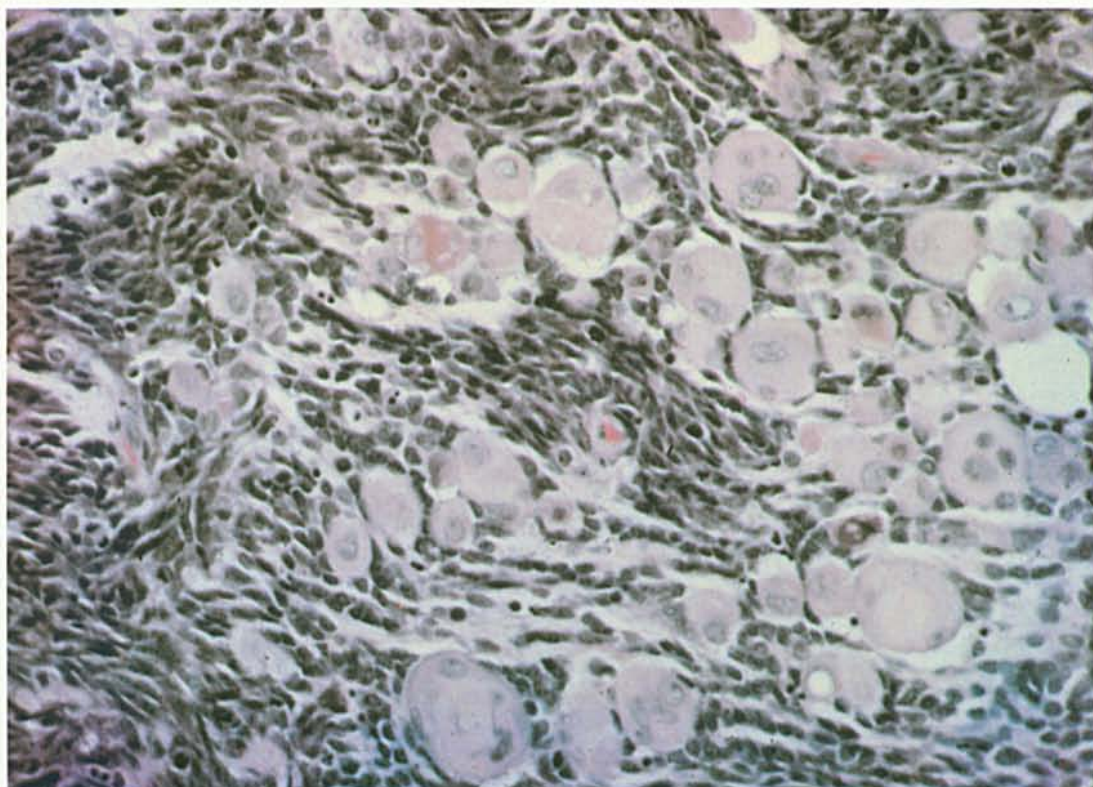
*Fig. 7. Low magnification of pineal gland tumor.*



