

We can now use such figures with confidence when discussing likely outcomes of projected procedures with our patients and, hopefully, with a clear conscience.

It may therefore come as a surprise to learn how much of our vaunted success is dependent on factors over which we have little influence but take for granted. In Britain at least our patients are still reasonably compliant. What the doctor says tends to go. It does not occur to us that patients will fail to attend for postoperative follow-up appointments, fail to use the prescribed drops, or decline to be tested for or wear necessary spectacles.

In this issue a paper by Dr Al Faran reports the results of modern cataract surgery undertaken at the King Khaled Eye Hospital in Riyadh. The study was made because the staff at the hospital considered that their results were not matching those achieved elsewhere. They report, for instance, final acuities of 6/12 (20/40) or better in 37% of patients, with commensurate figures for those seeing less well. The major responsible factor is the patients' failure to attend for refraction or to wear a spectacle correction. In many parts of the Islamic world and elsewhere the wearing of glasses is equated with blindness and can constitute a serious social stigma. The recorded acuities above are mostly uncorrected and are probably no worse than those achieved in many Western 'centres of excellence', where, as in Riyadh, many contributing surgeons are at various stages of their surgical training. Imperfect techniques and inexperience are bound to be associated with a higher rate of operative misadventure and a wider margin for error with preoperative biometry.

We all have our own favourite parameters for assessing the results of anterior segment surgical procedures. Two valuable ones are the postoperative incidence of retinal detachment and bullous oedema of the cornea. Al Faran reports a detachment rate of 1% and no cases of persistent corneal oedema. Admittedly the follow-up time (mean of nine months only) is far too short to be dogmatic, but one sees nothing here to suggest that the surgeons involved have cause for reproof. A 6.4% rate of vitreous loss following capsular rupture is what one might expect from a surgical team including those in training, while transient postoperative oedema in as few as 4.5% has to be regarded as excellent and

unlikely to be followed by significant numbers suffering late decompensation.

Al Faran's problems are related to factors beyond his control. The high incidence of endemic sight-impairing disease, particularly trachoma and climatic droplet keratopathy (25% in this study), are gradually being overcome with improvements in community health. In my experience droplet keratopathy is more prevalent in the poorer strata of Middle Eastern society and often superimposed on pre-existing corneal scarring, due either to trachoma or smallpox. The elimination of these conditions should therefore be followed by a similar fall in the incidence of droplet keratopathy.

The problems concerned with the refusal of large sections of a community to wear glasses where these are indicated are likely to respond only to the influence of effective universal education, and in Saudi Arabia will take one or two generations. The same applies to the reported sex differences in the patients of this study. The older age groups contain fewer females despite the higher incidence of cataract in Saudi women. For the age groups under 50 the sexes are equally represented, which hopefully indicates already some modification of traditional social behaviour. In time, therefore, Al Faran or his successors will be able to serve a population who will not only be more prepared to report their difficulties but also more inclined to keep their postoperative appointments!

Overseas students in London have frequently complained (to me) that sophisticated surgical techniques which have so dramatically altered patients' expectations have no relevance to the developing world. Poorer conditions called for inferior methods – intracapsular extraction and the Graefe knife. Dr Al Faran has demonstrated how wrong this is. How much worse off his patients would have been had they not had the benefit of excellent modern management. Other surgeons of whom we hear, working under even worse constraints, both physical and cultural, struggle to follow the precepts of their teachers and to maintain the highest possible standards. They must be given every possible encouragement to persevere.

ARTHUR STEELE

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.¹ 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.² Later still Wintersteiner described rosettes in a series of cases and substituted the term neuroepithelioma for glioma, whether or not rosetting was present.³ 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 1926.⁴ In the same year Bailey and Cushing produced a classification of brain tumours based on histogenesis.⁵ 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.⁶⁻¹⁰ Using silver impregnated preparations, Muñoz-Urra identified spongioblasts as well as astroblasts and astrocytes in the histogenesis of retinoblastoma.⁶

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.⁷ 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 neuroectodermal 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 neuroblastomas or medulloblastomas, of neuroepithelioma type when partial differentiation was indicated by rosette formation like that of primitive spongioblastic cells, and of astrocytoma 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.¹¹⁻¹³ Grinker was in agreement with his predecessors that the presence of rosettes was indicative of an origin from primitive rods and cones, 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.⁸

