Historical Development of the Classification of Brain Tumours and the New Proposal of the World Health Organization (WHO).

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We described the historical development of the endeavours to develop a systematic classification of intracranial tumours in 1939 (20) on the occasion of Cushing's 70th birthday and again in 1951 (21) and 1965 (22). We mentioned there the important contributions of Johannes Müller (10) and Lebert (9) which led to the later work of Virchow, who earlier described the neuroglia and related it to brain tumours. Moreover, he separated the "gliomas" from the other "sarcomas of the nervous system" and defined the particular types of tumours (19). We will now pass quickly over the intervening period, from Virchow to Pick and Bielschowsky (14), who first devised a classification of the tumours of the neuronal cells. Ribbert (15) finally gave a description of the different stages of maturation of the gliomas: spongioneuroblastoma → spongioblastoma → glioblastoma → glioma (neuroblastoma) and thus created the basis for the modern work in classification.

Neurosurgery, in the meantime, had made rapid strides; Cushing (4a) had developed it into a teachable discipline and it had branched off as a surgical speciality. The concentration of so many brain-tumour patients in one clinic afforded the pathologist unusual opportunities for research, especially when the clinician himself was interested in pathology, as Percival Bailey was. This kind of research was urgently needed since the available pathological information was insufficient to answer the clinician's principal question – that of a tumour's biological significance.

P. Bailey (1,2,) – with the help of the metal impregnation techniques of the Spanish school of Ramon y Cajal (4) and Del Rio Hortega (16) – undertook the demonstration of the cell types present in brain tumours. These were compared with the cells of normal tissue and their developmental stages, according to the cytogenetic principles established by the German (7) and Spanish schools. Thus, it became possible to correlate the different types of cells and their stages of development with the corresponding gliomas. The result was the famous first classification published by Bailey and Cushing in 1926/30 (1,2).

Furthermore, we have already previously compared this classification of Bailey and Cushing with that of Roussy and Oberling (17), Penfield (12,13), Bergstrand (3), and Del Rio Hortega (16).

In his review of the gliomas F. Henschen (6) aligned himself – with only minor exceptions – with Hortega's classification. But in his "Handbuch" article later in 1955 Henschen (6) accepted the schema of Bailey and Cushing (1,2). On the other hand Kernohan and his group (8) proposed a new simplified classification based upon a revised cytogenetic interpretation. This proposal grew out of the commendable desire to make the classification of brain tumours also comprehensible and acceptable to the general pathologists. Kernohan looked upon the different tumour types as having arisen by anaplasia of cellular development. He "graded" the tumours according to the percentage of dedifferentiated tumour cells, ending in four grades of malignancy. This classification has now been accepted worldwide.

After this summary of existing classifications it seems unnecessary to emphasize the "Babel-like discrepancies" existing in the terminology. Our personal endeavours to unify the various classifications by an International Symposium in Cologne (26) and a former classification meeting with the Spanish school (11) had failed. Even our attempts to expand an existing international system – namely the terminology of the Unio Internationalis Contra Cancrum (UICC), which had been already published (18) – by our "Atlas of the Histology of Brain Tumors" (23) and also later by the "Atlas of Gross Neurosurgical Pathology" (24) similarly had no effect, because this classification of the UICC was never used by pathologists.

Fortunately at that time the *World Health Organization* felt that among the prerequisites for comparative

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studies of cancer an international agreement on histological criteria for the classification of cancer types and a standardized nomenclature were necessary. Therefore, study groups on the histological classification of cancer were selected for each tumour site and a tentative histopathological typing and classification was drawn up by groups of experts consisting of up to ten pathologists working in the field in question.

WHO has established 23 centres since 1958 covering tumours of most of the organ systems. Most of these centres have already completed their work and published the classifications.

For the study of the histological classification of tumours of the central nervous system (CNS) a reference centre and a number of collaborating laboratories were then designated by WHO, and in 1970 L. J. Rubinstein and myself were asked to develop a preliminary classification of tumours of the CNS.

The centre (Fig. 1) has distributed histological sections from 230 cases which were studied and reviewed. Comments were sent back to the reference centre and then a final comment was made and returned to the collaborating centres. Thus a permanent feedback of opinions was guaranteed.

Meanwhile meetings of the study group for the classification of tumours of the CNS were held in Geneva in 1974 and 1976 and the preliminary classification discussed and improved in the light of the experience with the cases distributed.

Finally, a report was submitted to the WHO for publication in the series "International Histological Classification of Tumours" (so-called "Blue Books" (25), edited by K. J. Zülch).

