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VOLUME 16

TUMOURS OF THE BRAIN AND SKULL
PART I

TUMOURS OF THE BRAIN AND SKULL

PART I

Edited by

P. J. VINKEN and G. W. BRUYN

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Foreword to volumes 16, 17 and 18

The tumours of the central nervous system have constituted as bleak a chapter as that of the 'degenerative' diseases in the theory and practice of neurology. Even if, since the beginning of this century, neurological surgery has succeeded to a considerable extent in alleviating suffering and preserving life, there has been only partial improvement in the rather grim outlook. Since the 1950's, awareness has been growing that it is the chemical compound rather than the scalpel which must provide Medicine's answer to this dreadful group of disorders.

The volumes on tumours of the brain and its coverings reflect this state of affairs. Both traditional and current means of diagnosis, both neurosurgical and non-sanguinous methods of treatment have been reviewed against a frame of design, in which the sites and the nature of space-occupying processes had been chosen as the absciss and the ordinate. Modern immunological concepts containing the promise of rewarding treatment have been accorded due attention, while the main emphasis has, of course, remained a clinical neurological one, in line with the underlying concept of the Handbook. Professor Zülch, in his many conversations and correspondence with us, was actively engaged in the 'engineering' of these particular volumes. We are much in his debt.

Originally conceived as a single work, it soon became clear that, if adequate coverage of basic concepts was to be achieved, three volumes would be needed to present in anything like a comprehensive way the status in this field in the mid-1970's. Although tentatively planned for publication in 1972/73, the schedule was adversely affected as a result of an unusually large number of contributors being unable to complete their respective assignments within the agreed time-limits.

Voltaire once said that 'le secret d'ennuyer est ... de tout dire'. Although the Editors have no wish to bore the reader, they feel they owe to him and to those contributors who did manage to work within the often pressing demands of our production schedule some words of explanation of the various difficulties which beset the publication of these volumes.

Although it had been otherwise intended, these volumes have had to appear without the chapters on tumours of the optic chiasma and on craniopharyngioma. The author invited to deal with the former was the victim of an unhappy series of unavoidable problems which effectively conspired to make it impossible for him, even with repeated extensions of the deadline, to give that degree of priority to the completion of his manuscript which both he and the Editors would have wished. The craniopharyngioma chapter came to grief on the rocks of procrastination and prevarication, amidst a sea of broken promises.

Professor Zülch was a tower of strength in assisting us with the problems arising from the difficulties encountered by a number of authors in coping with clinical, academic and administrative duties, concurrent with the preparation of their respective chapters. Had it not been for Professor Zülch's tireless help, the Editors would have had to apologize for the non-inclusion of more chapters.

The assembling of the total manuscript for a volume is always an uphill task, but the difficulties and delays did not cease with the receipt of the final chapter. Much effort and time-consuming correspondence was involved in ensuring that translated texts kept faithfully to the spirit of the foreign originals; many manuscripts had to be returned for updating, checking, completing.

It was with great sadness that we learned, in August 1973, of the death of Professor A. Biemond, shortly after he had completed the revision of his chapter. We are indebted to his successor, Professor Den Hartog Jager and to Dr. De Jong for having provided the final touches to this chapter on cerebellar tumours.

The various problems indicated above obliged us to ask the majority of contributors to update their chapters at the galley-proof stage. The co-operation we received was of such a high order that further delays in publication were reduced to a minimum.

As we go to press, the world is preoccupied with its oil, paper and transport crises. Despite past experiences, the Editors are optimistic enough to believe that the enduring constancy of the quality of our contributors will enable us to triumph in the end over these and other troubles.

P. J. V.
G. W. B.

Acknowledgement

Several illustrations and diagrams in this volume have been obtained from other publications. Some of the original figures have been slightly modified. In all cases reference is made to the original publications in the figure caption. The full sources can be found in the reference lists at the end of each chapter. The permission for the reproduction of this material is gratefully acknowledged.

List of contributors

F. Marguth

Neurological Clinic, University of Munich 341

John Mealey, Jr.