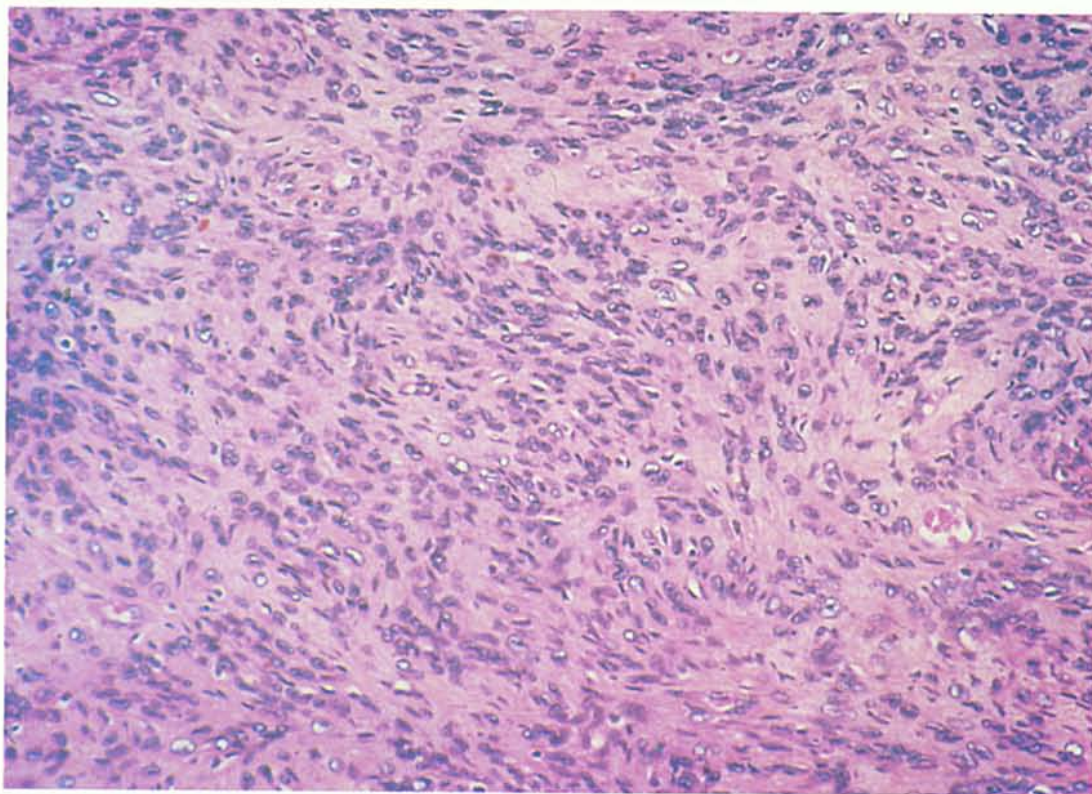
*Fig. 8. Poorly differentiated pineal gland tumor characterized by marked cellular atypia.*



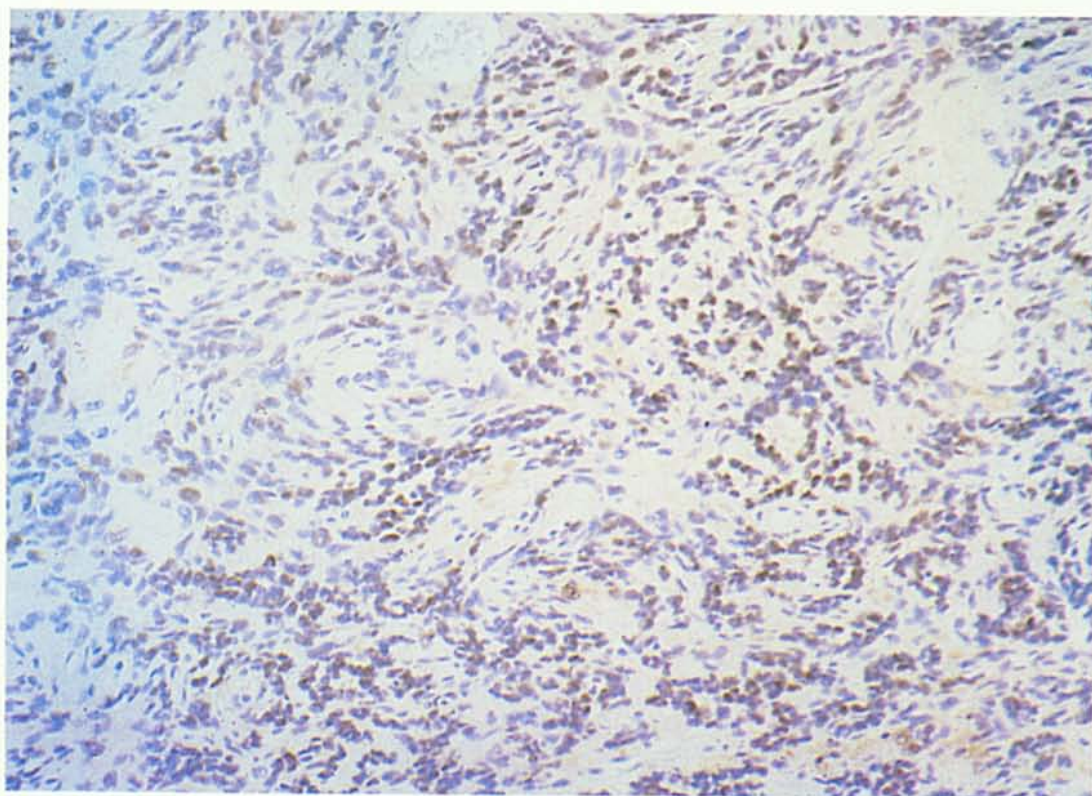
*Fig. 9. Medulloblastoma characterized by high cellularity, hyperchromatic, carrot-shaped nuclei, and ill-defined, scanty cytoplasm.*