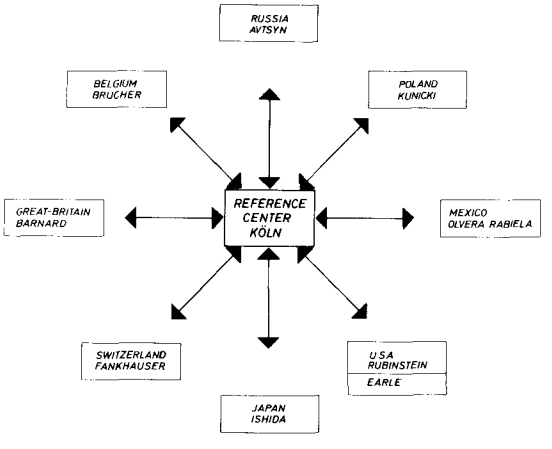

Fig. 1.

It is hoped that an international agreement on the histological criteria for classification may develop, since the WHO is aware that at present pathologists use different terms for the same pathological entity and the same terms are sometimes applied to lesions of different types.

In what follows the discussion will be in two parts: classification and grading.

Classification:

Before presenting the various groups some remarks seem to be in order.

1) The classification cannot solve all the unresolved problems of interpretation, such as the correct position of some tumour types. In this particular case two classifications will be possible according to one's own scientific background and training.

2) It must be taken into account that tumours very often consist of a mixture of cells and yet, if possible, have to be classified according to the prevailing type of cell. Therefore, when classification is possible only with difficulty, some mixed groups are foreseen.

3) The process of malignant dedifferentiation is accounted for, in all groups where such changes occur, by the introduction of a higher grade which is called "anaplastic". The term "anaplasia" includes all morphological features associated with malignant biological behaviour: cellular pleomorphism, increased cellularity, greater mitotic activity, dedifferentiation, abnormal stroma reaction, vascular proliferation, and necroses with or without pseudopalisading of nuclei.

4) The terms preferred in the book are not always those which are in widest use although they seem to be the most correct from the scientific point of view. Synonyms are always given in brackets in order to make understanding easier.

5) It was felt necessary to give a prognosis of the tumour type by grading and the difficulties of this will be later emphasized.

In addition, the predilection of specific types of tumour for the roughly circumscribed age groups of childhood and adolescence, the middle decades of life, and the later decades, is discussed and emphasized. Even the sex incidence of some tumour groups is noted in the text.

The classification as such was subdivided according to the following table:

Tab. 1. New Histological Classification of Tumours of the Central Nervous System (World Health Organization)

	Grade Malignancy:
I. Tumours of neuroepithelial tissue	
A. Astrocytic tumours	
1. Astrocytoma	II
a. fibrillary	
b. protoplasmic	
c. gemistocytic	
2. Pilocytic astrocytoma	I
3. Subependymal giant cell astrocytoma (ventricular tumour of tuberous sclerosis)	I
4. Astroblastoma	II–IV?
5. Anaplastic (malignant) astrocytoma	III
B. Oligodendroglial tumours	
1. Oligodendroglioma	II
2. Mixed oligoastrocytoma	II
3. Anaplastic (malignant) oligodendroglioma	III
C. Ependymal and choroid plexus tumours	
1. Ependymoma	I
Variants:	
a. Myxopapillary ependymoma	I, II
b. Papillary ependymoma	I
c. Subependymoma	I
2. Anaplastic (malignant) ependymoma	III, IV
3. Choroid plexus papilloma	I
4. Anaplastic (malignant) choroid plexus papilloma	III, IV
D. Pineal cell tumours	
1. Pineocytoma (pinealocytoma)	I–III
2. Pineoblastoma (pinealoblastoma)	IV
E. Neuronal tumours	
1. Gangliocytoma	I
2. Ganglioglioma	I, II
3. Ganglioneuroblastoma	III
4. Anaplastic (malignant) gangliocytoma and ganglioglioma	III, IV
5. Neuroblastoma	IV
F. Poorly differentiated and embryonal tumours	
1. Glioblastoma	IV
Variants:	
a. Glioblastoma with sarcomatous component (mixed glioblastoma and sarcoma)	IV IV
b. Giant cell glioblastoma	IV
2. Medulloblastoma	IV
Variants:	
a. Desmoplastic	III, IV
b. Medullomyoblastoma	III, IV
3. Medulloepithelioma	IV
4. Primitive polar spongioblastoma	IV
5. Gliomatosis cerebri	?
II. Tumours of nerve sheath cells	
A. Neurilemmoma (schwannoma, neurinoma)	I
B. Anaplastic (malignant) neurilemmoma (schwannoma, neurinoma)	III
C. Neurofibroma	I
D. Anaplastic (malignant) neurofibroma (neurofibrosarcoma, neurogenic sarcoma)	III, IV
III. Tumours of meningeal and related tissues	
A. Meningioma	
1. Meningotheliomatous (endotheliomatous, syncytial, arachnotheliomatous)	I
2. Fibrous (fibroblastic)	I
3. Transitional (mixed)	I
4. Psammomatous	I
5. Angiomatous	I
6. Haemangioblastic	II
7. Haemangiopericytic	II
8. Papillary	II, III
9. Anaplastic (malignant) meningioma	II, III
B. Meningeal sarcomas	
1. Fibrosarcoma	III, IV
2. Polymorphic cell sarcoma	III, IV
3. Primary meningeal sarcomatosis	IV
C. Xanthomatous tumours	
1. Fibroxanthoma	?
2. Xanthosarcoma (malignant fibroxanthoma)	?
D. Primary melanotic tumours	
1. Melanoma	IV
2. Meningeal melanomatosis	IV
E. Others	
IV. Primary malignant lymphomas	III, IV
V. Tumours of blood vessel origin	
A. Haemangioblastoma (capillary haemangioblastoma)	I
B. Monstrocellular sarcoma	IV
VI. Germ cell tumours	
A. Germinoma	II, III
B. Embryonal carcinoma	IV
C. Choriocarcinoma	IV
D. Teratoma	I

