Published in final edited form as:

J Glaucoma. 2008 ; 17(4): 318–328. doi:10.1097/IJG.0b013e31815a343b.

Premise and Prediction – How Optic Nerve Head Biomechanics Underlies the Susceptibility and Clinical Behavior of the Aged Optic Nerve Head

Claude F. Burgoyne, MD^{1,3} and J. Crawford Downs, PhD^{2,3}

¹Optic Nerve Head Research Laboratory, Discoveries in Sight Research Laboratories, Devers Eye Institute, Legacy Health System, Portland, Oregon

²Ocular Biomechanics Laboratory, Discoveries in Sight Research Laboratories, Devers Eye Institute, Legacy Health System, Portland, Oregon

³Department of Biomedical Engineering, Tulane University, New Orleans, Louisiana

Abstract

We propose that age-related alterations in optic nerve head (ONH) biomechanics underlie the clinical behavior and increased susceptibility of the aged ONH to glaucomatous damage. The literature which suggests that the aged ONH is more susceptible to glaucomatous damage at all levels of intraocular pressure is reviewed. The relevant biomechanics of the aged ONH are discussed and a biomechanical explanation for why, on average, the stiffened peripapillary scleral and lamina cribrosa connective tissues of the aged eye should lead to a shallow (senile sclerotic) form of cupping is proposed. A logic for why age-related axon loss and the optic neuropathy of glaucoma in the aged eye may overlap is discussed. Finally, we argue for a need to characterize all forms of clinical cupping into prelaminar and laminar components so as to add precision to the discussion of clinical cupping which does not currently exist. Such characterization may lead to the early detection of ONH axonal and connective tissue pathology in ocular hypertension and eventually aid in the assessment of etiology in all forms of optic neuropathy including those that may be purely age-related.

The Susceptibility of the Aged Optic Nerve Head (ONH)

A variety of data suggest that the ONH becomes more susceptible to progressive glaucomatous damage as it ages, though this concept remains unproven through direct experimentation, and may not be true for every aged eye. These data can be summarized as follows. First, in most¹⁻⁵, but not all^{6, 7}, population based studies, intraocular pressure (IOP) either does not increase with age or if it does, the magnitude of increase is not likely to be clinically important. Thus, the fact that the prevalence of the neuropathy increases with age⁸ is likely explained by a greater susceptibility to IOP and other non-IOP-related risk factors, rather than a higher prevalence of IOP elevation, with increasing age. Second, in an extensive review of the literature, we can find only a few reports of the onset and progression of normal tension glaucoma (NTG) in infants, children and young adults⁹. While we acknowledge that accurate NTG prevalence estimates require long-term telemetric characterization of untreated IOP and rigorous population based ONH and visual field examinations, all existing studies suggest that NTG is most commonly a disease of the elderly¹⁰⁻¹⁵ and by most measures exists only rarely

Name and Address for correspondence: Claude F. Burgoyne, MD, Optic Nerve Head Research Laboratory, Discoveries in Sight Research Laboratories, Devers Eye Institute, 1225 NE 2nd Ave, Portland, OR 97232, Tel: 503-413-5441, Fax: 503-413-5179, Email cfburgoyne@deverseye.org.

in the young⁹. Third, age is an independent risk factor for both the prevalence¹⁶ and progression of the neuropathy at all stages of damage¹⁷⁻¹⁹.

The Clinical Behavior of the Aged ONH

Apart from the issue of ONH susceptibility, we predict that if all aspects of insult are equal (alterations in IOP, the volume flow of blood and nutrient transfer from the laminar capillary to the ONH astrocyte are all of the same magnitude, duration and fluctuation), the aged eye will demonstrate clinical cupping that is on average shallow and pale (at all stages of field loss) compared to the eye of a child or young adult. This clinical behaviour in its most recognizable form is described as senile sclerotic cupping²⁰⁻²⁶. In the sections that follow we propose an overlap between the optic neuropathy of aging and the optic neuropathy of glaucoma in the aged eye and a biomechanical explanation for why the aged eye should demonstrate a shallow form of clinical cupping in which pallor more than deformation predominates.

The Optic Nerve Head (ONH)

While glaucomatous damage to the visual system likely includes important pathophysiologies within the retinal ganglion cell (RGC) body²⁷⁻³², photoreceptors³³⁻³⁷, lateral geniculate body³⁸⁻⁴⁰ and visual cortex⁴⁰, strong evidence suggests that damage to the retinal ganglion cell axons within the lamina cribrosa of the ONH⁴¹⁻⁴⁶ is the central pathophysiology underlying glaucomatous vision loss. Recent studies in the monkey⁴⁵⁻⁵⁰ and rat⁵¹⁻⁵³ support the importance of the ONH, by describing profound alterations within the prelaminar, laminar and peripapillary scleral tissues of the ONH at the earliest detectable stage of experimental glaucoma.

