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MINIREVIEW

Critical Remarks on the International WHO Classification of Rodent Central Nervous System (CNS) Tumours

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Accurate classification of rodent CNS tumours is needed for the evaluation of animal experiments carried out to test the effects of chemical, biological or physical agents, or to study the pathogenesis of natural and induced tumours in man and animals. The use of standard nomenclature makes it possible to obtain mutually compatible research data, amenable to intra- and inter-laboratory comparison.

The International Classification of Rat CNS Tumours has been recently published as publication No. 122 of the International Agency for Research on Cancer (IARC, Lyon, France) (Cardesa *et al.* 1994), and that for the mouse is in preparation. These classification systems have been created in cooperation of the European Registry of Industrial Toxicology Animal-Data (RITA) with the North American Society of Toxicologic Pathologists (STP) and numerous internationally renowned experts, under the auspices of the International Life Science Institute (ILSI, Washington D.C., U.S.A.) and IARC. Publishing these diagnostic criteria represents great progress and provides an urgently needed basis for routine diagnostics. Inevitably, such consensus work is tainted by weak points justifying criticism. The present critical remarks attempt to shed some light on such weak points and unsolved problems hidden behind the facade, in order to promote the improvement and further development of the criteria.

Naturally occurring, "spontaneous" rodent CNS tumours were practically unknown as long as the experimental work was carried out on young animals (Stochdorph 1958). They became apparent only after the advent of long-term studies on aging animals, designed mainly for testing chronic toxicity and carcinogenicity of chemicals. Although the incidence of brain tumours depends on the accuracy of microscopic CNS examination, it can be generally concluded that in the animals observed during their life-span, or at least a substantial period of their life, one or only a few CNS tumours occur in 100 rats or 10 000 mice. Consequently, spontaneous tumours appear to be 100 times less frequent in mice than in rats.

The most frequent tumours in rats are meningiomas, most of which contain granular cells, sometimes consisting predominantly of granular cells, so that the denomination "granular cell meningioma" has been proposed (Krinke *et al.* 1985). Rat astrocytomas are diffuse, invasively growing, perivascular, frequently multifocal lesions. Their neoplastic cells never stain positively with astrocytic marker GFAP (glial fibrillary acidic protein). In contrast to rat oligodendroglial tumours, they react positively for lectin (RCA-1) binding (Krinke and Germer 1993). In some cases, they have been confused with inflammatory or neoplastic mesenchymal cell lesions and considered as "inflammatory or neoplastic reticulosis" (Krinke *et al.* 1985). Rat oligodendroglial tumours are well circumscribed, show characteristic grouping of cells in rows and circles, and frequently grow subependymally in the walls of brain ventricles. They have been confused with malignant ependymomas and denominated "ependymal glioma" (Stochdorph 1958, Krinke *et al.* 1985). Primitive neuroectodermal tumours of rats, such as pineal tumours and medulloblastomas, appear to have

Results were preliminary presented at "CNS – Advance in Research of Normal and Neoplastic Cells" which was held in Brno (April 25, 1996) as the satellite minisymposium of the 42nd International Congress of the European Tissue Culture Society (Krinke 1996).

features similar to those in man and other species. In mice, the meningeal tumours seem to be mostly devoid of granular cells, in contrast to rats. Mouse astrocytomas are similar to those occurring in rats, and spontaneous oligodendrogliomas are extremely rare. Tumour-like lesions such as lipomatous hamartomas or epidermoid cysts are quite frequent in the mouse CNS.

The spectrum of tumour types experimentally induced in rodent CNS differs substantially from that of spontaneous tumours and depends on the employed experimental procedure (Jänisch 1990, Walker *et al.* 1994). Implantation of pellets with polycyclic aromatic hydrocarbons induced tumours in tissues contacting the pellets, so that the topographical positioning of the pellet affected the tumour type induced. Systemic administration of alkylating N-nitrosamides induced mainly tumours of a type resembling spontaneous oligodendrogliomas. There seems to be a difference between the chemically induced and spontaneous tumours, and some of the induced tumours may not have a natural counterpart.