Division of Neurological Surgery, Indiana University Medical Center, Indianapolis, Ind. 661

H. D. Mennel

Department of General Neurology, Max Planck Institute of Brain Research and Neurological Clinic, Municipal Hospital Cologne-Merheim 1, 89

Hans-Georg Mertens

Neurological Clinic and Polyclinic, University of Würzburg 209

Donald W. Mulder

Department of Neurology and Department of Psychiatry and Clinical Psychology, Mayo Clinic and Mayo Foundation, Rochester, Minn. 727

Hanna M. Pappius

The Donner Laboratory of Experimental Neurochemistry, Montreal Neurological Institute and the Department of Neurology and Neurosurgery, McGill University, Montreal 167

John Primrose

Oldchurch Hospital, Romford 270

E. Graeme Robertson

Consultant Neurologist, Royal Melbourne Hospital and Royal Children's Hospital, Melbourne 530

J. Sayk

Department of Neurology, University of Rostock 360

Wolfgang Schiefer

Neurosurgical Clinic, University of Erlangen 455

Klaus Schimrigk

Neurological Clinic and Polyclinic, University of Würzburg 209

Wendell M. Swenson

Department of Neurology and Department of Psychiatry and Clinical Psychology, Mayo Clinic and Mayo Foundation, Rochester, Minn. 727

V. Zimmermann

Department of General Neurology, Max Planck Institute of Brain Research and Neurological Clinic, Municipal Hospital Cologne-Merheim 89

K. J. Zülch

Department of General Neurology, Max Planck Institute of Brain Research and Neurological Clinic, Municipal Hospital Cologne-Merheim 1, 89

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CHAPTER 1

The biology of brain tumours

K.J. ZÜLCH and H.D. MENNEL

General Neurology, Max Planck Institute of Brain Research

and

Neurological Clinic, Municipal Hospital, Cologne-Merheim

There is need for a more detailed system of tumour-classification of benign and malignant neoplasms based on their histological structure, which would indicate the pattern of their biological behaviour, i.e. tumours with the morphological characteristics termed 'malignant' would be those which grew more quickly and were dangerous to the patient. The increase of volume resulting from neoplastic growth in the intracranial space is dangerous because expansion of this space is impossible (see Chapter 3).

Historical review

In studying the general pathology of neoplasms, the earliest attempts at classification grouped together tumours of similar morphology and defined their behaviour in terms of relatively benign or malignant growth, either in the viscera or the brain. The first exhaustive studies were made in the 19th century by, among others, Lebert (1851) who contrasted intracranial 'carcinomas' and 'fibroblastic' tumours which had a much better prognosis in terms of the length of survival of the patient.

Morphological classification. Classification based on biological criteria such as the duration of survival was only possible if the tumours could be distinguished morphologically. Johannes Peter Müller (1838), the great physiologist and histologist, in his atlas on 'Structure and Form of Neoplasms' proposed a new method of classifying tumours. They were to be characterised and arranged according to their 'chemical nature, microscopical structure, their mode of development and their embryological origin', thus predicting present-day studies of detailed structure, staining properties and histochemical reactions. Virchow (1847, 1863) provided the first useful criteria for classification in his work on the glia. From his studies on the normal brain, he concluded that glial cells formed a non-neuronal interstitial tissue. In examining brain tumours, he also discovered similarities between the neoplastic cells and the basic structure of glial cells. In this way he first distinguished 'gliomas' from the remaining 'sarcomas', and was the first to subdivide gliomas into 'myxogliomas, gliosarcomas, glioma durum, glioma haemorrhagicum', etc. Virchow also distinguished 'sacral tumours' which had a cell structure similar to that of the cerebellar cortex; these probably belonged to the group of ependymomas. Virchow considered tumours of the VIIIth cranial nerve to be outgrowths of brain tissue developing from the perineurium (in his opinion, a neuroglial tissue); he also found tumours of this type in the spinal cord. He made a particular study of tumours of the dura, which he distinguished from dural sarcomas by the presence

