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The New WHO Classification of Brain Tumours

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The new edition of the World Health Organization (WHO) book on 'Histological Typing of Tumours of the Central Nervous System' reflects the progress in brain tumour classification which has been achieved since publication of the first edition in 1979. Several new tumour entities have been added, including the pleomorphic xanthoastrocytoma, central neurocytoma, the infantile desmoplastic astrocytoma / ganglioglioma, and the dysembryoplastic neuroepithelial tumour. The list of histological variants has also been expanded. In line with recent morphological and molecular data on glioma progression, the glioblastoma is now grouped together with astrocytic tumours. The classification of childhood tumours has been largely retained, the diagnosis primitive neuroectodermal tumour (PNET) only being recommended as a generic term for cerebellar medulloblastomas and neoplasms that are histologically indistinguishable from medulloblastoma but located in the CNS at sites other than the cerebellum. The WHO grading scheme was revised and adapted to new entities but its use, as before, remains optional.

Compiling the first edition of the World Health Organization's consensus book on brain tumour classification (1) took almost a decade. At that time, pathologists had wide-ranging and often conflicting views on the terminology of central nervous system (CNS) neoplasms and, particularly, their histogenesis. Considering that immunohistochemistry was not yet available, the task was enormous. However, the result of the collaborative effort was quite successful as the "Blue Book" rapidly gained popularity worldwide. Preparation of the second edition, just published, was initiated during a consensus meeting held in Houston, Texas, in 1988 (2). The "Blue Book" still has the same scope, i.e., to propose a uniform nomenclature for CNS neoplasms that can be used internationally and which serves as a reliable guideline in day-to-day surgical pathology and as a unifying basis for the evaluation of brain tumour therapy trials. In this article, the major alterations and amendments are briefly reviewed, some with comments on the opinions expressed by participants of the WHO working group.

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Astrocytic Tumours and Glioma Progression

The working group unanimously proposed that a clear line be drawn between the more circumscribed lesions (e.g., the pilocytic astrocytoma, the pleomorphic xanthoastrocytoma and the subependymal giant cell astrocytomas associated with tuberous sclerosis) on the one hand and diffusely infiltrating astrocytomas typically located in the cerebral hemispheres on the other. Only the latter group shows an inherent tendency for progression to anaplastic astrocytoma and, ultimately, to glioblastoma multiforme. Most participants, though not all, therefore voted to classify the glioblastoma as an astrocytic tumour while in the first edition, it was grouped together with 'poorly differentiated and embryonal tumours' (1). Although some participants contended that anaplastic oligodendrogliomas and even ependymomas may, during advanced malignant progression, turn into a tumour that fulfills the criteria for diagnosis as glioblastoma, these neoplasms usually also show evidence of astrocytic differentiation.
The view adopted by the WHO working group, i.e., that the glioblastoma is essentially an astrocytic neoplasm, is supported by recent molecular genetic studies on the evolution of human gliomas (Table 1). It appears that in low grade astrocytomas (WHO Grade II), mutations of the *p53* tumour sup-

Table 1 Comparison of the World Health Organization (WHO) and St. Anne / Mayo grading system for astrocytomas

WHO Grade	*WHO Designation*	*St. Anne / Mayo Designation*	*St. Anne / Mayo Histological Criteria*	*Associated Genetic Alterations*
I	Pilocytic astrocytoma			
II	Astrocytoma (Low grade)	Astrocytoma Grade 1 Astrocytoma Grade 2	Zero criterion One criterion, usually nuclear atypia	*p53* mutation & LOH 17p
III	Anaplastic astrocytoma	Astrocytoma Grade 3	Two criteria, usually nuclear atypia and mitotic activity	*p53* mutation & LOH 17p, LOH 19q
IV	Glioblastoma multiforme	Astrocytoma Grade 4	Three criteria, usually nuclear atypia, mitoses, endothelial proliferation and/or necrosis	*p53* mutation & LOH 17p, LOH 19q & LOH 10, EGF-R amplification

Abbreviations: LOH, loss of heterozygosity; EGF-R, epidermal growth factor receptor.

pressor gene with or without loss of heterozygosity on chromosome 17p occur in approximately 30% of cases and constitute the earliest detectable genetic alteration in diffusely infiltrating astrocytomas (3,4), although isolated cases with loss of heterozygosity on chromosomes 13 and 22 have been reported (5). Anaplastic astrocytomas (WHO Grade III) often develop over a course of several years from low grade astrocytomas but may also arise *de novo*, i.e., without clinical or histopathological evidence of a preceding low grade glioma and contain *p53* mutations at a similar incidence of 29 to 36% (3,6). In addition, more than 40% of anaplastic astrocytomas show loss of heterozygosity on chromosome 19q (7). Glioblastomas frequently develop from low grade or anaplastic astrocytomas ('secondary glioblastoma') but may also primarily arise after a short clinical history, with no evidence of a less malignant precursor lesion ('primary glioblastoma'). In three independent studies, *p53* mutations were identified in approximately one third of glioblastomas (6,8,9). The observation of a similar overall incidence of *p53* mutations in low grade astrocytomas, anaplastic astrocytomas and glioblastoma multiforme may indicate that this gene is involved during a rather early stage of neoplastic transformation. One study suggests that the progression to glioblastoma is characterized by a clonal expansion of cells carrying a *p53* mutation, presumably due to a selective growth advantage (10). In addition to *p53* mutations, more than 70% of glioblastoma multiforme have loss of chromosome 10 (11,12). In contrast to low grade and anaplastic astrocytomas, glioblastomas contain, in approximately one third of cases, amplification of the epidermal growth factor receptor gene (EGF-R), sometimes in a truncated form (11,13,14). Although the scheme shown in Table 1 is undoubtedly far from complete, there is increasing evidence that in human astrocytomas genetic events may occur in a typical sequence which parallels histopathologically defined stages of malignant progression. In contrast to diffusely infiltrating astrocytomas, non-astrocytic brain tumours and pilocytic astrocytomas do not or very rarely contain *p53* mutations, thus suggesting a different genetic basis for these CNS neoplasms (4,15).

Pleomorphic Xanthoastrocytoma (PXA)

The participants unanimously accepted the pleomorphic xanthoastrocytoma as a clinicopathologic entity. Details on the nosologic evolution of this tumour entity are provided by J. Kepes, elsewhere in this issue (16). In brief, the lesion is defined as a generally superficial, compact neoplasm, with abundant reticulin and, frequently, perivascular chronic inflammatory cells. Marked cellular pleomorphism is a consistent finding. Lipidization of the neoplastic cells is variable, being scant in some cases and overt in others (17). The classic lesion is noted for the absence of mitotic figures, vascular proliferation and necrosis, but it is increasingly recognized that other-

wise typical lesions with mitoses are encountered. The histogenesis of the lesion remains controversial, but a glial origin was accepted by the Working Group in light of the immunohistochemical, histological, and ultrastructural features. Some cells are usually positive for glial fibrillary acidic protein. The resemblance of some cases to malignant fibrous histiocytomas has, to some observers, raised the possibility of a histiocytic origin (18). This is supported in part by immunohistochemical studies but the lack of specificity of these markers for histiocytes is widely recognized and immunoreactivity in a PXA by no means excludes a glial origin for this lesion (19).

Although there was consensus on the status of the PXA as an entity, questions remained regarding the biological behavior and grading of this lesion. Some PXAs, for example, have an infiltrating component the significance of which is not clear. In regard to the issue of grading, the original supposition that these were only low grade tumours is contradicted from time to time in practice, in the face of mitotically active neoplasms discussed above. In addition, some typical PXAs undergo anaplastic change (20,21). At this point, grading of this lesion remains controversial as does the tumour's relation to the giant cell glioblastoma.