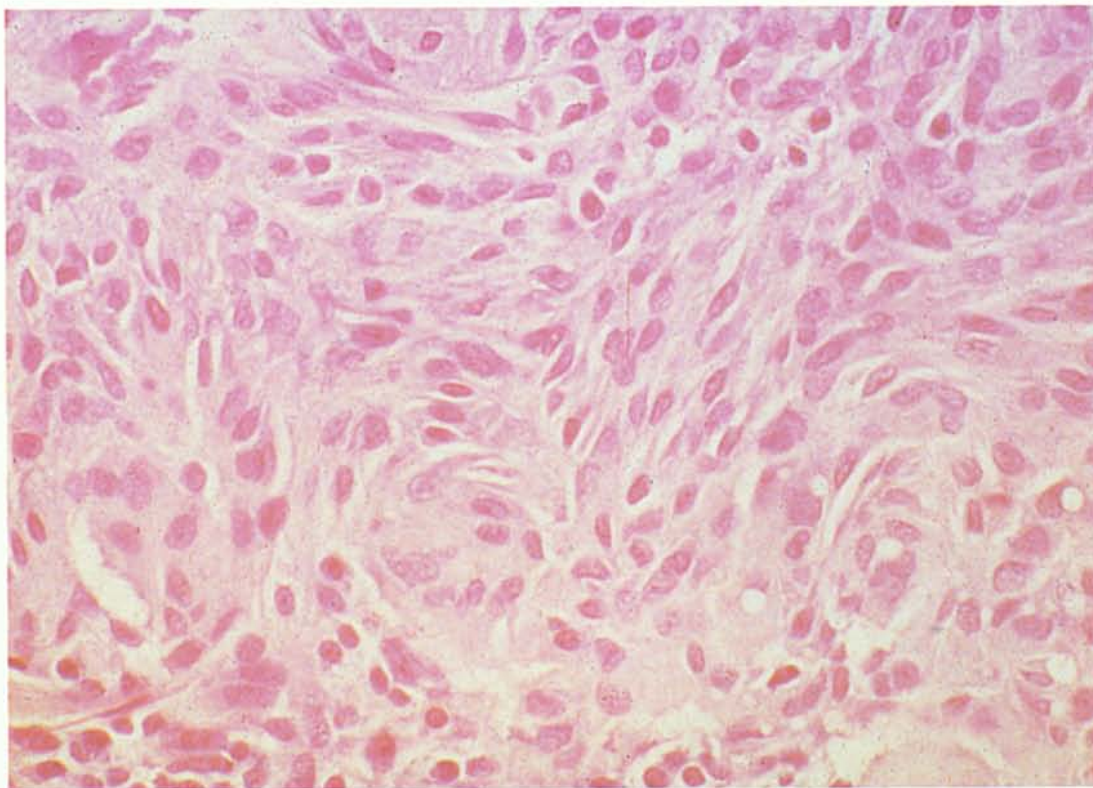
*Fig. 10. Medulloblastoma showing neuronal cell differentiation.*



