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Editorials

The "thin man" phenomenon: imperfect filling in of visual space

Normal people do not perceive an "empty" region in the portion of their visual field corresponding to the physiological blind spot. Instead, the visual system perceptually fills in the blind spot with information surrounding it. Similar types of perceptual filling in also occur in patients with pathological monocular and binocular homonymous scotomas.[1 2] Furthermore, stabilising the image of a spot on the retina leads to perceptual filling in of the spot with the surrounding background.[3] Perceptual filling in of stabilised images can also be demonstrated for colour, brightness, and texture.[4–10] Safran *et al* have previously shown that a spatial distortion of images occurs in the field surrounding a scotoma.[11] They have now shown that the filling in phenomenon itself is not precise (see p 137, this issue). They report two patients with right inferior homonymous paracentral scotomas resulting from ischaemic brain insults in whom field defects were markedly smaller when tested with an Amsler grid than with a tangent (Bjerrum) screen. In addition, after both patients fixated another person's face or neck for 5–10 seconds, the other person's left shoulder (corresponding to the region of the field defect) appeared narrower than the right shoulder. Safran *et al* call this perceptual alteration "the thin man" phenomenon. Some patients with this alteration are aware of it; others are not, at least not until they are specifically questioned about it.

Filling in of a pathological homonymous scotoma is apparently related to expansion of receptive fields in the visual cortex,[12 13] with the responsible neural mechanisms localised in retinotopic visual areas.[3] The time required for this filling in to occur depends in part on the size, shape, and location of the scotoma. It appears to reflect the time required for figure ground segregation to fail rather than a slow spread of a surface feature from one region of the visual field into another,[3] and it may be related to horizontal connections between pyramidal neurons in the extrastriate cortex.[14]

The findings reported here by Safran *et al* raise numerous questions with regard to the "thin man" phenomenon. Does it occur with homonymous field defects on both sides of visual space or only with right sided defects? Does it occur only for homonymous paracentral scotomas or for more peripheral scotomas as well? Does the size of the defect influence the severity of the phenomenon and in what way? We look forward to further work by Safran and his colleagues as well as others for the answers to these and other questions. In the meantime, we agree with Safran *et al* that patients who complain of blurred vision, particularly after a known or suspected stroke, should be carefully tested for an homonymous paracentral scotoma, the clue to which may be the patient's spontaneous or queried observation of apparent asymmetry of a symmetric complex image in a particular region of visual space during the clinical examination.

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The healing optic nerve in glaucoma: transforming growth factor β and optic nerve head remodelling

Despite the many advances in the therapy and diagnosis of primary open angle glaucoma, and the recognition of intraocular pressure as the major modifiable risk factor,[1 2] the pathogenesis of the disease still remains unclear. The most pathognomonic feature of glaucoma is optic disc cupping and the primary site of glaucomatous optic nerve damage appears to be at the optic nerve head.[3] However, the exact mechanisms by which this damage occurs have not been elucidated. Changes in lamina cribrosa morphology and nerve fibre bundle pore morphometry[4 5] have been documented in this disease, in association with alterations in the surrounding extracellular matrix.[6–11] The tortuous course of the individual nerve fibres may also play a role.[12] In this issue of the *BJO* (p 209), Pena *et al* have found that the production of a growth factor, transforming growth factor β (TGF-β2) is considerably increased in the optic nerve heads of patients with open angle glaucoma but not in normal individuals. This finding is important because of its implications for the pathogenesis of glaucomatous damage. Like all interesting research findings, it raises further intriguing questions. Is TGF-β2 stimulated in response to nerve axon loss or changes in extracellular environment such as intraocular pressure induced compression, stretching, and shearing forces? Is TGF-β2 production neuroprotective or do its effects on extracellular matrix compromise nerve fibre function and integrity?