Dysembryoplastic Neuroepithelial Tumour

This recently described (22) morphologically unique and surgically curable lesion, dysembryoplastic neuropeithelial tumour (DNT), has also been included in the new WHO classification (23). It is typically associated with medically intractable seizures of partial complex type. To date, neither neurologic deficit nor an association with a phakomatosis or mental retardation have been reported. In most cases, the patient's age at onset of symptoms is less than 20 years. Most affect the temporal or frontal lobe; parietal, and particularly occipital involvement is infrequent. All DNTs are supratentorial and intracortical. Computer tomagraphy (CT) scans show DNTs to be well-defined, with little or no accompanying edema. Mass effect and effacement of cortical architecture is subtle in small lesions, but their inherent nodularity may be appreciated on magnetic resonance (MR) scans. Focal contrast enhancement, calcification, or cystic change is present in a small minority. Deformity of the overlying calvarium is common, attesting to their long-standing nature. At low-power, multinodularity is a key feature. The constituent cells include primarily oligodendrocytes and, to a lesser extent, astrocytes often of pilocytic type. A recent detailed immunochemical and ultrastructural study indicated that in a minority of cases the oligodendroglia-like cells demonstrate astrocytic or early neuronal differentiation (24). The surrounding extranodular cortex exhibits the so-called 'specific component' of DNT, one rich in oligodendrocytes and a mucinous matrix within which neurons appear to 'float'. Such neurons vary from small to large and from uni- to occasionally multinucleate. Surrounding cortical dysplasia is also a common feature. A detailed morphological description of DNTs is provided by C. Daumas-Duport in this issue, together with a proposal to distinguish between simple and complex forms of the lesion (25).

Since the original report (22), few additional cases have been reported (26,27). Despite incomplete or subtotal removal of nearly half of reported lesions, long-term follow-up reveals neither clinical nor radiological evidence of recurrence. Not only has no benefit of radiotherapy been noted, but recognition of DNT as a clinicopathologic entity is of importance since aggressive therapy must be avoided.

Desmoplastic Infantile Ganglioglioma (DIG)

This is a relatively recent recognized entity noted for its early age of onset, superficial position, and frequent association with a large cyst (28). Histologically, multiple tissue patterns have been encountered, but the most distinctive is paucicellular desmoplastic tissue in which astrocytes and neurons are inconspicuous unless immunohistochemistry for neuronal and glial markers (GFAP) is applied. An associated tissue pattern in some cases is a cellular and, sometimes mitotically active, component which can prompt the diagnosis of a malignant neoplasm such as malignant glioma or gliosarcoma. Experience with DIG is limited and the clinical behavior of this lesion remains to be defined. Nevertheless, the cases that have been followed have suggested that this is a low grade process, despite mitotic activity and occasional small cell component. Many patients appear to be cured by simple excision. Although this lesion has generally been encountered in the first year of life, cases in adults have been recognized (29). In one case studied postmortem, a DIG was associated with a more conventional ganglioglioma, raising the question as to how distinct this entity is from the traditional classic ganglion cell neoplasms (30).

Desmoplastic cerebral astrocytoma of infancy. Ever since the initial report by Taratuto et al., in 1984, (31) it has become increasingly evident that there is a group of infantile desmoplastic tumours with neoplastic astrocytes but which lack the neuronal component of the DIG (32-34). Since their clinical behaviour is similarly benign (35), it has been proposed to use the generic term 'desmoplastic supratentorial neuroepithelial tumours of infancy' for these lesions (36).

Central Neurocytoma

The participants of the WHO working group unanimously voted to include this new entity, defined by J. Hassoun in 1982 (37), in the new classification.

Over the past decade, this lesion has become a well-established clinico-pathological entity with more than 125 documented and published cases. Its clinical and morphologic characteristics are summarized elsewhere in this issue (38). Briefly, this often calcified tumour is characterized by its manifestation in young adults, and by its typical supratentorial location in the lateral ventricles in the region of the foramen of Monro. Histologically, the lesion is moderately cellular and consists of isomorphous round cells which alternate with patchy islands of a fibrillar 'neuropil' matrix. Central neurocytomas consistently show evidence of neuronal differentiation which can easily be assessed by immunohistochemistry (synaptophysin) and electron microscopy (EM) wherein of synapses and dense-core vesicles are seen. Differential dignoses are oligodendroglioma, ependymoma and cerebral neuroblastoma. Following surgical resection, the clinical outcome is usually favourable although recurrencies have been reported. Although some neurocytomas show significant mitotic activity, occasional necrosis and vascular proliferation, reported follow-up studies so far do not support the concept of a frankly malignant variant.

Neuroepithelial Tumours of Uncertain Origin

In this category, three lesions were grouped together: the astroblastoma, the polar spongioblastoma and gliomatosis cerebri. Although undoubtedly of neuroepithelial origin, their histogenesis has to date remained enigmatic. This is particularly true for astroblastoma and polar spongioblastoma; some participants of the WHO working group considered them sufficiently defined clinico-pathological entities while others regard them merely as a typical but unspecific growth pattern which may occur in several of the more ordinary gliomas.

Astroblastoma. For some members of the Working Group, the controversy as to whether this highly characteristic pattern of glial neoplasia represents a clinicopathologic entity or simply a focal morphologic expression has been settled in favor of the former by the report by Bonnin and Rubinstein (39). Nonetheless, the nature of astroblastoma remains an issue of contention. A tumour of the young, most are well-defined contrast-enhancing masses involving the cerebral hemispheres. Some, but not all, are periventricular in location. Despite obvious similarities to ependymoma, broad rather than narrow tapering cell processes comprise astroblastoma pseudorosettes, as does lack of PTAH-positive cytoplasmic fibrils despite strong GFAP reactivity. Conspicuous vascular hyalinization may also distinguish astroblastoma. A similarity to ependymoma is also evident at the ultrastructural level. In the new classification, astroblastoma is defined on the basis of the typical histologic pattern but it is also stated that astroblastic features may be present in low grade and anaplastic astrocytomas, and in the glioblastoma multiforme. Thus, foci of astroblastic differentiation in otherwise ordinary gliomas do not qualify for the designation as astroblastoma.

Polar spongioblastoma. The histopathological feature of this neoplasm is quite unique as it is composed of unipolar or bipolar glial cells, the tumour nuclei being arranged in parallel, forming a typical palisading pattern. The presence of this pattern can be focally observed in a variety of glial neoplasms, particularly during tumour progression, most notably in oligodendrogliomas, pilocytic astrocytomas and cerebellar medulloblastomas. Nevertheless, some members of the Working Group maintained the view that there is a 'true' polar spongioblastoma, which occurs usually in children and young adults and in which the spongioblastic pattern is typically present throughout the neoplasms (40,41). Sporadic cases of polar spongioblastoma continue to be published (42-44). In a recent study of 16 neoplasms with spongioblastic differentiation, Schiffer et al. (45) found only two tumours that showed this pattern throughout, but there were features of ependymal differentiation in one case and neuroblastic differentiation in the other. The authors concluded that in embryonal tumours of the CNS the characteristic palisading pattern may dominate the entire surgical specimen. In their view, a true polar spongioblastoma does not exist. This view is, in part, supported by a report in which spongioblastic differentiation was observed in a medulloepithelioma (46).