CNS tumours induced with viruses also appear to have a different, agent-specific spectrum. Avian sarcoma virus and murine sarcoma virus were observed to induce astrocytomas, glioblastomas and sarcomas in rats and mice; human adenovirus 12 medulloblastomas and medulloepitheliomas in rats and neuroblastomas and retinoblastomas in mice; human BK virus malignant ependymomas in mice. Transgenic mice containing SV40 promoter and enhancer sequences and the gene coding for the T antigen developed choroid plexus tumours, and those with other SV40 constructs developed primitive neuroectodermal tumours, pineal tumours, or ependymomas. Transgenic mice bearing *neu* oncogene combined with transcriptional regulatory elements for myelin basic protein developed gliomas expressing both GFAP and myelin basic protein (reviewed in Jänisch 1990, Krinke and Kaufmann 1996).

The International Classification for rodents attempts to discriminate between spontaneous and induced tumours. It does not, however, indicate the incidences of spontaneous lesions, allowing for an erroneous impression that the tumour spectrum observed in rodents is well comparable to that observed in man. However, an "anthropomorphic" 1:1 correlation of rodent with human CNS neoplasms can hardly be feasible. Rodent tumours, in comparison to man, are generally less well differentiated, show a high proportion of malignant entities, and do not represent the exact spectrum of lesions recognized in humans. Among the spontaneous and induced CNS tumours described in rodents, the "embryonic" forms may be better comparable with human tumours than the "adult" forms, which generally do not exhibit the degree of differentiation known from human lesions. The terminology selected for denomination of rodent tumours has been influenced by the ultimate goal of extrapolating observations from animals to humans: terms known in human pathology have been preferred, and lesions similar to those occurring in man have been looked for in rodents. The classification of rodent tumours is based on their phenotypic features, which, in the absence of specific markers, are insufficient for detection of their virtual identity. There is a need for better molecular biologic characterization of these lesions.

Some of the entities defined by the International Classification for rodents reflect the controversies persisting in the new WHO Classification of Brain Tumours in humans (Kleihues *et al.* 1993). For instance, some of human neuropathologists contend that malignant oligodendrogliomas and ependymomas may progress to glioblastomas, while other consider glioblastoma as essentially an astrocytic neoplasm. In the rodent Classification, glioblastoma is only mentioned in the comment to malignant astrocytoma and malignant mixed glioma. The entity of mixed gliomas, however, is also a matter of controversy. In particular, the arbitrary criterion that in rodent mixed gliomas either cell type must represent at least 20 % of neoplastic cells is devoid of scientific rationale, although it may be helpful as a practical standard. Furthermore, in the rodent Classification the denomination of malignant meningeal tumours as "meningeal sarcomas" instead of "malignant meningiomas" does not appear to be consequent in view of the use of "benign meningiomas".

CNS tumours of various histogenetic categories may be further characterized according to the degree of malignancy. In medicine, the purpose of such grading is the assessment of prognosis and the choice of appropriate therapy. The new WHO Classification of human CNS tumours uses four grades of malignancy, starting with grade one for low, and ascending to grade four for high malignancy. In this system, selected kinds of astrocytomas can be attributed one of the four grades, oligodendrogliomas and mixed gliomas grade two or three, meningiomas and ependymomas one to three, choroid plexus papilloma grade one, and carcinoma grade three or four. Embryonic tumours, such as medulloblastoma, are invariably attributed grade four.

Although in rodents there is little need for individual prognosis of disease outcome, and usually no therapy is applied, the assessment of tumour malignancy helps to better characterize neoplastic lesions observed in animal experiments. Therefore, the International Classification of rodent tumours has implemented a simple grading system, discriminating for most lesions their benign and malignant counterparts. In contrast to benign lesions, expected to be confined to single CNS regions, malignant forms would affect multiple CNS regions, destroying them by

invasion and exhibiting cellular pleomorphism and necrosis indicating rapid growth. This simple approach implies a possible progression of initial small lesions to more advanced, extensive neoplasms. Needless to say that this approach gives rise to criticism, since large lesions can still be benign, while some malignant lesions can be small in size.

Last but not least, some of the rodent lesions have strain-specific or hybrid stock-specific features. Since the pathologists usually work with a restricted spectrum of selected strains and hybrid stocks, they have little chance to compare the lesions they are familiar with to those occurring in other animal colonies. For this reason, world-wide compilation of experimental animal data is extremely difficult and international cooperation is much needed.

Despite all its shortcomings, there is a hope that the International Classification of Rodent CNS Tumours will be accepted by the scientific community as a practical means of communication and a basis of future developments.

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