The main structural component of the optic nerve head is the lamina cribrosa through which pass all the optic nerve fibres exiting the eye. It is continuous with the sclera, and consists of stacks of fenestrated connective tissue plates (cribriform plates), each pore allowing passage of nerve fibre axons.[13] It has long been accepted that the lamina cribrosa is the weakest part of the sclera. If the intraocular pressure (IOP) is raised for a prolonged period, as in cases of chronic glaucoma, the lamina cribrosa bows outwards producing a "cupped" optic disc.[14] This bowing can also be induced in the short term at higher levels of IOP. These structural change are very similar even in patients with so called normal tension glaucoma, suggesting that physical forces at the nerve head do play a role in cupping, whatever the level of IOP. Histological analysis has demonstrated regional differences in lamina cribrosa structure with the superior and inferior areas being weakest and hence most susceptible to damage from raised IOP, with collapse and prominent posterior bowing in advanced glaucomatous disease.[15] Differences in primary structure and cellular responses to "stress" including production of growth factors may explain in part the individual variation in the pattern of optic nerve damage seen with similar levels of IOP.

TGF-β is a multifunctional growth factor found throughout the body, and implicated in the processes of scarring.[16–19] In the eye, TGF-β2 appears to be the predominant isoform.[20–23] Pena *et al* suggest the TGF-β2 in glaucomatous eyes is produced by astrocytes in the lamina cribrosa, which as a consequence take up a "reactive" phenotype, seen characteristically in various neurological disorders—Alzheimer's disease,[24] multiple sclerosis,[25] and after neuronal injury. This phenotype is implicated in the development of glial scar formation,[26] and in its remodelling. Although no gliosis is seen in glaucomatous optic neuropathy, they postulate that TGF-β may activate astrocytes to stimulate extracellular matrix remodelling of the lamina cribrosa. TGF-β is a prominent component of the healing response to damage in many parts of the body, and the optic nerve head may be no exception.

The cellular responses at the optic nerve head to changes in IOP are not yet known. However, the effects of different types of forces on a variety of cell types has been studied, most extensively in endothelium, where shear stress has been shown to produce vasodilatation, a process mediated by nitrous oxide and probably a change in cell-cell interactions via expression of integrins.[27] Centrifugal tension has been shown to increase expression of growth factor receptors in fibroblasts, via stimulation of β1 integrin expression,[28] and dermal fibroblasts alter production of matrix metalloproteases (MMP) in response to different tensile loads.[29] It is therefore conceivable that changes in the IOP produce cellular responses in the lamina cribrosa, altering gene expression and the synthesis or degradation of extracellular components, and ultimately the support structure of the nerve fibres.

The idea that the optic nerve head may respond to dynamic physical force changes in its environment via alterations in TGF-β activity is very important. Historically, TGF-β was believed to stimulate scarring by inhibiting MMP production and stimulating tissue inhibitors of MMPs (TIMPs).[30] Work in our laboratory suggests, however, that the cellular effects of TGF-β depend on interactions with the surrounding extracellular matrix[31]—TGF-β inducing different MMP and TIMP profiles in different extracellular environments. Cell-matrix interactions are mediated via integrin receptors,[32] and TGF-β is known to directly affect integrin expression, which in turn determines MMP production.[33] Hence, TGF-β is a potent modulator of extracellular remodelling.

Pena *et al* also comment on TGF-β having a neuroprotective effect in glaucoma. A number of possible mechanisms of neuroprotection have been reviewed by Flanders *et al* in the context of neurodegenerative diseases,[34] including antioxidant properties of TGF-β, its enhancement of mitochondrial potential, its maintenance of neuronal calcium homeostasis, and finally its inhibitory effects on apoptosis. Again, although these areas are currently being explored, the significance of these processes in glaucomatous optic neuropathy is not yet established.

As we approach the next millennium, this is an exciting period in glaucoma research. Technological advances in imaging have made it possible to visualise the lamina cribrosa pores in vivo.[35 36] If we can now correlate in vivo features with changes at a cellular and molecular level, the processes occurring within the lamina cribrosa may provide us with an alternative tool not only to diagnose and monitor glaucoma but also to treat this fascinating but complex group of diseases.

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