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,^{14,15} 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.¹⁶ 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 oncogene *N-myc* is expressed in retinoblastoma tumours and in fetal retina but not in adult retina.¹⁷ 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.¹⁸⁻²¹ Tissue culture experiments have shown that the differentiation of retinoblastoma cells may be modulated by chemical substances.^{22,23} Both glial and neuronal differentiation have been observed.^{24,25} The expression of retinol and retinoic acid binding proteins is a sign of differentiation²⁶ and proliferation of retinoblastoma cells,²⁷ and those of other tumours which contain these binding proteins²⁸ may be inhibited by retinoids. Immunohistochemical studies performed with antibodies to substances specific to the retina, including retinal S-antigen,²⁹⁻³² S-100 protein,³³ neuronal markers such as neuron specific enolase,^{24,31,33-35} and glial markers such as glial fibrillary acidic protein^{24,31,33,35-38} have indicated both a neuronal and a glial origin for retinoblastoma.

In their article in the present issue of the *BJO* 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 multipotential cell with the capacity to develop into an inner or outer retinal cell so that the resultant tumour cell population is heterogeneous.

JOHN HUNGERFORD

- 1 Virchow R. *Die Krankhaften Geschwülste*. Berlin: Hirschwald, 1864; 2: 151.
- 2 Flexner S. A peculiar glioma (neuroepithelioma?) of the retina. *Bull Johns Hopk Hosp* 1891; 2: 115-9.
- 3 Wintersteiner H. *Das Neuroepithelioma retinae: eine anatomische und klinische Studie*. Leipzig: Deuticke, 1897.
- 4 Verhoeff FH, Jackson E. Minutes of the proceedings of the sixty-second annual meeting. *Trans Am Ophthalmol Soc* 1926; 24: 38-43.
- 5 Bailey P, Cushing H. *A classification of tumors of the glioma group on a histologic basis with a correlated study of prognosis*. Philadelphia: Lippincott, 1926.
- 6 Muñoz-Urra F. Ueber die feine Gewebsstruktur des Glioms der Netzhaut. *Graefes Arch Clin Exp Ophthalmol* 1923; 112: 133-51.
- 7 Parkhill EM, Benedict WL. Gliomas of the retina: a histopathologic study. *Am J Ophthalmol* 1941; 24: 1354-73.
- 8 Grinker RR. Gliomas of the retina; including the results of studies with silver impregnations. *Arch Ophthalmol* 1931; 5: 920-35.
- 9 Favaloro G. Sui glioblasto-spongioblastomi anaplastici e differenziati della retina. *Ann Ottalmol Clin Oculist* 1937; 65: 881-918.
- 10 Sussman W. Intraocular tumours. *Br J Ophthalmol* 1938; 22: 722-37.
- 11 Broders AC. Cancer's selfcontrol. *Med J Rec* 1925; 121: 133-5.
- 12 Broders AC. Practical points on the microscopic grading of carcinoma. *NY State J Med* 1932; 32: 667-71.
- 13 Broders AC. The grading of cancer: its relationship to metastasis and prognosis. *Texas J Med* 1933; 29: 520-5.
- 14 Tso MOM, Zimmerman LE, Fine BS. The nature of retinoblastoma: I. Photoreceptor differentiation: a clinical and histologic study. *Am J Ophthalmol* 1970; 69: 339-49.
- 15 Tso MOM, Fine BS, Zimmerman LE. The nature of retinoblastoma: II. Photoreceptor differentiation: an electron microscopic study. *Am J Ophthalmol* 1970; 69: 350-9.
- 16 Sang DN, Albert DM. Catecholamine levels in retinoblastoma. In: Jakobiec, FA ed. *Ocular and adnexal tumors*. Birmingham: Aesculapius, 1978.
- 17 Squire J, Goddard AD, Canton M, Phillips RA, Gallie BL. Tumour induction by the retinoblastoma mutation is independent of *N-myc* expression. *Nature* 1986; 322: 555-7.