Gliomatosis cerebri. The term gliomatosis cerebri engendered considerable discussion as to the origin of this lesion and its entitlement to the status of a clinicopathologic entity. There was general consensus that the lesion is a glioma but little agreement as to cytogenesis. There was also disagreement whether gliomatosis was a non-specific pattern of infiltration or was sufficiently distinctive to be discussed separately. The Working Group opted for the latter but with the qualification that the 'entity' was controversial. Although the lesion is often felt to represent an infiltrating astrocytic tumour, lesions with oligodendrocyte phenotype have also been reported (47,48). The general consensus was that this lesion is a clinical and radiographic entity as much as a pathologically defined process. The term "gliomatosis" was not felt to be appropriate unless large areas (at least two, usually three lobes) of the brain are involved.

Histologically, the features, which are shared by a diverse group of infiltrating gliomas include a diffusion of small, usually elongated cells (47-51). Secondary structures in the cerebral cortex such as perivascular accumulation, perineuronal satellitosis, and subpial aggregation are common. Diffuse neoplasms with a markedly cellular, centrally necrotic epicenter would generally be considered glioblastoma rather than gliomatosis.

Primitive Neuroectodermal Tumours (PNET)

The nomenclature of embryonal CNS tumours was among the most fervently discussed issues of the Working Group. Origin of the dispute is the still unresolved histogenesis of the cerebellar medulloblastoma. There appears to be general agreement that this tumour is embryonal, i.e., derived from an immature precursor cell which was initially proposed to be the embryonal medulloblast. This precursor cell was never identified in the human CNS although a recent experimental study suggests that a cerebellar stem cell with potential for neuronal, glial and muscle cell differentiation may exist (52). Pathologists have been intrigued by the observation that occasionally, medulloblastoma-like tumours occur in the cerebral hemispheres and it was proposed by Hart and Earle in 1973 (53), that this group of embryonal neoplasms should be named primitive neuroectodermal tumours (PNETs). In 1983, L. Rorke suggested that this term be applied to a large variety of embryonal CNS tumours, including medulloblastoma, ependymoblastoma, neuroblastoma and the pineoblastoma. The conceptual basis for this nomenclature was the assumption that PNETs share a common progenitor cell population, believed to be the subependymal matrix layer and that their neoplastic transformation at various levels of the CNS leads to tumours with similar morphology and biology (54). Whether and to what extent this concept holds true is still a matter of controversy although most authors now acknowledge that the cerebellar medulloblastoma arises from the external granular layer which is the matrix zone for granular neurons but not for glial cells. Extensive immunohistochemical studies have indeed shown that medulloblastomas consistently express neuronal marker proteins (55,56) and often develop a morphological phenotype resembling immature or fully developed ganglion cells. Astrocytic differentiation is less common, focal and usually restricted to a small rim of GFAP immunoreactivity in the perikaryon (57). Further, although supratentorial PNETs are now subjected to a therapy protocol similar to that of the cerebellar medulloblastoma, their clinical course appears to be less favourable; the results of prospective therapy trials are still pending.

Most members of the Working Group held the view that the WHO classification should avoid this controversy and voted to largely retain the classification of 'embryonal childhood tumours' and recommended to use the diagnosis 'primitive neuroectodermal tumour' (PNET) restrictively as a generic term for cerebellar medulloblastomas and for neoplasms morphologically indistinguishable from the medulloblastomas but located at other sites in the CNS.

Cranial Nerve Tumours

The spectrum of nerve sheath tumours encountered in the peripheral nerve system are also noted in central portions of cranial and spinal nerves. Newcomers to the spectrum of schwannoma (neurilemmoma, neurinoma) include the cellular and melanotic variants.

Cellular schwannoma. This variant of schwannoma consists largely of cellular, Antoni A tissue exhibiting variable mitotic activity. As such, it mimics malignant peripheral nerve sheath tumour (MPNST). Small, non-representative biopsies are particularly troublesome since the distinction of cellular schwannoma from MPNST requires attention to architectural as well as cytologic and immunochemical features. Distinguishing features of schwannoma include encapsulation, vascular hyalinization, perivascular hemosiderin deposition, occasional foci of Antoni B pattern, strong generalized S-100 protein immunoreactivity and frequent, albeit patchy staining for Leu-7, myelin-basic protein and glial fibrillary acidic protein. Electron microscopy shows highly developed schwann cell features including extensive basal lamina formation and, in the minority of cases, long-spacing collagen.

Since its original description (58), several series have confirmed the essentially benign nature of this lesion (59-62). Although approximately one-third of intracranial and intraspinal tumours recur (62), a figure considerably higher than in peripheral nerves (5%), none have been reported to metastasize. No association with neurofibromatosis has been noted.

Pigmented schwannoma. Unlike ordinary schwannomas, the clinical behavior of melanotic schwannomas is variable. Approximately one-third are paraaxial in location and nearly 10% arise within the CNS. No association with neurofibromatosis has been noted. Fully 20% are histologically malignant and of these, nearly one-third metastasize (63,64).

A subset of melanotic schwannomas demonstrate psammomatous calcifications. Of these, one-half are associated with a clinical syndrome (Carney's Complex) of spotty pigmentation, myxomas, and endocrine overactivity, usually Cushing's disease (65).

Meningioma Variants

Of tumours derived from components of the meninges, only those composed of or differentiating toward arachnoidal cells are included in the present classification of meningiomas. As a result, non-meningothelial tumours, other mesenchymal neoplasms, and those of uncertain histogenesis are separately grouped under benign and malignant mesenchymal neoplasms as well as tumours of uncertain origin. In addition to meningothelial (syncytial), fibrous, transitional, psammomatous, and metaplastic variants, a number of new variants have been included in the new WHO classification (66).

Secretory meningioma. This variant exhibits glandular metaplasia as evidenced by intracytoplasmic

lumen formation. Such gland-like spaces contain a conspicuous PAS-positive secretion (67). Cells surrounding such 'pseudopsammoma bodies' show clear evidence of epithelial differentiation. Immunostains demonstrate keratin, carcinoembryonic antigen (CEA), and secretory component staining (68, 69). At the ultrastructural level, the intracytoplasmic lumina contain microvilli and amorphous secretions (70). The clinical behavior of secretory meningiomas resembles that of more ordinary variants. The demonstration of obvious meningothelial or transitional features in other portions of most tumours prevents their confusion with metastatic carcinoma.

Microcystic meningioma. This unusual form of meningioma, once termed "humid" (71), differs from more ordinary meningiomas in displaying a less pronounced female sex predilection (72,73). Occasionally grossly cystic, it is characterized by a wet, glistening cut surface. Microscopically, the distinctive microcystic pattern results from accumulation of extracellular fluid between attenuated processes of neoplastic cells. Meningothelial cytology, including nuclear-cytoplasmic inclusions, is often noted but whorl formation is inconspicuous.

Clear cell meningioma. This distinctive variant of meningioma is characterized by sheet-like proliferation of clear, polygonal cells, the cytoplasm of which contains abundant glycogen. Meningothelial features are inapparent and at most consist of vague whorl formation. Coarse, blocky, stromal and perivascular collagen deposition is a conspicuous degenerative feature in tumours of long-standing. In view of its high content of glycogen, this form of meningioma must be distinguished from metastatic renal cell carcinoma, a tumour with stronger, more uniform keratin and epithelial membrane antigen immunoreactivity as well as lack of S-100 protein staining. Clear cell meningiomas may recur or seed.

Lymphoplasmacyte-rich meningioma. This uncommon tumour is characterized by a prominent lymphoplasmacytoid reaction superimposed upon a more ordinary, often meningothelial or transitional meningioma (74,75). Germinal centers, Russell body-containing plasma cells, and even amyloid may be noted. Lymphoplasmacytoid meningiomas have been associated with polyclonal hypergammaglobulinemia which remits with resection and reappears with tumour recurrence. This variant of meningioma must be distinguished from plasma cell granuloma (76) and meningeal plasmacytoma (77).