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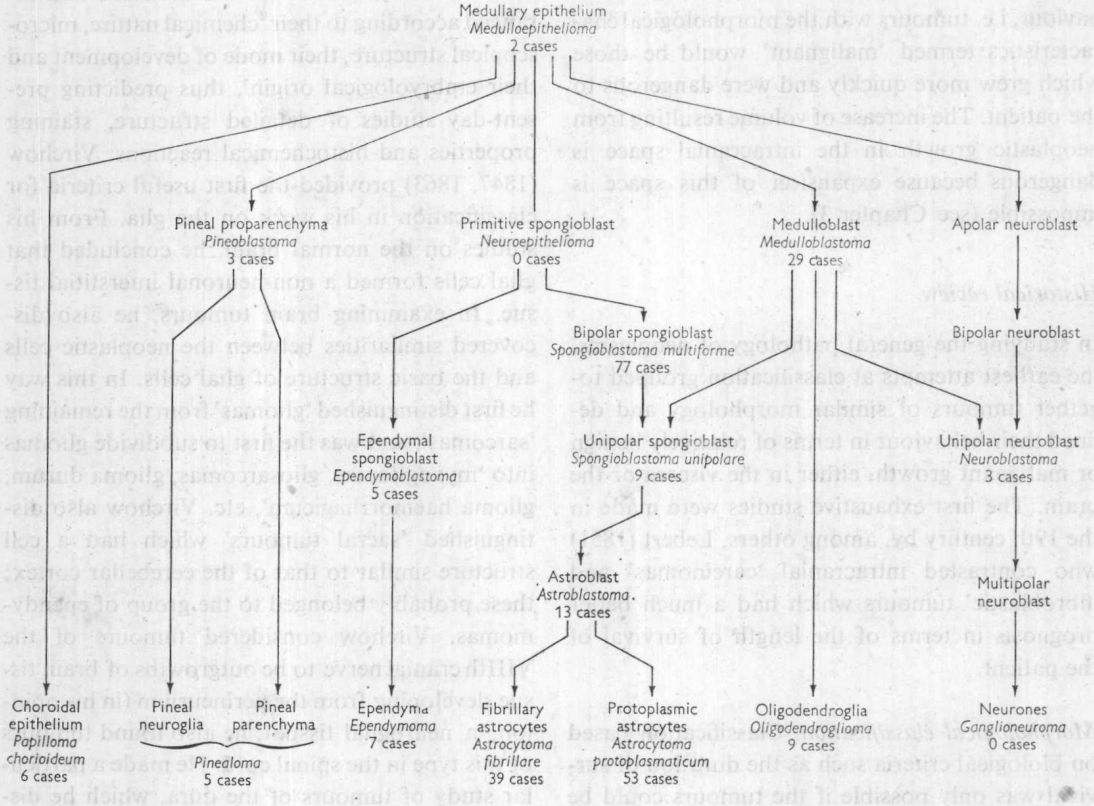
of psammoma bodies in the former; on this, Virchow based the concept of psammomas which – wrongly – also included calcified pinealomas and plexus papillomas. The detailed historical development of this field will not be discussed here (the reader is referred to Zülch 1939, 1951, 1956), but it should be noted that the principle of comparing neoplastic cells with those occurring in normal neural tissue has long been established as of fundamental importance in the classification of intracranial growths. The recognition of normal astrocytes ('spider cells', Jastrowitz 1870–72) led to the description of similar brain tumours, recognition of blepharoplasts in the ependyma (Mallory 1902) to the definition of the corresponding neoplasm 'ependymoma', and the characterisation of Schwann's cells to the identification of neurinomas (Von Recklinghausen 1882; Verocay 1908, 1910; Antoni 1920).

Borst (1902) introduced the first classification of tumours based on histological criteria derived from the study of normal cells. The more detailed schema in current use was first proposed by Bielschowsky and Pick (1911) from their study of ganglion cell tumours, and by Ribbert (1918) from his study of gliomas. Stimulated by Cohnheim's (1878) teachings on the pathogenesis of tumours, Ribbert advanced a system of classification dependent on the 'degree of maturation' of the neoplastic cells. He defined other subgroups in addition to gliomas, one consisting of 'spongioneuroblastic cells' which were bipotential cells ('spongioneuroblastomas') and developed into spongioblastic cells ('spongioblastomas'), and glioblastic cells ('glioblastomas' and 'gliomas') or they matured into neuroblastic cells ('neuroblastomas'). He then used the names of the corresponding maturation stages in the development of normal cells for the nomenclature of the neoplasms (see above). Refined and enlarged by Bailey and Cushing (1926), this remains the basis of our present system of classification and



Scheme 1.