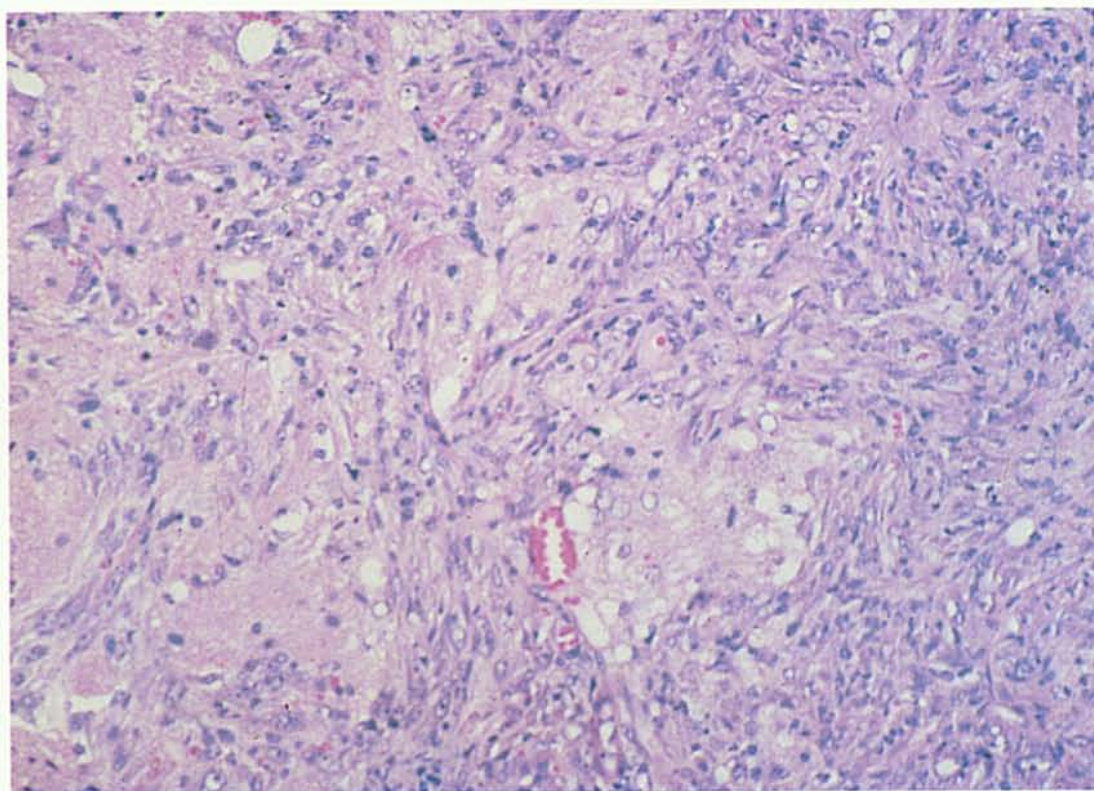
*Fig. 11. Malignant schwannoma composed mainly of Antoni type A tissue.*



*Fig. 12. Immunostaining of malignant schwannoma with S-100 protein. Note the predominantly positive nuclear staining.*



*Fig. 13. Fibroblastic meningioma composed of cells with abundant cytoplasm and spheroid to elongated nuclei.*