Chordoid meningioma. Due to their lobular, low-power architecture and production of stromal mucosubstances, chordoid meningiomas mimic chordoma. Neuroradiologic and immunochemical studies aid in the differential diagnosis. In contrast to chordoid meningiomas, chordomas affect the midline skull base, are permeative of bone, lack a hyperostotic reaction, are strongly immunoreactive for epithelial membrane antigen and cytokeratin, and often (50%) show widespread S-100 staining. Chordoid meningiomas usually show only scant reactivity for these antigens. Several examples have been associated with a Castleman-like syndrome (78).

Atypical and Malignant Meningiomas

In the previous WHO classification (1), the anaplastic (malignant) form of meningioma was recognized. During the past decade, there was, however, increasing evidence of the presence of a meningioma with intermediate biologic behaviour, i.e., the atypical meningioma. Although the definition of atypical meningioma varied somewhat between the participants of the Working Group, its inclusion in the new WHO classification was readily adopted.

Atypical meningioma. Although the biologic behavior of meningiomas is affected by radiographic and operative features, e.g., invasiveness, multifocality, and extent of resection, histologic studies demonstrate an association of recurrence with brisk mitotic activity, hypercellularity, high nuclear cytoplasmic ratio, nuclear atypia and nucleolar prominence, uninterrupted patternless growth ('sheeting') and the presence of zonal necrosis (79-86). Tumours exhibiting these features, but lacking frank anaplasia, are termed "atypical meningiomas". In a retrospective clinico-pathological review of 1,799 meningiomas, Maier et al. (87) confirmed the intermediate clinical behaviour of atypical meningioma but defined the lesion more narrowly. In their view, increased cellularity and brisk mitotic activity (at least five mitotic figures in ten high-power fields) are sufficient to allow the diagnosis of atypical meningioma.

Malignant meningioma. With the exclusion of hemangiopericytoma, considered sarcoma in the new WHO classification, the proportion of truly malignant meningiomas is significantly reduced. Such tumours are either anaplastic from their onset or occur in transition from ordinary or atypical meningiomas. It is notewothy that not all clinically malignant tumours, i.e. those exhibiting brain invasion or distant metastasis, are frankly anaplastic.

Papillary meningioma. The histologic appearance of clinically or histologically malignant meningiomas covers the spectrum of morphologic variants, but papillary meningioma deserves special mention. This aggressive form of meningioma has long been considered 'malignant by definition' (88). A recent review of the literature found not only a high frequency of brain or local invasion, recurrence, and metastasis but a 50% likelihood death of disease (89). The papillary pattern predominates in only a minority of cases and most tumours demonstrate a clearly recognizable meningioma pattern.

Deletion

The monstrocellular sarcoma is no longer contained in the WHO classification since immunohistoche-

Table 2 World Health Organization (WHO) grading system (malignancy scale) of CNS tumours.

Tumour Group	*Tumour Type*	*Grade I*	*Grade II*	*Grade III*	*Grade IV*
Astrocytic tumours	Subependymal giant cell	•			
	Pilocytic	•			
	Low grade		•		
	Pleomorphic xanthoastrocytoma		•	•	
	Anaplastic			•	
	Glioblastoma				•
Oligodendrogliomas	Low grade		•		
	Anaplastic			•	
Oligo-astrocytomas	Low grade		•		
	Anaplastic			•	
Ependymal tumours	Subependymoma	•			
	Myxopapillary	•			
	Low grade		•		
	Anaplastic			•	
Choroid plexus tumours	Papilloma	•			
	Carcinoma			•	•
Neuronal / glial tumours	Gangliocytoma	•			
	Ganglioglioma	•	•		
	Desmoplastic infantile ganglioglioma	•			
	Dysembryoplastic neuroepithelial tumour	•			
	Central neurocytoma	•			
Pineal tumours	Pineocytoma		•		
	Pineocytoma / pineoblastoma			•	•
	Pineoblastoma				•
Embryonal tumours	Medulloblastoma				•
	Other PNETs				•
	Medulloepithelioma				•
	Neuroblastoma				•
	Ependymoblastoma				•
Cranial & spinal nerve tumours	Schwannoma	•			
	Malignant peripheral nerve sheath tumour			•	•
Meningeal tumours	Meningioma	•			
	Atypical meningioma		•		
	Papillary meningioma		•	•	
	Hemangiopericytoma		•	•	
	Anaplastic meningioma			•	

mical studies clearly showed that tumour cells consistently express GFAP (90). Thus, this neoplasm has to be regarded as a variant of the glioblastoma, i.e., a giant cell glioblastoma with sarcomatous component.

WHO Grading of CNS Tumours

Although the difficulties in tissue sampling are recognized, the participants were committed to the concept that many gliomas, particularly the astrocytic tumours, require stratification into levels of differing histological 'malignancy'. The process of grading, as applied to diffuse or fibrillary astrocytic tumours, is plagued by variation of grade within a given neoplasm as well as the decided tendency for such tumours to undergo anaplastic transformation over time, thus providing an essentially 'moving target'. As expected, there were disagreements as to how this stratification should be accomplished, e.g., which numbers or verbal descriptions, or both, were preferable. The numbers of steps or grades were also a point of discussion. In regard to the astrocytic tumours, the group elected to retain a three-tiered system similar to that of the previous WHO volume (1) and similar to that proposed by Ringertz in 1951 (91). This system is also similar to the St. Anne / Mayo classification published by Daumas-Duport et al. (92) discussed below (Table 1) since astrocytomas entitled to the grade I designation by the latter classification are very uncommon (92).

The group retained the general approach utilized in the prior edition of the WHO "Blue Book", which established a malignancy scale based on the histologic features (Table 2). Grade I lesions, exemplified by the pilocytic astrocytoma, generally included tumours with a low proliferative potential, a frequently discrete nature, and the possibility of cure following surgical resection alone. Lesions designated grade II are generally infiltrating and low in mitotic activity, but recur. Some tumour types tend to progress to lesions with higher grades of malignancy. The well differentiated astrocytomas, oligodendrogliomas and ependymomas are typical examples of grade II tumours. The designation grade III was reserved for lesions with histologic evidence of malignancy, generally in the form of mitotic activity, clearly expressed infiltrative capabilities and anaplasia. The designation grade IV was assigned to mitotically active, necrosis-prone neoplasms, generally associated with a rapid pre- and postoperative evolution of the disease. Examples include most of the embryonal neoplasms, the glioblastoma multiforme and occasional highly malignant choroid plexus carcinomas. Although not a diagnostic criteria for a grade IV tumour, infiltration of adjacent tissue, and propensity for dissemination within the central nervous system in some cases, is a common feature of grade IV neoplasms.

Comparison of Grading System for Astrocytic Tumours

Significant indicators of anaplasia in astrocytic tumours are generally agreed upon and include cytologic atypia, mitotic atypia, high cellularity, vascular proliferation, and necrosis with or without pseudopalisading. Of these, all but cellularity readily lend themselves to quantification. Several histologic grading systems are in use for the division of astrocytic tumours into prognostically meaningful groups.

Kernohan grading. Both three-tiered and four-tiered grading schemes have been introduced. Of the latter, the best known is the Kernohan method (93), an outgrowth of the still popular four-tiered Broder's classification (94) applied successfully to a variety of systemic tumours. Like most methods, that of Kernohan shows correlation between patient age, tumour grade, and length of postoperative survival. Significant detractions of the system are its 'lumping' of fibrillary and pilocytic astrocytoma as well as the equation of the term "glioblastoma" with tumours of both grades 3 and 4. Rather than distinguishing four separate survival curves, however, tumours tend to fall into low grade (1-2) and high grade (3-4) groups. Furthermore, the individual criteria of the Kernohan method are verbally expressed in such a way as to foster subjectivity and inter-observer variation.

