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Commentary

The review by Morgan considers evidence from our laboratory that chronic human glaucoma and experimental glaucoma in monkeys cause a more rapid loss of larger retinal ganglion cells. This work has now been confirmed in chronic glaucoma tissues by three other research groups (his references 18, 37, 41). The evidence includes measurements of ganglion cell body size by three different histological techniques, measures of axon diameter, and quantitative patterns of axonal transport and trans-synaptic effects in the lateral geniculate body (LGN). Morgan suggests alternative explanations for our data. However, each of the possible explanations that he considers have been adequately discussed in our previous publications. I am grateful to the editor of the *British Journal of Ophthalmology* for allowing me to comment.

Morgan invokes cell shrinkage to explain selective large cell loss, pointing out that we considered this 'as a mechanism to account for the cell size distributions'. We did discuss but dismissed shrinkage as an explanation, since it is an implausible event that does not fit the data. Only with a contrived match of shrinkage in *all* ganglion cells to cell loss is it possible to model our data to simulate no selective effect. In addition, the amount of putative shrinkage has to differ with various degrees in cell loss in exactly the correct proportion, or the result does not match observed data. Why would the amount of shrinkage change as percentage cell loss increases? Furthermore, we have recently reported that cell death by apoptosis occurs in glaucomatous ganglion cells (his reference 25), but this is 'unlikely to generate large populations of shrinking cells' - in fact, the number of cells dying at any point in time by apoptosis is very small, since it occurs so rapidly. Hence, shrinkage as a confounder is not only 'entirely theoretical', it is unsupported by data on primary ganglion cell degeneration.

Morgan suggests that we confused amacrine cells for ganglion cells, citing 'subjective judgment'. I have studied inner retinal anatomy for over 20 years and this research included quantitative studies of cell size and cytology in masked tissues of glaucoma, optic nerve transection, and normal specimens. While no experiment is perfectly objective, our reported ganglion cell body data do not include cells of the same size or morphology as amacrines that normally

reside in the ganglion cell layer. The numerical data to demonstrate this have been published.

Morgan has interpreted our LGN data to imply that anterograde axonal transport is a poor indicator of cell body health. We found a selectively greater, statistically significant decrease in axonal transport to magnocellular layers compared with that to parvocellular layers. His shrinkage argument cannot explain the data, since we controlled the observations by comparing LGN transport from the experimental glaucoma eye with those from control and acute glaucoma eyes. His presentation therefore, on the ratio of cells, laminar volumes, and arborisation patterns cannot explain the data. Either there was less transport by larger cells or the terminal arborisations of large cells were drastically altered compared with smaller cells. Both conclusions are compatible with a selectively greater susceptibility to chronic experimental glaucoma among the magnocellular projecting cells. Furthermore, the topography of transport decrease shows it to be greatest in LGN areas corresponding with the mid retina, sparing the macular and nasal peripheral projection zones. The damage pattern is exactly what would be expected from the loss of ganglion cells in the upper and lower optic nerve (from the arcuate retina) and supports the relevance of anterograde transport decrease to glaucomatous damage.

Among the possible explanations for our findings and those of others, it is most likely that larger ganglion cells are selectively susceptible to injury. Morgan seems to suggest that other possibilities have not been considered. This is far from the case, as can be seen from reading the discussion sections of our work.

Our group and others continue to study the details of glaucoma damage to ganglion cells, particularly effects on the many cells that are not M cells. M cells are thought to comprise only 10% of all primate ganglion cells. If glaucoma causes loss of one third or one half of the optic nerve, the clinical findings are still mild. But, many of the cells that are dead at this stage must be non-M types. We have recently reported central ganglion cell damage in glaucoma that may be relevant to blue-yellow sensitivity loss.

As to the implications of larger ganglion cell loss for

psychophysical testing in glaucoma, there are other data from a number of laboratories which suggest that this may be a fruitful area of research, including tests of temporal contrast, motion, and scotopic sensitivity. This has been reviewed separately in the context of determining the relevance of the histological findings for psychophysical testing in glaucoma.¹

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Commentary

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