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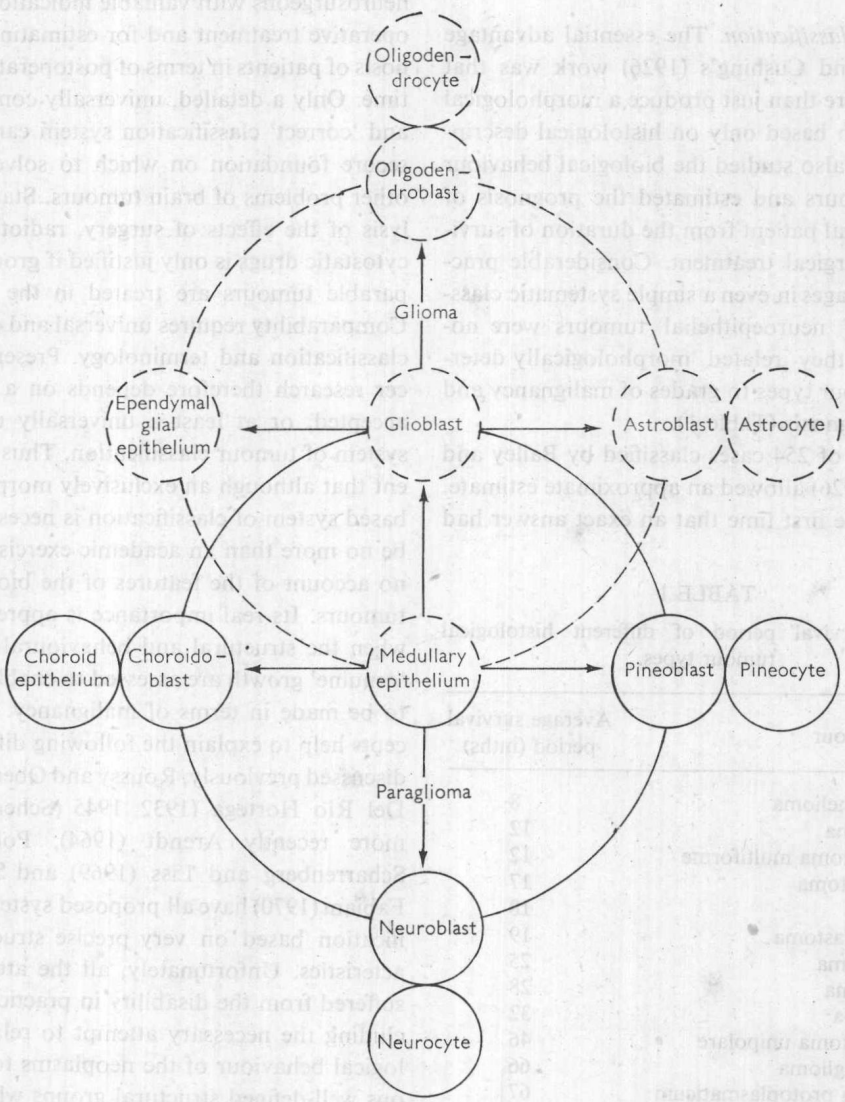
provides a certain biological evaluation of the degree of malignancy. Development of a more detailed morphological classification was dependent upon sufficiently detailed characterisation of the distinctive features of normal brain tissue and meningeal cells and the stages of their development. This was provided by the Italian (Golgi 1884), the German (Deiters 1865; Jastrowitz 1870–72; Boll 1874; Kölliker 1879; Von Lenhossek 1895) and the Spanish schools (Ramòn y Cajal 1908; Del Rio Hortega 1921).