Ringertz system. Currently used three-tier schemes, ones based upon the Ringertz system (91), designate tumours of differing grade by name rather than number. The Ringertz method, as well as modifications thereof (95-98), is limited in its application to astrocytoma, anaplastic astrocytoma, and glioblastoma. Pilocytic and other special variants of astrocytoma are not graded by these methods. Furthermore, they apply the designation "glioblastoma" only to tumours of grade 4. As a rule, these schemes consider the well-differentiated lesion (grade 2, or astrocytoma) to show atypia but only rare mitoses and no vascular proliferation or necrosis, the intermediate lesion (grade 3, or anaplastic astrocytoma) to be a more cellular, mitotically active lesion with little if any vascular proliferation and no necrosis, and the least differentiated (grade 4, or glioblastoma) to be cellular, pleomorphic, and mitotically active with neovascularization and necrosis. Significant differences in survival are noted in each grade. Like the Kernohan scheme, subjectivity and inter-observer variation may pose a significant problem.

WHO grading. The previous WHO classification also employs a three-tier system similar to the Ringertz scheme (1). Feature definitions are verbal, subjective, and thus permit considerable inter-observer variation. Astrocytic tumours of the diffuse or fibrillary type are considered grade II (astrocytoma), grade III (anaplastic astrocytoma) and grade IV (glioblastoma), respectively. Tumours of grade I

comprise only pilocytic astrocytoma and other special variants.

St. Anne/Mayo system. More recently, the St. Anne/Mayo system was introduced for application to diffuse or fibrillary astrocytic tumours (92). It employs a four-tiered approach based upon the presence or absence of four variables including nuclear atypia, mitoses, endothelial proliferation and necrosis. Feature definition is important to this approach. Atypia is defined as variation in nuclear shape or size with accompanying hyperchromasia. Mitoses must be bona fide but no special recognition is given to their number or morphology. Endothelial proliferation is also strictly defined as apparent multi-layering of endothelium rather than simple hypervascularity composed of glomeruloid capillaries with but a single layer of endothelium. Necrosis must be a definite finding, but palisading need not be present. Simple opposition of cellular zones suggestive of incipient necrosis is insufficient. Tumours devoid of any of these features are rare and are designated grade 1; those demonstrating only one variable are considered grade 2; those showing two variables are grade 3; and lesions with three or four features are designated grade 4. In practice the grade 1 designation is so rarely used that the method in fact is three-tiered, identifying astrocytomas of grades by 2, 3 and 4. It is noteworthy that the parameters make their appearance in a predictable sequence, i.e., atypia being followed in turn by mitoses and endothelial proliferation or necrosis (Table 1). Retrospectively applied to a large series of similarly treated patients with long follow-up, this method provides highly reproducible and prognostically useful results (92).

The new World Health Organization (WHO) classification largely resembles the St. Anne/Mayo scheme (Table 1). Tumours with cytologic atypia alone are considered grade 2, those which in addition show mitoses are considered grade 3, whereas tumours showing atypia, mitoses, endothelial proliferation or necrosis are grade 4. Noteworthy is the fact that cellularity is not a pivotal criterion and that neoplasms with atypia and mitoses qualify as grade 3 lesions. Furthermore, although both endothelial proliferation and necrosis are often present, the former, in addition to atypia and mitotic activity, is sufficient to warrant a grade 4 (glioblastoma) diagnosis. Given the high degree of inter-observer reproducibility in the recognition of these features, as well their strong correlation with patient survival, the new WHO approach to grading should permit reliable comparison of inter-institutional experience and the results of multi-institutional therapeutic protocols.

References

1. Zülch KJ (1979) *Histologic Typing of Tumours of the Central Nervous System*, World Health Organization: Geneva
2. Fields WS (1989) *Primary Brain Tumours. A Review of Histologic Classification*, Springer-Verlag: New York, Berlin
3. von Deimling A, Eibl RH, Ohgaki H, Louis DN, von Ammon K, Petersen I, Kleihues P, Chung RY, Wiestler OD, Seizinger BR (1992) p53 mutations correlate with 17p allelic loss in grade II and grade III astrocytomas. *Cancer Res* 52: 2897-2990
4. Ohgaki H, Eibl RH, Schwab M, Reichel MB, Mariani L, Gehring M, Petersen I, Höll T, Wiestler OD, Kleihues P (1993) Mutations of the p53 tumour suppressor gene in neoplasms of the human nervous system. *Mol Carcinogenesis* (in press)
5. James CD, Carlbom E, Dumanski JP, Hausen M, Nordenskjöld MD, Collins VP (1988) Clonal genomic alerations in gliomas malignancy stages. *Cancer Res* 48: 5546-5551
6. Fults D, Brockmeyer D, Tullous MW, Pedone CA, Cawthon RM (1992) p53 mutation and loss of heterozygosity on chromosome 17 and 10 during human astrocytoma progression. *Cancer Res* 52: 674-679
7. von Deimling A, Louis DN, von Ammon K, Petersen I, Wiestler OD, Seizinger BR (1992) Evidence for a tumour suppressor gene on chromosome 19q associated with astrocytomas, ologodendrogliomas and mixed gliomas. *Cancer Res* 52: 4277-4299
8. Frankel RH, Bayona W, Koslow M, Newcomb EW (1992) p53 mutations in human malignant gliomas: Comparison of loss of heterozygosity with mutation frequency. *Cancer Res* 52: 1427-1433
9. Louis DN, von Deimling A, Chung RY, Rubio MP, Whaley JM, Eibl RH, Ohgaki H, Wiestler OD, Thor AD, Seizinger BR (1993) Comparative study on p53 gene and protein alteration in human astrocytomas. *J Neuropathol Exp Neurol* 52: 31-38
10. Sidranski D, Mikkelsen T, Schwechheimer K, Rosenblum ML, Cavanee W, Vogelstein B (1992) Clonal expansion of p53 mutant cells is associated with brain tumour progression. *Nature* 355: 846-847
11. von Deimling A, Louis DN, von Ammon K, Petersen I, Höll T, Chung RY, Martuza RL, Schoenfeld DA, Yasargil MG, Wiestler OD, Seizinger BR (1992) Association of epidermal growth factor receptor gene amplification with loss of chromosome 10 in human glioblastoma multiforme. *J Neurosurg* 77: 295-301
12. Ransom DT, Ritland SR, Moertel CA, Dahl RJ, O'Fallon JR, Scheithauer BW, Kimmel DW, Kelly PJ, Olopade OI, Diaz MO, Jenkins RB (1992) Correlation of cytogenetic analysis and loss of heterozygosity studies in human diffuse astrocytomas and mixed oligo-astrocytomas. *Genes Chromosom Cancer* 5: 357-374
13. Bigner SH, Vogelstein B (1990) Cytogenetics and molecular genetics of malignant gliomas and medulloblastoma. *Brain Pathol* 1: 12-18
14. Ekstrand AJ, James CD, Cavanee WK, Seliger B, Pettersson RF, Collins VP (1991) Genes for epidermal growth factor receptor, transforming growth factor alpha, and epidermal growth factor and their expression in human gliomas in vivo. *Cancer Res* 51: 2164-2172
15. Ohgaki H, Eibl RH, Wiestler OD, Yasargil MG, Newcomb EW, Kleihues P (1991) p53 mutations in non-astrocytic human brain tumours. *Cancer Res* 51: 6202-6205
16. Kepes J (1993) Pleomorphic xanthoastrocytoma: The birth of a diagnosis and a concept. *Brain Pathol* 3: 269-274
17. Kepes JJ, Rubinstein LJ, Eng LF (1979) Pleomorphic xanthoastrocytoma: A distinctive meningeal glioma of young subjects with relatively favorable prognosis. A study of 12 cases. *Cancer* 44: 1839-1852