*Fig. 14. Poorly differentiated meningeal sarcoma.*

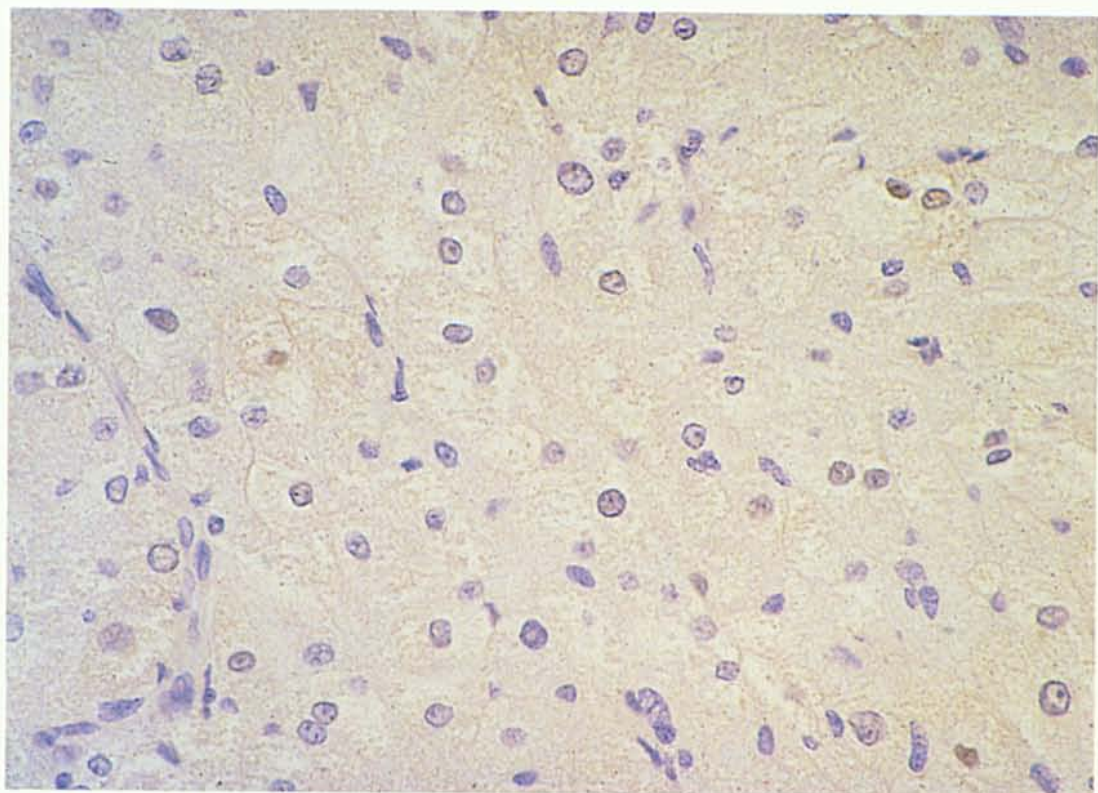


Fig. 15. Meningeal granular cell tumor characterized by cells with a granular cytoplasm and vesicular nuclei.