The proposal of Bailey and Cushing (1926) for classification of neoplasms followed the basic concept of Müller (1838) whereby normal or 'developing' (or 'maturing') cells are compared with those found in typical examples of tumours. His well-known classification (Scheme 1) associated each variety of neuroepithelial neoplasm with the preponderant type of identifiable normal or maturing cell found in it. He distinguished 22 types of neuroepithelial tumour which, by the work of Bergstrand (1932, 1933), Penfield (1927, 1932) and the present author (Zülch 1939, 1956), have been reduced to 10 basic types. The French school worked along similar lines and the terminology used in their invaluable colour atlas



Scheme 2.

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(Roussy and Cornil 1928; Roussy and Oberling 1932) is comparable to that of Bailey and Cushing (1926). The Spanish school also attempted a classification of neoplasms, and that proposed by Del Rio Hortega (1932, 1945) is based on the same concept of comparison of normal and maturing cell types (Scheme 2). However, the terminology and morphological description of the tumours differ in important details and definitions from that of Bailey and Cushing (1926), particularly in the groups of spongioblastomas and astroblastomas as emphasised in the review by Polak (1966).

Biological classification. The essential advantage of Bailey and Cushing's (1926) work was that they did more than just produce a morphological classification based only on histological descriptions. They also studied the biological behaviour of the tumours and estimated the prognosis of the individual patient from the duration of survival after surgical treatment. Considerable practical advantages in even a simple systematic classification of neuroepithelial tumours were noticeable, as they related morphologically determined tumour types to grades of malignancy and thus to prognosis (Table 1).

A review of 254 cases classified by Bailey and Cushing (1926) allowed an approximate estimate. This was the first time that an exact answer had been found to the working hypothesis that tumours with little cell differentiation grew quickly and those with more highly developed forms, slowly.

TABLE 1

Average survival period of different histological tumour types.

Type of tumour	Average survival period (mths)
Medulloepithelioma	8
Pineoblastoma	12
Spongioblastoma multiforme	12
Medulloblastoma	17
Pinealoma	18
Ependymoblastoma	19
Neuroblastoma	25
Astroblastoma	28
Ependymoma	32
Spongioblastoma unipolare	46
Oligodendroglioma	66
Astrocytoma protoplasmaticum	67
Astrocytoma fibrillare	86

The importance of Bailey and Cushing's (1926), and of Kernohan's classification (Kernohan et al. 1949) which was largely derived from it, must be envisaged from this point of view. Their usefulness has to be compared with that of other systems for typing and analysing neoplasms which do not take into account the degree of malignancy. Present day work on classification of brain neoplasms has to be based on the principle of biological behaviour, and provides neurologists and neurosurgeons with valuable indications for both operative treatment and for estimating the prognosis of patients in terms of postoperative survival time. Only a detailed, universally comprehensive and 'correct' classification system can provide a secure foundation on which to solve the many other problems of brain tumours. Statistical analysis of the effects of surgery, radiotherapy and cytostatic drugs is only justified if groups of comparable tumours are treated in the same way. Comparability requires universal and comparable classification and terminology. Present day cancer research therefore depends on a universally accepted, or at least a universally understood, system of tumour classification. Thus it is apparent that although an exclusively morphologically based system of classification is necessary, it will be no more than an academic exercise if it takes no account of the features of the biology of the tumours. Its real importance is appreciated only when the structural and behavioural features of 'genuine' growth are assessed to enable prognosis to be made in terms of malignancy. These concepts help to explain the following difficulties: as discussed previously, Roussy and Oberling (1932), Del Rio Hortega (1932, 1945 (Scheme 2)), and more recently Arendt (1964), Polak (1966), Scharrenberg and Liss (1969) and Schiffer and Fabiani (1970) have all proposed systems of classification based on very precise structural characteristics. Unfortunately, all the attempts have suffered from the disability in practice of not including the necessary attempt to relate the biological behaviour of the neoplasms to their various well-defined structural groups which had already been expressed by Bailey and Cushing in