18. Paulus W, Peiffer J (1988) Does the pleomorphic xanthoastrocytoma exist? Problems in the application of immunological techniques to the classification of brain tumours. *Acta Neuropathol (Berl)* 76: 245-252

19. Grant JW, Gallagher PJ (1986) Pleomorphic xanthoastrocytoma: Immunohistochemical methods for dififferentiation from fibrous histiocytomas with similar morphology. *Am J Surg Pathol* 10: 336-341

20. Allegranza A, Ferraresi S, Bruzzone M, Giombini S (1991) Cerebromeningeal pleomorphic xanthoastrocytoma. Report on four cases: Clinical, radiologic and pathological features (including a case with malignant evolution). *Neurosurg Rev* 14: 43-49

21. Weldon-Linne CM, Victor TA, Groothuis DR, Vick NA (1983) Pleomorphic xanthoastrocytoma: Ultrastructural and immunohistochemical study of a case with a rapidly fatal outcome following surgery. *Cancer* 52: 2055-2063

22. Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, Laws ER, Vedrenne C (1988) Dysembryoplastic neuroepithelial tumour: A surgically curable tumour of young patients with intractable partial seizures. *Neurosurgery* 23: 545-556

23. Kleihues P, Burger PC, Scheithauer BW (1993) The new WHO classification of brain tumours. *Brain Pathol* 3: 255-268

24. Hirose T, Scheithauer BW, Lopes BM, VandenBerg SR (1993) Dysembryoplastic neuroepithelial tumour (DNT): An immunohistochemical and ultrastructural study. *J Neuropathol Exp Neurol* 52: 327 (abstr)

25. Daumas-Duport C (1993) Dysembryoplastic neuroepithelial tumours. *Brain Pathol* 3: 283-295

26. Koeller KK, Dillon WP (1992) Dysembryoplastic neuroepithelial tumours: MR appearance. *Am J Neuroradiol* 13: 1319-1325

27. Prayson RA, Estes ML (1992) Dysembryoplastic neuroepithelial tumour. *Am J Clin Pathol* 97: 398-401

28. VandenBerg SR, May EE, Rubinstein L (1987) Desmoplastic supratentorial neuroepithelial tumours of infancy with divergent differentiation potential ("desmoplastic infantile gangliogliomas"). Report on 11 cases of a distinctive embryonal tumour with favorable prognosis. *J Neurosurg* 66: 58-71

29. Kuchelmeister K, Bermann M, von Wild K, Hochrenther D, Busch G, Gullotta F (1993) Desmoplastic ganglioglioma: Report of two non-infantile cases. *Acta Neuropathol (Berl)* 85: 199-204

30. Parisi JE, Scheithauer BW, Priest JR, Okazaki H, Komori T (1992) Desmoplastic infantile ganglioglioma (DIG): A form of ganglioglioma. *J Neuropathol Exp Neurol* 51: 365 (abstr)

31. Taratuto AL, Monges J, Lylyk P, Leiguarda R (1984) Superficial astrocytoma attached to dura. Report of six cases in infants. *Cancer* 54: 2505-2512

32. Louis DN, von Deimling A, Dickersin GR, Dooling EC, Seizinger BR (1992) Desmoplastic cerebral astrocytomas of infancy: A histopathologic, immunohistochemical, ultrastructural, and molecular genetic study. *Hum Pathol* 23: 1402-1409

33. Rushing EJ, Rorke LB, Sutton B (1993) Problems in the nosology of desmoplastic tumours of childhood. *Pediatr Neurosurg* 19: 57-62

34. Aydin F, Ghatak NR, Muizelaar P (1993) Desmoplastic cerebral astrocytoma of infancy (DCAI). *J Neuropathol Exp Neurol* 52: 326 (abstr)

35. VandenBerg S (1993) Desmoplastic infantile ganglioglioma and desmoplastic cerebral astrocytoma of infancy. *Brain Pathol* 3: 275-281

36. Paulus W, Schlote W, Perentes E, Jacobi G, Warmuth-Metz M, Roggendorf W (1992) Desmoplastic supratentorial neuroepithelial tumours of infancy. *Histopathology* 21: 43-49

37. Hassoun J, Gambarelli D, Grisoli F, Pellet W, Salamon G, Pellissier JF, Toga M (1982) Central neurocytoma. An electron-microscopic study of two cases. *Acta Neuropathol (Berl)* 56: 151-156

38. Hassoun J, Söylemezoglu F, Gambarelli D, Figarella-Branger D, von Ammon K, Kleihues P (1993) Central neurocytoma: A synopsis of clinical and histological features. *Brain Pathol* 3: 297-306

39. Bonnin JM, Rubinstein LJ (1989) Astroblastomas: A pathological study of 23 tumours, with a postoperative follow-up in 13 patients. *Neurosurgery* 25: 6-13

40. Russell DL, Cairns H (1947) Polar spongioblastomas. *Arch Histol Norm Patol* 3: 423-441

41. Russell DS (1989) *Pathology of Tumours of the Nervous System*, 5th ed., Edward Arnold: London, Melbourne, Auckland

42. Jansen GH, Troost D, Dingemans KP (1990) Polar spongioblastoma: An immunohistochemical and electron microscopical study. *Acta Neuropathol (Berl)* 81: 228-232

43. Ben-Arush MW, Doron Y, Braun J, Mendelsson E, Dar H, Robinson E (1990) Brain tumour as a second malignant neoplasm following neuroblastoma stage IV S. *Med Pediatr Oncol* 18: 240-245

44. Albert FK, Gaedicke G, Wenzel D, Merk J, Heymer B, Lampl L (1989) Congenital brain tumours: Diagnostic and therapeutic approach. With a report of 3 cases. *Zentralbl Neurochir* 50: 101-105

45. Schiffer D, Cravioto H, Giordana MT, Migheli A, Pezzulo T, Vigliani MC (1993) Is polar spongioblastoma a tumour entity? *J Neurosurg* 78: 587-591

46. Caccamo DV, Herman MM, Rubinstein LJ (1989) An immunohistochemical study of the primitive and maturing elements of human cerebral medulloepitheliomas. *Acta Neuropathol (Berl)* 79: 248-254

47. Artigas J, Cervos-Navarro J, Iglesias JR, Ebhardt G (1985) Gliomatosis cerebri: Clinical and histological findings. *Clin Neuropathol* 4: 135-148

48. Balko MG, Blisard KS, Samaha FJ (1992) Oligodendroglial gliomatosis cerebri. *Hum Pathol* 23: 706-707

49. Kandler RH, Smith CML, Broome JC, Davies-Jones GAB (1991) Gliomatosis cerebri: A clinical, radiological and pathological report of four cases. *Brit J Neurosurg* 5: 187-193

50. Kawano N, Miyasaka Y, Yada K, Atari H, Sasaki K (1978) Diffuse cerebrospinal gliomatosis: Case report. *J Neurosurg* 49: 303-307

51. Nevin S (1938) Gliomatosis cerebri. *Brain* 61: 170-191

52. Valtz NL, Hayes TE, Norregaard T, Liu SM, McKay RD (1991) An embryonic origin for medulloblastoma. Source (Bibliographic Citation): *New Biol* 3: 364-371

53. Hart NM, Earle KM (1973) Primitive neuroectodermal tumours in children. *Cancer* 32: 172-188

54. Rorke LB (1983) The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumours. *J Neuropath Exp Neurol* 42: 1-15

55. Schwechheimer K, Wiedermann B, Franke WW (1987) Synaptophysin: A reliable broad-range marker for medulloblastomas. *Virchows Arch (Pathol Anat)* 411: 53-59