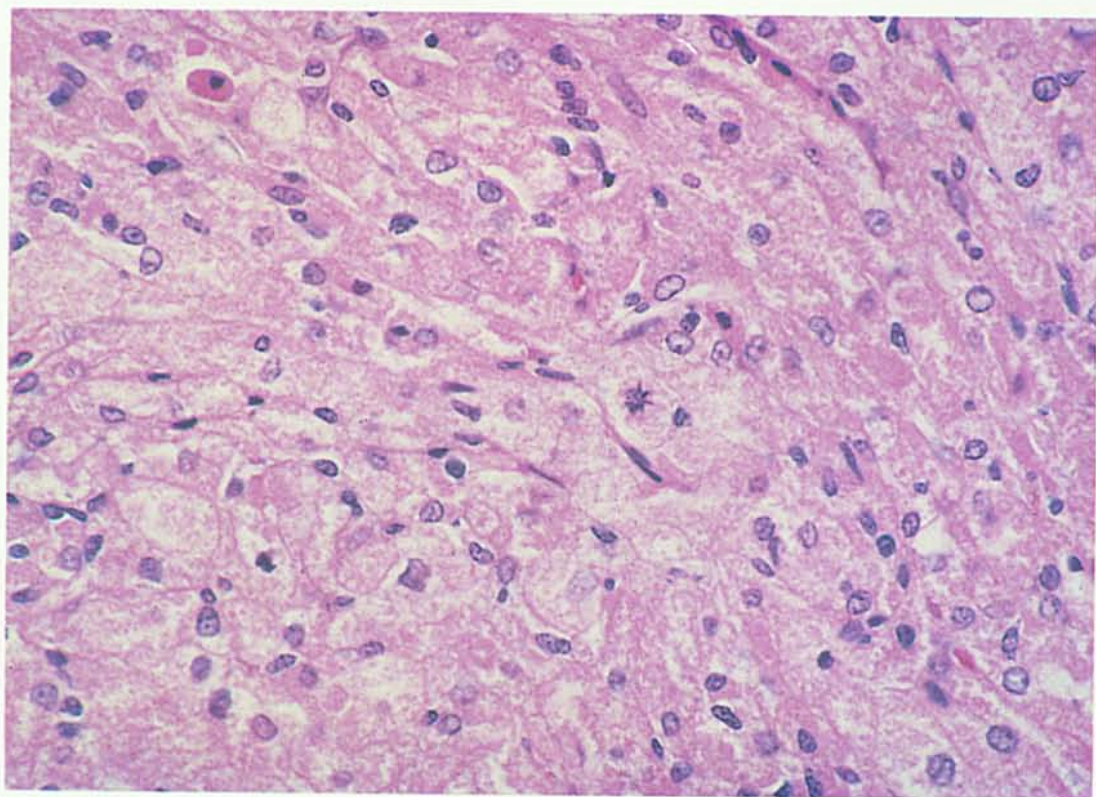
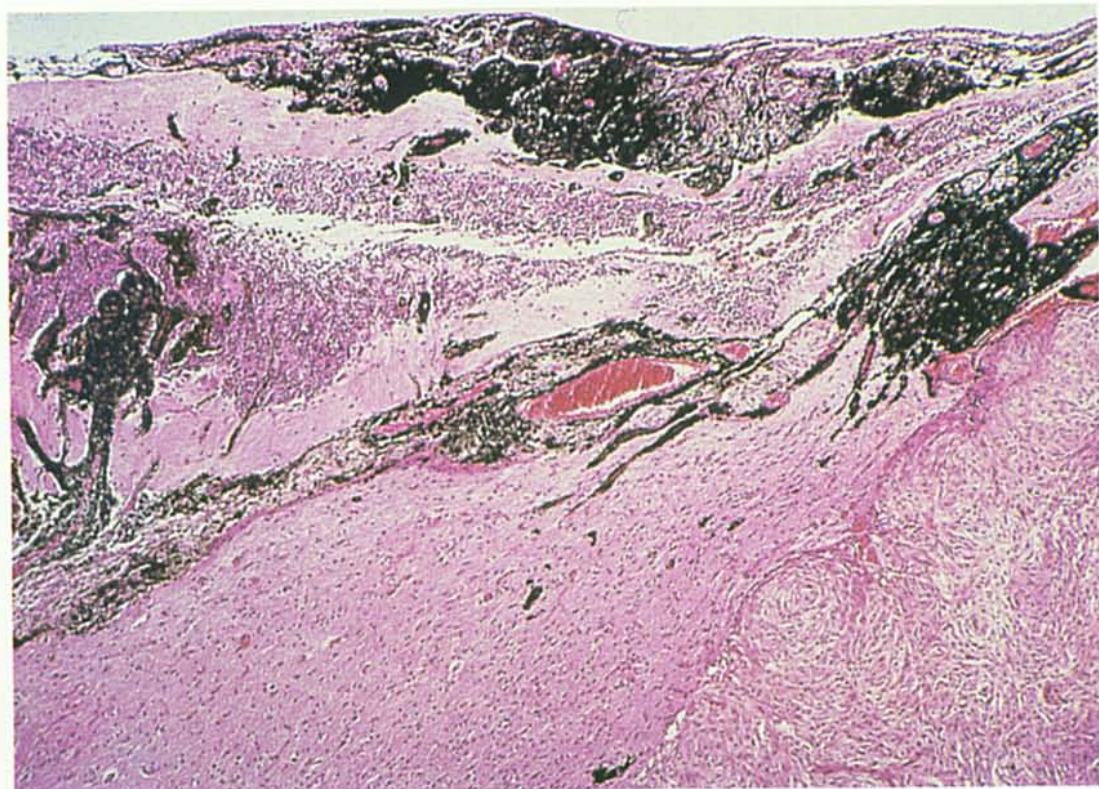
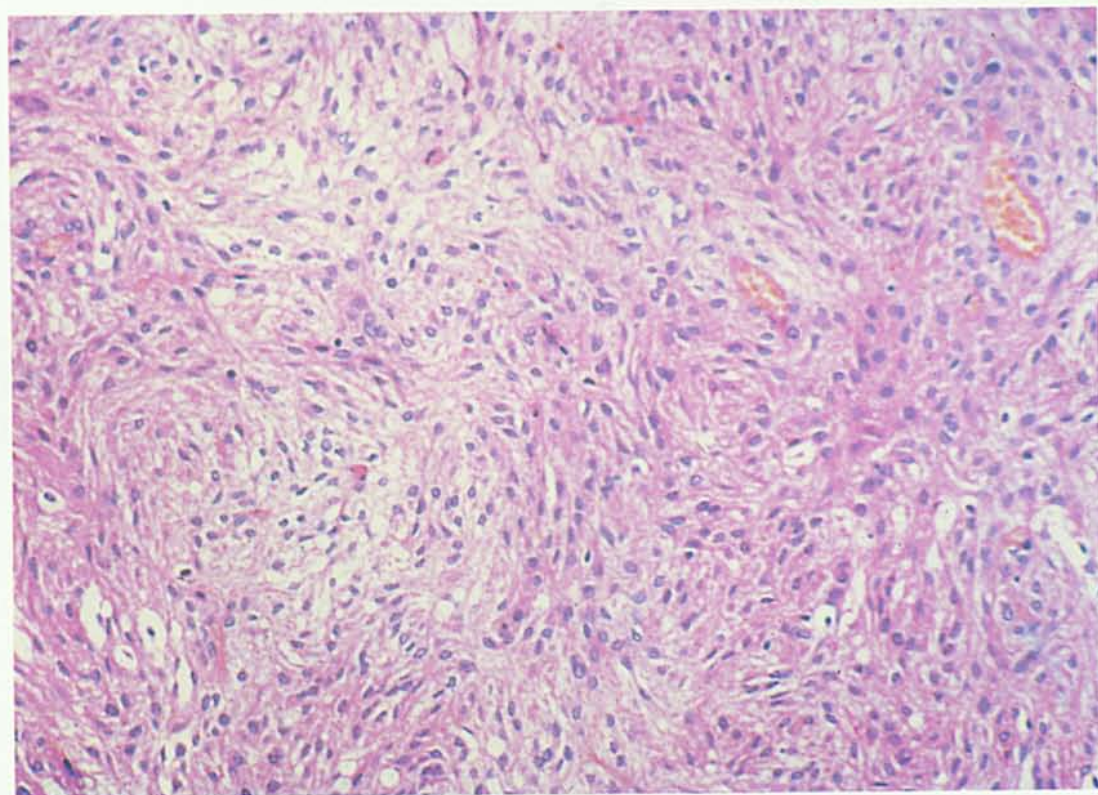


