Histogenesis of retinoblastoma

More than a century of controversy has surrounded the cell of origin of retinoblastoma. At the outset Virchow described the tumour as a glioma in the belief that it arose from the glial cells of the retina. Subsequently, in a report of a single case, Flexner was the first to describe the rosettes which may be present in retinoblastomas and to designate this tumour a neuroepithelioma. Later still Winderstein described rosettes in a series of cases and substituted the term neuroepithelioma for glioma, whether or not rosetting was present. Both authors regarded rosettes as an attempt to form photoreceptors, leading Verhoeff to suggest the description 'retinoblastoma' in order to indicate the origin of all histological variants of the tumour from embryonic retinal cells and to parallel the name 'neuroblastoma'.

The term retinoblastoma was adopted by the American Ophthalmological Society in 1926. In the same year Bailey and Cushing produced a classification of brain tumours based on histogenesis. The medullary epithelium lining the embryonic neural tube differentiates into three groups of cells: the neuroblastic series which gives rise to neurons, the spongioblastic series which forms the glia, and the medulloblastic series of cells which are primitive and undifferentiated and which may lead to either glia or neurons. Using gold and silver stains they classified each tumour according to the type of cell predominating. Several attempts were made to apply the same principles to retinoblastoma. Using silver impregnated preparations, Muñoz-Urra identified spongioblasts as well as astroblasts and astrocytes in the histogenesis of retinoblastoma.

Parkhill and Benedict could not demonstrate any cell processes or fibrils indicative either of glia or of neurons using special stains and regarded the cells they saw as primitive and undifferentiated. They postulated that the tumour was derived by dedifferentiation of normal astrocytes or Müller cells rather than from primitive precursors. They argued that the rosettes in retinoblastoma represented an attempt to
reproduce the primitive epithelium of ependymal cells in the embryonic neural tube. Similar rosettes are seen in ependymomas. Because of this, and in accord with the wide acceptance of the term glioma for all brain tumours of neuroepithelial origin, they chose to revert to the glioma description for the retinal tumour, subclassifying the neoplasms as of retinoblastoma type when the cells were undifferentiated like those of neuroblastosomas or medulloblastomas, of neuroepithelia type when partial differentiation was indicated by rosette formation like that of primitive spongioblastic, and of astrocitary type in the rare examples when the tumour cells were nearly as well differentiated as normal astrocytes.

On similar principles, Broders graded retinoblastomas from I for true gliomas composed of more or less mature astrocytes to IV for the majority of retinoblastomas with no cellular differentiation. Grinker was in agreement with his predecessors that the presence of rosettes was indicative of an origin from primitive and more neural crest, and he retained the term neuroepithelioma for tumours with this feature. However, he considered that tumours without rosettes arose from primitive retinal epithelial cells capable either of neuroepithelial differentiation to neurons or of spongioblastic differentiation to glia.

More recently, using histochemical stains and electron microscopy, Tso et al. found that the cells of rosettes have morphological features in common with photoreceptor cells, while Sang and Albert demonstrated uptake of catecholamine precursors in retinoblastoma cell cultures suggestive of the production by the tumour of similar neural transmitters to those found in normal retina. Synaptic vesicles may be seen in retinoblastomas with photoreceptor differentiation. Retinoblastoma cells have been shown to have features in common with embryonic retina. For example, the oncoprotein N-myc is expressed in retinoblastoma tumours and in fetal retina but not in adult retina. Biochemical studies have demonstrated the ability of retinoblastoma cells to synthesise substances present in normal maturing and adult photoreceptors such as binding proteins for retinol and retinoic acid. Tissue culture experiments have shown that the differentiation of retinoblastoma cells may be modulated by chemical substances. Both glial and neuronal differentiation have been observed. The expression of retinol and retinoic acid binding proteins is a sign of differentiation and proliferation of retinoblastoma cells, and those of other tumours which contain these binding proteins may be inhibited by retinooids. Immunohistochemical studies performed with antibodies to substances specific to the retina, including retinal S-antigen, S-100 protein, neuronal markers such as neuron specific enolase, and glial markers such as glial fibrillary acidic protein have indicated both a neuronal and a glial origin for retinoblastoma.

In their article in the present issue of the BJ JT Tarlton and Easty have further explored the immunohistological reactivity of retinoblastoma using a panel of monoclonal antibodies to achieve a more specific immunolocalisation. Their data suggest that the tumour arises from an early multipotent cell with the capacity to develop into an inner or outer retinal cell so that the resultant tumour cell population is heterogeneous.