Forts. Tab. 1.

	Grade Malignancy:
II. Other malformative tumours and tumour-like lesions	
A. Craniopharyngioma	I
B. Rathke's cleft cyst	
C. Epidermoid cyst	
D. Dermoid cyst	
E. Colloid cyst of the third ventricle	
F. Enterogenous cyst	
G. Other cysts	I?
H. Lipoma	
I. Choristoma (pituicytoma, granular cell "myoblastoma")	
J. Hypothalamic neuronal hamartoma	
K. Nasal glial heterotopia (nasal glioma)	
VIII. Vascular malformations	
A. Capillary telangiectasia	
B. Cavernous angioma	
C. Arteriovenous malformation	
D. Venous malformation	I?
E. Sturge-Weber disease (cerebrofacial or cerebrotrigeminal angiomatosis)	

	Grade Malignancy:
IX. Tumours of the anterior pituitary	
A. Pituitary adenomas	
1. Acidophil	I
2. Basophil (mucoid cell)	I
3. Mixed acidophil-basophil	I
4. Chromophobe	I
B. Pituitary adenocarcinoma	III
X. Local extensions from regional tumours	
A. Glomus jugulare tumour (chemodectoma, paraganglioma)	?
B. Chordoma	See similar tumours elsewhere in the body
C. Chondroma	
D. Chondrosarcoma	
E. Olfactory neuroblastoma (esthesioneuroblastoma)	
F. Adenoid cystic carcinoma (cylindroma)	
G. Others	
XI. Metastatic tumours	
XII. Unclassified tumours	

These various groups were defined and sufficiently described for recognition.

Grading

A broad discussion took place on the criteria for the diagnosis of "malignancy". Here, it was emphasized that the criteria for histological and biological malignancy adopted in other neoplasms, were inadequate for the following reasons:

a) The fact that the tumours within the confines of the skull form a space-occupying and expanding lesion, inevitably leads to a fatal termination which by definition is equated with "clinical malignancy" (Zülch (24), pp. 31–32).

b) There may be a local pressure effect on vital structures – herniation – irrespective of the histological type of the tumour. The obstructive effect of a growing tumour may lead to secondary obstructive hydrocephalus and

c) the criteria of growth which define malignancy of other neoplasms are different in intracranial tumours and have therefore to be modified by the evaluation of the malignant behaviour of central nervous system tumours in surgical and non-operated cases.

The details included in these statements have to be looked up in the final of issue of the "Histological Typing of Tumours of the Central Nervous System" (25). A numerical grading is based upon the histological criteria of malignancy and the experience of the neurosurgeons and other clinicians with the various types of tumour. The numerical grade I is considered the most benign ("benign"), grade II as a "semibenign", grade III as a "relatively malignant", and grade IV as a "highly malignant" new growth, so that the scale from I to IV indicates increasing degrees of malignancy.

However, this form of grading does not correspond to the suggestion of Broders (3a) on one side and of Kernohan and Sayre (8a) on the other, but it is based on the biological behaviour of the various tumour groups, e. g. the experience of the clinicians and neuropathologists.

The pitfalls of a grading on the basis of the histological classification are well known.

a) The sample of tissue will not be representative of the tumour as a whole.

b) The problem of mixed cell populations may make a cytological grading extremely difficult, however, it seemed to be the duty and prerogative of the pathologist to provide his clinical colleagues with an informed opinion on the likely evolution of a particular tumour.

We may finish this discussion and recommendation of the new classification by repeating a part from the preface of this book:

"It will, of course, be appreciated that the classification reflects the present state of knowledge, and modifications are almost certain to be needed as experience accumulates. Although the present classification has been adopted by the members of the group, it necessarily represents a view from which some pathologists may wish to dissent. It is nevertheless hoped that, in the interest of international cooperation, all pathologists will try to use the classification as put forward. Criticism and suggestions for its improvement will be welcomed."

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