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TABLE 2

New names	Old names (with new names in parentheses)
Astrocytoma grades I–IV	Astrocytoma (astrocytoma grade I)
	Astroblastoma (astrocytoma grade II)
	Spongioblastoma polare (left out)
	Glioblastoma multiforme (astrocytoma grades III and IV)
Ependymoma grades I–IV	Ependymoma (ependymoma grade I)
	Ependymoblastoma (ependymoma grades II–III)
	Neuroepithelioma (left out)
	Medulloepithelioma (ependymoma grade IV)
Oligodendroglioma grades I–IV	Oligodendroglioma (oligodendroglioma grade I)
	Oligodendroblastoma (oligodendroglioma grades II–IV)
Neuroastrocytoma	Neurocytoma
	Ganglioneuroma (neuroastrocytoma grade I)
	Gangliocytoma
	Ganglioglioma
	Neuroblastoma
	Spongioneuroblastoma (neuroastrocytoma grades II–IV)
	Glioneuroblastoma
Medulloblastoma	Medulloblastoma

terms of survival times (Table 1). With Kernohan's system of classification (Kernohan et al. 1949; Table 2), on the other hand, the great advantage was that it incorporated aspects of the biological behaviour of cerebral neoplasms, for example in the diagnosis of an astrocytoma, an oligodendroglioma, an ependymoma, or a neuroastrocytoma Grades I–IV, and that the patient's approximate prognosis was made apparent by the nomenclature. The work of the Mayo Clinic group on classification, although excellent in concept, had a basic weakness in that, with the exception of the astrocytomas which were defined in detail, little was done to properly define and differentiate the other types of gliomas. Also no attempt was made to ensure uniformity and comparability of the grades of malignancy, so that the behaviour of a Grade II astrocytoma might be somewhat dissimilar to that of a Grade II oligodendroglioma because both were based on morphological grounds and not on statistics. A morphological basis, however, for grading malignancy raised certain difficulties. It was Broders (1920) who developed this system of 'grading' in which the degree of malignancy was based on the various cell types found. Dedifferentiated cells were counted and the frequency of their occurrence in the tumour was estimated. If 25% of the cells were dedifferentiated, the neoplasm was considered to be of Grade I malignancy, if 50% – Grade II, 75% – Grade III and so on. This system has proved its worth, particularly for carcinomas of the gastro-intestinal tract and the female genital system. The classification of carcinomas of the stomach, rectum and cervix based on this principle, has been of great assistance to surgeons and is still used today in its original form.

In astrocytomas and oligodendrogliomas, however, it is very difficult to define the exact state of 'abnormal' cells because of their variable forms caused not only by previous simple degeneration, differentiation and increasing anaplasia, but also by the very features upon which would depend the proportionate cell count and the resultant grading. Great efforts have been made in the authors' laboratory to produce a classification on these lines for neuroepithelial and most other tumours, as the importance has been recognised of being able to refer to a uniform graded scale of malignancy. However, according to the present authors' experiences, it has not been possible to allocate each neuroepithelial tumour to four grades of malignancy on the basis of its biological behaviour, nor, when distinguished in terms of their clinical characteristics, has it been possible to place these neoplasms in four structural groups. In general, only two or sometimes three grades of malignancy of each intracranial and spinal tumour have been reliably recognised in daily routine work.

Ringertz (1950), Khominsky (1969), Müller and Schröder (1968) and Schröder et al. (1968, 1970) have preferred a three grade system of malignancy which, however, did not reach general acceptance.

In order to arrive at a generally applicable classification, the basic concepts of Broders (1920), and Kernohan (1952), have been accepted and an

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attempt made to incorporate data about the biological behaviour of the neoplasm too; this is used in the diagnosis of the 'degree' of malignancy (Rössle 1950). This system reverted to the terms 'benign', 'semi-benign', 'semi-malignant' and 'malignant' used by classical pathologists. The direction of this work deviated from that which led the Mayo Clinic group to define four grades of malignancy. It is necessary to recall how Bailey and Cushing (1926) arrived at their definition of the biological behaviour of the neoplasms in their patients. In Phase I, the groups were defined structurally, and in Phase II correlations were made to the mean patient survival time in each group.