56. Gould VE, Jansson DS, Molenaar WM, Rorke LB, Trojanowski JQ, Lee VM, Packer RJ, Franke WW (1990)

Primitive neuroectodermal tumours of the central nervous system. Patterns of expression of neuroendocrine markers, and all classes of intermediate filament proteins. *Lab Invest* 62: 498-509

57. Mannoji H, Takeshita I, Fukui M, Ohta M, Kitamura K (1981) Glial fibrillary acidic protein in medulloblastoma. *Acta Neuropathol (Berl)* 55: 63-69
58. Woodruff JM, Godwin TA, Erlandson RA, Susin M, Martini N (1981) Cellular schwannoma: A variety of schwannoma sometimes mistaken for a malignant tumour. *Am J Surg Pathol* 5: 733-744
59. Fletcher CD, Davies SE (1986) Benign plexiform (multinodular) schwannoma: A rare tumour unassociated with neurofibromatosis. *Histopathology* 10: 971-980
60. Lodding P, Kindblom LG, Angervall L, Stenman G (1990) Cellular schwannoma. A clinicopathologic study of 29 cases. *Virchows Arch Pathol A Anat Histopathol* 416: 237-248
61. White W, Shiu MH, Rosenblum MK, Erlandson RA, Woodruff JM (1990) Cellular schwannoma. A clinicopathologic study of 57 patients and 58 tumours. *Cancer* 66: 1266-1275
62. Scheithauer BW, Casadei GP, Manfrini M, Wood MB (1993) Cellular Schwannoma: A clinicopathologic study of 56 cases. *J Neuropathol Exp Neurol* 52: 289 (abstr)
63. Font RL, Truong LD (1984) Melanotic schwannoma of soft tissues. Electron-microscopic observations and review of literature. *Am J Surg Pathol* 8: 129-138
64. Killeen RM, Davy CL, Bauserman SC (1988) Melanocytic schwannoma. *Cancer* 62: 174-183
65. Carney JA (1990) Psammomatous melanotic schwannoma. A distinctive, heritable tumour with special associations, including cardiac myxoma and the Cushing syndrome. *Am J Surg Pathol* 14: 206-222
66. Scheithauer BW (1990) Tumours of the meninges: Proposed modifications of the World Health Organization classification. *Acta Neuropathol (Berl)* 80: 343-354
67. Kepes JJ (1961) Observations on the formation of psammoma bodies and pseudopsammoma bodies in meningiomas. *J Neuropathol Exp Neurol* 20: 255-262
68. Budka H (1982) Hyaline inclusions (Pseudopsammoma bodies) in meningiomas: Immunocytochemical demonstration of epithel-like secretion of secretory component and immunoglobulins A and M. *Acta Neuropathol (Berl)* 56: 294-298
69. Winek RR, Scheithauer BW, Wick MR (1989) Meningioma, meningeal hemangiopericytoma (angioblastic meningioma), peripheral hemangiopericytoma, and acoustic schwannoma. A comparative immunohistochemical study. *Am J Surg Pathol* 13: 251-261
70. Kepes JJ (1975) The fine structure of hyaline inclusions (pseudopsammoma bodies) in meningiomas. *J Neuropathol Exp Neurol* 34: 282 (abstr)
71. Masson T (1956) *Les Tumeurs Humaines*, 2nd ed., Maloine: Paris
72. Michaud J, Gagne F (1983) Microcystic meningioma: Clinicopathologic report of eight cases. *Arch Pathol Lab Med* 197: 75-80
73. Ng HK, Tse CC, Lo ST (1989) Microcystic meningiomas - An unusual morphological variant of meningiomas. *Histopathology* 14: 1-9
74. Horten BC, Urich H, Rubinstein LJ, Montague SR (1979) The angioblastic meningioma: A reappraisal of a nosological problem. Light, electron-microscopic, tissue and organ culture observations. *J Neurol Sci* 31: 387-410
75. Stam FC, van Alphen HAM, Boorsma DM (1980) Meningioma with conspicuous plasma cell components. A histopathological and immunohistochemical study. *Acta Neuropathol (Berl)* 49: 241-243
76. Mirra SS, Tindall SC, Check IJ, Brynes RK, Moore WW (1983) Inflammatory meningeal masses of unexplained origin. An ultrastructural and immunological study. *J Neuropathol Exp Neurol* 42: 453-468
77. Prichard PBI, Martinez RA, Hungerford GE, Powers JM, Perot PLJ (1983) Dural plasmacytoma. *Neurosurgery* 12: 576-579
78. Kepes JJ, Chen WY, Connors MH, Vogel FS (1988) "Chordoid" meningeal tumours in young individuals with peritumoural lymphoplasmacellular infiltrates causing systemic manifestations of the Castleman syndrome. A report of seven cases. *Cancer* 62: 391-406
79. Baker DK, Meurer H, Gullotta F (1985) Recurring intracranial meningioma of some factors predisposing for tumour recurrence. *J Neurosurg Sci* 29: 11-17
80. Christensen D, Laursen H, Klinken L (1983) Prediction of recurrence in meningiomas after surgical treatment. A quantitative approach. *Acta Neuropathol (Berl)* 61: 130-134
81. de la Monte SM, Flickinger J, Linggood RM (1986) Histopathologic features predicting recurrence of meningiomas following subtotal resection. *Am J Surg Pathol* 10: 836-843
82. Fabiani A, Trebini F, Favero M, Peres B, Palmucci L (1977) The significance of atypical mitoses in meningiomas. *Acta Neuropathol (Berl)* 38: 229-231
83. Jaaskelainen J, Haltia M, Laasonen E, Wahlstrom T, Valtonen S (1985) The growth rate of intracranial meningiomas and its relation to histology. An analysis of 43 patients. *Surg Neurol* 24: 165-172
84. Jaaskelainen J, Haltia M, Servo A (1986) Atypical and anaplastic meningiomas: Radiology, surgery, radiotherapy, and outcome. *Surg Neurol* 25: 233-242
85. Jellinger K, Slowik F (1975) Histological subtypes and prognostic problems in meningiomas. *J Neurol* 208: 279-298
86. Skullerud K, Loken AC (1974) The prognosis in meningiomas. *Acta Neuropathol (Berl)* 29: 337-344
87. Maier H, Ofner D, Hittmair A, Kitz K, Budka H (1992) Classic, atypical, and anaplastic meningioma: Three histopathological subtypes of clinical relevance. *J Neurosurg* 77: 616-623
88. Ludwin SK, Rubinstein LJ, Russell DS (1975) Papillary meningiomas: A malignant variant of meningioma. *Cancer* 36: 1363-1373
89. Pasquier B, Gasnier F, Pasquier D, Keddari E, Morens A, Couderc P (1986) Papillary meningioma. Clinicopathologic study of seven cases and review of the literature. *Cancer* 58: 299-305
90. Zülch KJ (1986) *Brain Tumours. Their Biology and Pathology*, 3rd ed., Springer: Heidelberg
91. Ringertz J (1950) Grading of gliomas. *Acta Pathol Microbiol Scand* 27: 51-64
92. Daumas DC, Scheithauer B, O'Fallon J, Kelly P (1988) Grading of astrocytomas. A simple and reproducible method. *Cancer* 62: 2152-2165
93. Kernohan JW, Mabon RF, Svien HJ, Adson AW (1949) A simplified classification of gliomas. *Proc Staff Meet Mayo Clin* 24: 71-75
94. Broders AC (1925) The grading of carcinoma. *Minn Med* 8: 726-730