Fig. 16. Immunostaining of meningeal granular cell tumor with S-100 protein. Note lack of staining of tumor cells.

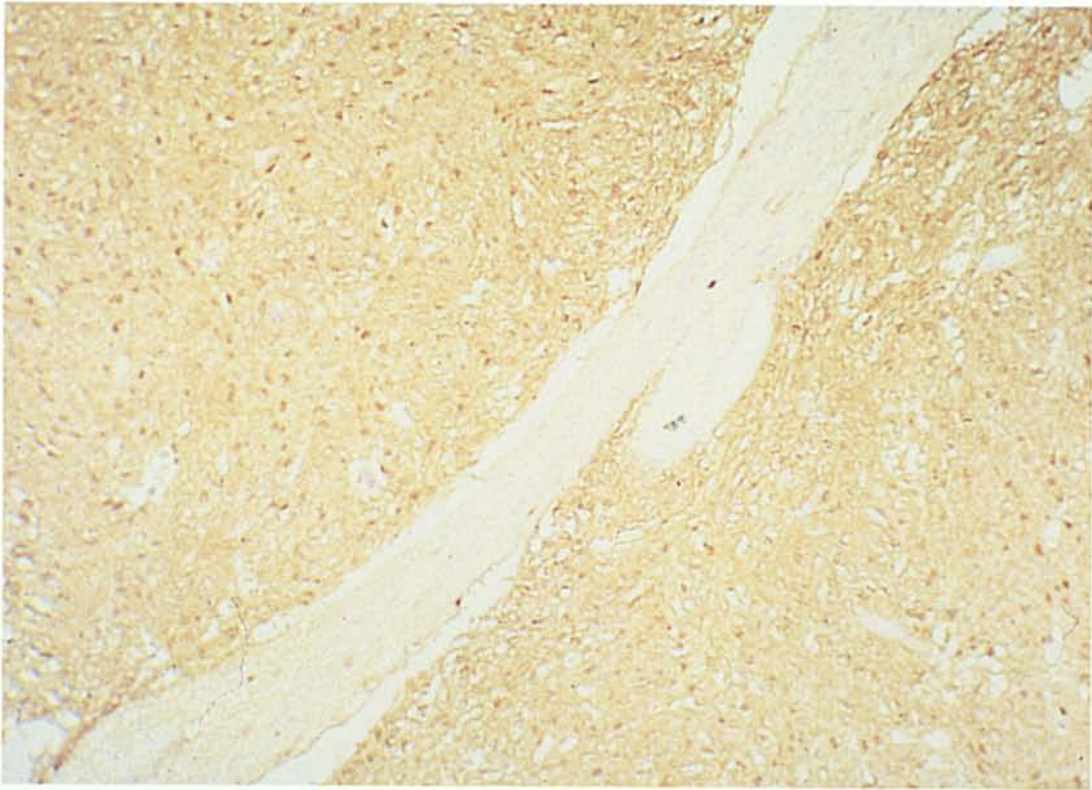
Figures 15 & 16 were  
inadvertently reversed