- 18 Saari JC, Futterman S, Stubbs GW, *et al*. Cellular retinol- and retinoic acid-binding proteins in transformed mammalian cells. *Invest Ophthalmol Vis Sci* 1978; 17: 988-92.
- 19 Chader GJ, Wiggert B, Russell P, Tanaka M. Retinoid-binding proteins of retina and retinoblastoma cells in culture. *Ann NY Acad Sci* 1981; 359: 115-33.
- 20 Fong S-L, Balakier H, Canton M, Bridges CDB, Gallie B. Retinoid-binding proteins in retinoblastoma tumors. *Cancer Res* 1988; 48: 1124-8.
- 21 Daxecker F, Daxenbichler G, Marth Ch. Cellular retinoic acid binding protein (CRABP) in retinoblastoma. *Ophthalmic Ped Gen* 1987; 8: 47-8.
- 22 Tso MOM. Clues to the cell of origin of retinoblastoma. *Int Ophthalmol Clin* 1980; 20: 191-210.
- 23 Kyritsis AP, Tsokos M, Triche TJ, Chader GJ. Retinoblastoma: a primitive tumor with multipotential characteristics. *Invest Ophthalmol Vis Sci* 1986; 27: 1760-4.
- 24 Messmer EP, Font RL, Kirkpatrick JB, Hopping W. Immunohistochemical demonstration of neuronal and astrocytic differentiation in retinoblastoma. *Ophthalmology* 1985; 92: 167-73.
- 25 Char DH, Wood IS, Huhta K, Rand N, Morita CT, Howes EL. Retinoblastoma: tissue culture lines and monoclonal antibody studies. *Invest Ophthalmol Vis Sci* 1984; 25: 30-40.
- 26 Bichler E, Daxenbichler G. Retinoic acid-binding protein in human squamous cell carcinomas of the ORL region. *Cancer* 1982; 49: 619-22.
- 27 Wiggert B, Russel P, Lewis M, Chader G. Differential binding to soluble nuclear receptors and effects on cell viability of retinol and retinoic acid in cultured retinoblastoma cells. *Biochem Biophys Res Commun* 1977; 79: 218-25.
- 28 Lotan R. Different susceptibilities of human melanoma and breast carcinoma cell lines to retinoic acid-induced growth inhibition. *Cancer Res* 1979; 39: 1014-9.
- 29 Mirshahi M, Boucheix C, Dhermy P, Haye C, Faure JP. Expression of the photoreceptor-specific S-antigen in human retinoblastoma. *Cancer* 1986; 57: 1497-500.
- 30 Donoso LA, Folberg R, Arbizo V. Retinal S antigen and retinoblastoma: a monoclonal antibody histopathologic study. *Arch Ophthalmol* 1985; 103: 855-7.
- 31 Rodrigues MM, Wiggert B, Shields J, *et al*. Retinoblastoma: immunohistochemistry and cell differentiation. *Ophthalmology* 1987; 94: 378-87.
- 32 Donoso LA, Rorke LB, Shields JA, Augsburg JJ, Brownstein S, Lahoud S. S-antigen: a monoclonal antibody, MAba-C6, histopathologic study of trilateral retinoblastoma. *Am J Ophthalmol* 1987; 103: 57-62.
- 33 Kyritsis AP, Tsokos M, Triche TJ, Chader GS. Retinoblastoma: origin from a primitive neuroectodermal cell? *Nature* 1984; 307: 471-3.
- 34 Molnar ML, Stefansson K, Marton LS, Tripathi R, Molnar GK. Immunohistochemistry of retinoblastoma in humans. *Am J Ophthalmol* 1984; 97: 301-7.
- 35 Terenghi G, Polak JM, Ballesta J, *et al*. Immunocytochemistry of neuronal and glial markers in retinoblastoma. *Virchows Arch (Pathol Anat)* 1984; 404: 61-73.
- 36 Tsokos M, Kyritsis AP, Chader GF, Triche TJ. Differentiation of human retinoblastoma in vitro into cell types with characteristics observed in embryonal or mature retina. *Am J Pathol* 1986; 123: 542-52.
- 37 Jiang Q, Lim R, Blodi FC. Dual properties of cultured retinoblastoma cells: immunohistochemical characterisation of neuronal and glial markers. *Exp Eye Res* 1984; 39: 207-15.
- 38 Lane JC, Klintworth GK. A study of astrocytes in retinoblastomas using the immunoperoxidase technique and antibodies to glial fibrillary acidic protein. *Am J Ophthalmol* 1983; 95: 197-207.