95. Rubinstein LJ (1982) *Tumours of the Central Nervous System. Atlas of Tumour Pathology,* Armed Forces Institute of Pathology: Washington, DC

96. Burger PC, Vogel FS (1982) *Surgical Pathology of the Nervous System and its Coverings,* 2nd ed., John Wiley & Sons: New York

97. Nelson JS, Tsukada Y, Schoenfeld D, Fulling K, Lamarche J, Peress N (1983) Necrosis as a prognostic criterion in malignant supratentorial, astrocytic gliomas. *Cancer* 52: 550-554

98. DeArmond SJ, Nagashma T, Cho KG, Murovic JA, Davis RL, Hoshino T (1987) Correlation of in situ cell kinetics and degree of anaplasia in human brain tumours. In: *Brain Oncology,* Chatel M, Darcel F, Pecker J (eds.), pp. 67-74, Martinus Nijhoff Publishers: Dordrecht

WHO Histological Typing of CNS Tumours

1 **Tumours of Neuroepithelial Tissue**

1.1 *Astrocytic tumours*
1.1.1 Astrocytoma
1.1.1.1 Variants: Fibrillary
1.1.1.2 Protoplasmic
1.1.1.3 Gemistocytic
1.1.2 Anaplastic (malignant) astrocytoma
1.1.3 Glioblastoma
1.1.3.1 Variants: Giant cell glioblastoma
1.1.3.2 Gliosarcoma
1.1.4 Pilocytic astrocytoma
1.1.5 Pleomorphic xanthoastrocytoma
1.1.6 Subependymal giant cell astrocytoma (Tuberous sclerosis)

1.2 *Oligodendroglial tumours*
1.2.1 Oligodendroglioma
1.2.2 Anaplastic (malignant) oligodendroglioma

1.3 *Ependymal tumours*
1.3.1 Ependymoma
1.3.1.1 Variants: Cellular
1.3.1.2 Papillary
1.3.1.3 Clear cell
1.3.2 Anaplastic (malignant) ependymoma
1.3.3 Myxopapillary ependymoma
1.3.4 Subependymoma

1.4 *Mixed gliomas*
1.4.1 Oligo-astrocytoma
1.4.2 Anaplastic (malignant) oligo-astrocytoma
1.4.3 Others

1.5 *Choroid plexus tumours*
1.5.1 Choroid plexus papilloma
1.5.2 Choroid plexus carcinoma

1.6 *Neuroepithelial tumours of uncertain origin*
1.6.1 Astroblastoma
1.6.2 Polar spongioblastoma
1.6.3 Gliomatosis cerebri

1.7 *Neuronal and mixed neuronal-glial tumours*
1.7.1 Gangliocytoma
1.7.2 Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
1.7.3 Desmoplastic infantile ganglioglioma
1.7.4 Dysembryoplastic neuroepithelial tumour
1.7.5 Ganglioglioma
1.7.6 Anaplastic (malignant) ganglioglioma
1.7.7 Central neurocytoma
1.7.8 Paraganglioma of the filum terminale
1.7.9 Olfactory neuroblastoma (Aesthesioneuroblastoma)
1.7.9.1 Variant: Olfactory neuroepithelioma

1.8 *Pineal parenchymal tumours*
1.8.1 Pineocytoma
1.8.2 Pineoblastoma
1.8.3 Mixed / transitional pineal tumours

1.9 *Embryonal tumours*
1.9.1 Medulloepithelioma
1.9.2 Neuroblastoma
1.9.2.1 Variant: Ganglioneuroblastoma
1.9.3 Ependymoblastoma
1.9.4 Primitive neuroectodermal tumours (PNETs)
1.9.4.1 Medulloblastoma
1.9.4.1.1 Variants: Desmoplastic medulloblastoma
1.9.4.1.2 Medullomyoblastoma
1.9.4.1.3 Melanotic medulloblastoma

2 **Tumours of Cranial and Spinal Nerves**

2.1 *Schwannoma (Neurilemmoma, Neurinoma)*
2.1.1 Variants: Cellular
2.1.2 Plexiform
2.1.3 Melanotic

2.2 *Neurofibroma*
2.2.1 Circumscribed (solitary)
2.2.2 Plexiform

2.3 *Malignant peripheral nerve sheath tumour (MPNST) (Neurogenic sarcoma, Anaplastic neurofibroma, "Malignant schwannoma")*
2.3.1 Variants: Epithelioid
2.3.2 MPNST with divergent mesenchymal and/or epithelial differentiation
2.3.3 Melanotic

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3	**Tumours of the Meninges**
3.1	*Tumours of meningothelial cells*
3.1.1	Meningioma
3.1.1.1	Variants: Meningothelial
3.1.1.2	Fibrous (fibroblastic)
3.1.1.3	Transitional (mixed)
3.1.1.4	Psammomatous
3.1.1.5	Angiomatous
3.1.1.6	Microcystic
3.1.1.7	Secretory
3.1.1.8	Clear cell
3.1.1.9	Chordoid
3.1.1.10	Lymphoplasmacyte-rich
3.1.1.11	Metaplastic
3.1.2	Atypical meningioma
3.1.3	Papillary meningioma
3.1.4	Anaplastic (malignant) meningioma
3.2	*Mesenchymal, non-meningothelial tumours*
	Benign neoplasms
3.2.1	Osteocartilaginous tumours
3.2.2	Lipoma
3.2.3	Fibrous histiocytoma
3.2.4	Others
	Malignant neoplasms
3.2.5	Hemangiopericytoma
3.2.6	Chondrosarcoma
3.2.6.1	Variant: Mesenchymal chondrosarcoma
3.2.7	Malignant fibrous histiocytoma
3.2.8	Rhabdomyosarcoma
3.2.9	Meningeal sarcomatosis
3.2.10	Others
3.3.	*Primary melanocytic lesions*
3.3.1	Diffuse melanosis
3.3.2	Melanocytoma
3.3.3	Malignant melanoma
3.3.3.1	Variant: Meningeal melanomatosis
3.4	*Tumours of uncertain histogenesis*
3.4.1	Haemangioblastoma (Capillary haemangioblastoma)
4	**Lymphomas and Haemopoietic Neoplasms**
4.1	Malignant lymphomas
4.2	Plasmacytoma
4.3	Granulocytic sarcoma
4.4	Others
5	**Germ Cell Tumours**
5.1	Germinoma
5.2	Embryonal carcinoma
5.3	Yolk sac tumour (Endodermal sinus tumour)
5.4	Choriocarcinoma
5.5	Teratoma
5.5.1	Immature
5.5.2	Mature
5.5.3	Teratoma with malignant transformation
5.6	Mixed germ cell tumours
6	**Cysts and Tumour-like Lesions**
6.1	Rathke cleft cyst
6.2	Epidermoid cyst
6.3	Dermoid cyst
6.4	Colloid cyst of the third ventricle
6.5	Enterogenous cyst
6.6	Neuroglial cyst
6.7	Granular cell tumour (Choristoma, Pituicytoma)
6.8	Hypothalamic neuronal hamartoma
6.9	Nasal glial heterotopia
6.10	Plasma cell granuloma
7	**Tumours of the Sellar Region**
7.1	Pituitary adenoma
7.2	Pituitary carcinoma
7.3	Craniopharyngioma
7.3.1	Variants: Adamantinomatous
7.3.2	Papillary
8	**Local Extensions from Regional Tumours**
8.1	Paraganglioma (Chemodectoma)
8.2	Chordoma
8.3	Chondroma Chondrosarcoma
8.4	Carcinoma
9	**Metastatic Tumours**
10	**Unclassified Tumours**