Some recent developments in ophthalmic pathology

Pathology as it is generally understood has to do with the study of disease in the laboratory and can be expressed in many ways. More and more the techniques of immunohistochemistry and molecular and cell biology have been added to the established methods, and their potential has not been ignored in the particular context of ophthalmic pathology.

One area to have benefited from the application of these newer approaches has been the study of proliferative processes in the retina and vitreous. Cell culture of epiretinal membranes, followed by staining with antigen-specific labelled antisera, has allowed the recognition of three types of cell: glia, fibroblasts, and retinal pigment epithelium. The relative proportions of these cells in a given membrane varies, but in-vitro testing of their individual contractile propensities indicates that the capacity for traction is predominantly attributable to the fibroblast element. Inflammatory factors appear to be of paramount importance in the pathogenesis of the membranes and related proliferative vitreoretinopathy, with macrophages having a key role. Such information concerning the nature and behaviour of what is essentially scar tissue opens up the prospect of pharmacological control, and already there have been some encouraging developments with respect to the use of sodium butyrate and certain other inhibitors.

A whole host of factors relating to proliferative and reparative phenomena within the eye have been described. Of particular relevance to retinal pathology is the identification of various substances able to stimulate neovascularisation and their specific demonstration in eyes with proliferative diabetic retinopathy. Polypeptides of differing sizes have been isolated, some closely similar, if not identical, to fibroblast growth factors, but also described is a factor specific for the endothelium of small blood vessels that weighs less than a few hundred daltons. Experimental work has demonstrated a marked increase in the level of the latter substance within the retina and vitreous in response to artificially induced retinal ischaemia. The retinal pigment epithelium also appears to be associated with the elaboration of factors able both to stimulate and to inhibit angiogenesis and it would seem that the level of vascularisation in health is very finely tuned.

There has been renewed interest in the origin and function of the spindle cells seen in the vanguard of the developing retinal vasculature, the numbers of which are considerably increased in the retinopathy of prematurity. Commonly regarded as primitive angioblasts, there is now evidence, based on a positive reaction for glial fibrillary acidic protein, that they may be a type of astrocyte. Moreover, irrespective of their histogenesis, an increase in the number of intercellular gap junctions has been reported in the retinopathy of prematurity; and it has been speculated that such spindle cells may be the source of the angiogenic stimulation in the proliferative phase of the disorder.

Still on the subject of cell proliferation but changing the terms of reference to neoplasia: a better understanding is slowly emerging of so-called pseudotumours of the orbit. These are lymphocytic lesions of unknown aetiology with hyperplastic germinal centres, presumed to be inflammatory and typically associated with a good response to corticosteroid therapy. There are, however, those cases in which the biopsy findings are equivocal, and it constituted a real advance when the application of immunohistochemical techniques made it possible to distinguish between monoclonal and polyclonal lymphoid proliferations.

Monoclonal disorders are recognised by the replication of seemingly identical cells derived from a single aberrant mutation. They can be recognised in the context of B cell disorders, which account for virtually all orbital lymphomas, by their restriction to the production of just one type of antibody with a single type of light chain. The inference is that such lesions are neoplastic, while those characterised by more than one sort of antibody are deemed to result from the reactive proliferation of an array of lymphocytes. Undoubtedly this has made for more accurate diagnosis, but still there are problems because occasional polyclonal lesions have been observed to disseminate. However, on the basis of gene rearrangements, the application of DNA probes has revealed that clones of mutant neoplastic cells can be embedded within lesions of this sort, suggesting that the lymphoid disorders of the orbit constitute a continuous spectrum from unquestioned inflammatory processes to frank lymphoma. If this proves to be the case, 'pseudotumours' of the orbit will probably come to be seen as manifestation of the mucosa associated lymphoid tissue (MAL'T) concept described in other areas of the body and so having an inherent if limited capacity for malignant transformation from the outset.

Study of the genetic abnormality in retinoblastoma has also been fruitful. Consequent on the mapping of the presumed defective gene on the long arm of chromosome 13 (13q14) other work has shown that tumorigenesis is linked to deletion of a gene at this position and not to altered gene behaviour. In other words the putative retinoblastoma gene behaves as an oncogene suppressor or antioncogene. It also appears that both allelic genes need to be deleted before a neoplasm ensues, which nicely conforms with the 'two hit' hypothesis formulated by Knudson to account for the inheritance of retinoblastoma. Other work, based on cell culture and immunocytochemistry, indicates that the tumour arises from a cell with potential for both neural and glial differentiation, even though it is the former option that is usually expressed.

The endothelial cells lining the trabecular tissue of the anterior chamber subserve several functions, including control of trabecular core hydration, glycosaminoglycan formation, and phagocytosis of cellular and other detritus reaching the outflow system. Their loss compromises drainage efficiency and may prove to be the single most important event in the pathogenesis of primary open angle glaucoma, since the normal age-related reduction in cellularity appears to be enhanced in this condition.

One of the more telling advances in the field of ocular immunopathology has been the demonstration that the surfaces of retinal vascular endothelial cells may bear normally covert class II major histocompatibility antigens, because this suggests that such cells can be involved in immune processes affecting the retina. The combination of local ocular antigens and class II HLA antigens on the cell membrane could serve to bind circulating activated CD4+ T cells and could account for the perivascular accumulation of lymphocytes commonly seen in retinal inflammation. The knowledge that activated T cells are responsible for perpetuating the inflammatory process in uveitis has led to
the beneficial application of immunosuppressive drugs such as cyclosporine which specifically target these cells.  

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