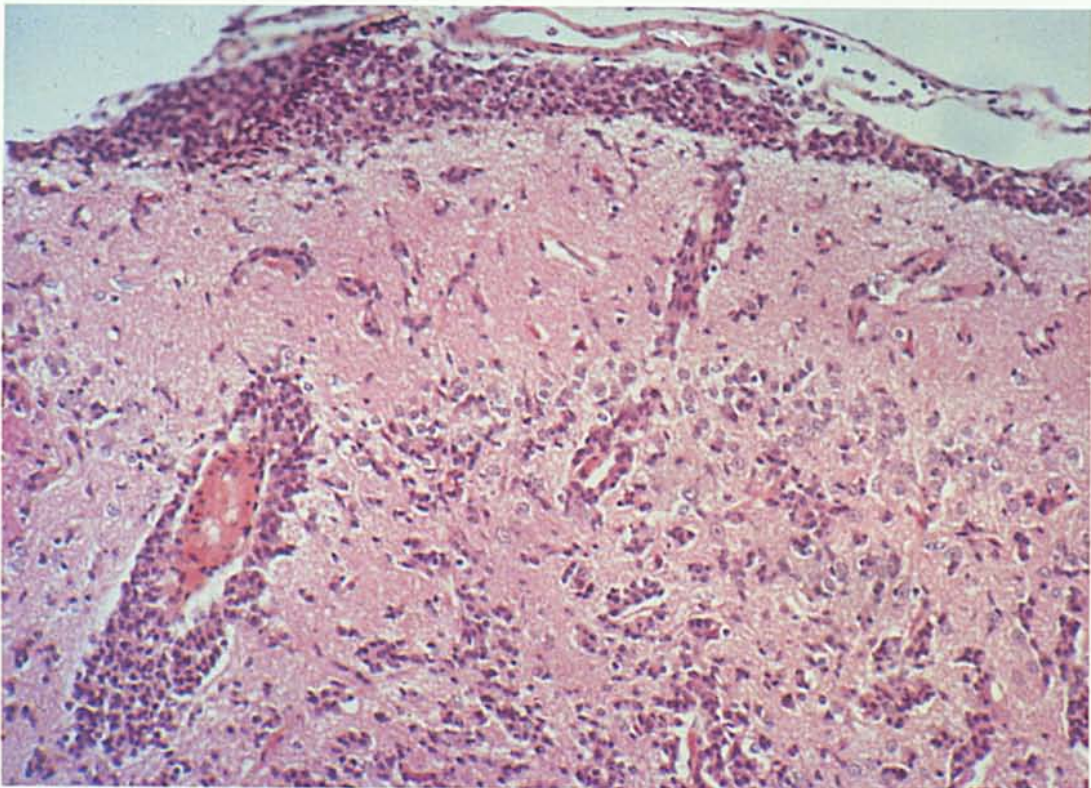
*Fig. 17. Malignant melanoma, partly pigmented and partly amelanotic.*



*Fig. 18. Amelanotic part of malignant melanoma which shows some resemblance to meningeal granular cell tumor.*



*Fig. 19. Immunostaining of amelanotic part of malignant melanoma with S-100. Note diffuse positive staining of tumor cells with S-100 which differentiates this tumor type from the granular cell tumor.*



*Fig. 20. Malignant reticulosis. Note marked infiltration of leptomeninges and perivascular infiltration. The infiltrates consist of a mixture of cells.*