The morphologically and biologically based system which we have developed makes use of these concepts of Bailey and Cushing. All neuroepithelial and other neoplasms of the nervous system and its meninges were re-examined and arranged in terms of gross differences in their cells and interstitial tissues. Particular note was saken of 'isomorphism' and 'polymorphism' in the interstitial tissue, the frequency of mitoses, the occurrence of degenerative changes and the development of the stroma (Zülch 1951/1965). As a result of this work and on the basis of the previous clinical history, neoplasms were divided into four groups of degrees of malignancy (Table 3). Using these criteria, the clinical postoperative findings (survival times) of Bailey and Cushing (1926), the Mayo Clinic group (Craig et al. 1949; Svien et al. 1949), Tönnis (1962), Olivecrona (1967) and personal observations have been critically reviewed. This work, using both structural and biological criteria, involved continuous reintegration and reorganisation. Four degrees of malignancy were defined using the time of survival of the patient after 'radical surgery' as a criterion, and the degree of malignancy occurring in each group of neoplasms was determined (see Table 3) without considering any additional treatment by radiation of the neoplasm, occlusion of the aqueduct or cytotoxic treatment.

This classification of malignancy only takes into account the biological behaviour of the tumour. As elaborated in detail in Chapter 3, however, the intracranial space and spinal canal respond characteristically to the increased volume of a growing neoplasm because their walls

TABLE 3

Classification of brain tumours and their different degrees of malignancy.

Degree of malignancy	Prognosis after 'total' removal	Tumours extracerebral	intracerebral
Grade I *benign*	Cure or at least survival time of 5 and more years	Neurinomas Meningeomas Pituitary adenomas Craniopharyngeomas	Gangliocytomas (temporo-basal) Ependymomas, ventricular Plexuspapillomas Spongioblastomas Pinealomas, isomorphous Angioblastomas (Lindau)
Grade II *semi-benign*	Postoperative survival time: 3–5 years	Pituitary adenomas, polymorphous	Gangliocytomas of other location Ependymomas, extraventricular Astrocytomas, isomorphous Oligodendrogliomas, isomorphous Pinealomas, anisomorphous
Grade III *semi-malignant*	Postoperative survival time: 2–3 years	Meningeomas, polymitotic Neurinomas, polymitotic	Gangliocytomas, polymorphous Ependymomas, polymorphous Plexuspapillomas, polymorphous Astrocytomas, polymorphous Oligodendrogliomas, polymorphous Pinealomas, polymorphous
Grade IV *malignant*	Postoperative survival time: 6–15 months	Sarcomas	Glioblastomas Medulloblastomas Primary sarcomas

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are hard and inflexible. Particularly in the adult, whose cranial walls are solid and inflexible ('a closed chamber'), even a slowly growing, but finally large benign meningioma or a benign spongioblastoma may cause dangerous symptoms of increased intracranial pressure. Even tumours which only cause pressure in the brain tissue may be fatal because of displacements and so-called 'herniations', (see Chapter 3 in this Volume), of particularly sensitive parts of the brain, such as the midbrain or the lower medulla oblongata, and may result in damage to autonomic control mechanisms. As these brain displacements and herniations differ according to the diverse positions of tumours and the reaction of the brain to the neoplasm, e.g. by oedema (see Chapter 3), the resultant malignancy depends on the type of growth, its position and its environmental reaction; for clinical purposes ('clinical malignancy'), the growth characteristics must be considered as well as the site of the tumour (Table 4). To conclude, the 'clinical malignancy' of intracranial

TABLE 4

Modified grading for tumours of the brain and related structures.

Tumours	Grade I benign	Grade II semi-benign	Grade III semi-malignant	Grade IV malignant
Gangliocytoma				
isomorphous	+	+		
polymorphous			+	
Ependymoma				
isomorphous	+	+		
polymorphous			+	
Plexuspapilloma				
isomorphous	+			
polymorphous			+	
Astrocytoma				
isomorphous		+		
polymorphous			+	
Oligodendroglioma				
isomorphous		+		
polymorphous			+	
Glioblastoma				+
Spongioblastoma				
isomorphous	+			
polymorphous			+	
Medulloblastoma				+
Pinealoma				
isomorphous	+			
anisomorphous		+		
polymorphous			+	
Neurinoma				
amitotic	+			
polymitotic			+	
Meningeoma				
amitotic				
oligomitotic	+			
polymitotic			+	
Angioblastoma				
(Lindau)	+			
Sarcoma				+
Pituitary adenoma				
isomorphous	+			
polymorphous		+		
Craniopharyngioma	+			

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