The ONH tissues make up a dynamic environment wherein 1.2 to 2.0 million retinal ganglion cell axons converge, turn, and exit the eye through the inner (Bruch's Membrane opening) and outer (scleral) portions of the neural canal (Figure 1). Within the scleral portion of the canal, the bundled axons pass, through a 3-dimensional (3D) meshwork of astrocyte-covered, capillary containing, connective tissue beams known as the lamina cribrosa (Figure 1). Within the lamina, axonal nutrition is dependant upon the movement of oxygen and nutrients from the laminar capillaries, through the laminar beam extracellular matrix, across the astrocyte basement membrane into the astrocyte, finally reaching the peripheral and central axons of each bundle, via cell processes⁵⁴.

The connective tissue beams of the lamina cribrosa are anchored via the neural canal wall to a circumferential ring of collagen and elastin fibers within the peripapillary sclera⁵⁵⁻⁵⁷ and are presumed to bear the forces generated by IOP (Figure 1). However, while IOP⁵⁸⁻⁶¹ has been shown to play a causative role in glaucomatous ONH damage at all levels of IOP, no agreement exists on the effects of IOP within the tissues of the ONH, no data exist that would allow one to predict a safe level of IOP for a given ONH, and there are no accepted explanations for the varied clinical manifestations of glaucomatous damage²⁶, glaucomatous cupping and glaucomatous visual field loss.

ONH Biomechanics

We propose that ONH biomechanics provides a framework for explaining how IOP-related stress (force/cross-sectional area of the tissue experiencing that force) and strain (a measure of local deformation of a tissue induced by applied stress) within the load-bearing tissues of the ONH influence the physiology and pathophysiology of all three ONH tissue types. These include: 1) the connective tissues (load-bearing connective tissues of the peripapillary sclera, scleral canal wall, and lamina cribrosa), 2) the neural tissues (retinal ganglion cell axons), and 3) the cells which exist alone or in contact with both 1 and 2 (astrocytes, glial cells, endothelial

cells, and pericytes and their basement membranes)⁶²⁻⁶⁴. ONH biomechanics, so defined, is simply the engineering of these tissues and, in our view, is the likely link by which non-IOP-related risk factors such as ischemia, inflammation, autoimmunity, astrocyte and glial molecular biology are influenced by or interact with the effects of IOP. ONH Biomechanics attempts to combine these factors with laminar and peripapillary scleral connective tissue geometry and material properties (strength, stiffness, structural rigidity, compliance and nutrient diffusion properties) to explain the physiology of normal ONH aging, ONH susceptibility to IOP, and the clinical manifestation of all forms of optic neuropathy. These are, at present, ideas which are the focus of active experimentation and have been described in greater detail in a previous report⁶⁴.

ONH Biomechanics and ONH Susceptibility (Figure 2)

The principal ocular determinants of ONH susceptibility to a given level of IOP are likely to be: 1) the level of IOP (both the magnitude and variation (potentially) over the period of exposure); 2) the geometry and material properties of the ONH and peripapillary scleral connective tissues; 3) the volume flow and perfusion pressure of blood within the laminar capillaries; 4) nutrient diffusion to the astrocyte for a given level of blood volume and pressure; 5) the molecular response of astrocytes and glia to physical strain within their basement membrane (BM) and the presence of physiologic stress within their micro-environment (Figure 2); and 6) RGC factors that make its axon more susceptible to damage within the ONH, or its stroma more susceptible to apoptosis in response to axonal distress. As can be inferred from the above description, systemic processes influence ONH susceptibility by having direct or indirect effects on these ocular determinants.

ONH Biomechanics and ONH Cupping

“Cupping” is a clinical term used to describe enlargement of the ONH cup in all forms of optic neuropathy⁶⁵⁻⁷². However, “cupping” is also used as a synonym for the pathophysiology of glaucomatous damage to the ONH^{44, 73-75}. Because the clinical and pathophysiologic contexts for “cupping” are seldom clarified there is a confusing literature regarding the presence, importance and meaning of “cupping” in a variety of optic neuropathies^{21, 76-89}.

We have previously proposed⁵⁰ that all optic neuropathies, regardless of the location and etiology of the primary insult to the visual system can demonstrate clinical cupping, and that all forms of clinical cupping have two principal pathophysiologic components - “prelaminar thinning” and “laminar deformation” (Figure 3). “Prelaminar thinning” is that portion of cup enlargement that results from net thinning of the prelaminar tissues due to physical compression and/or loss of RGC axons even in the presence of gliosis⁹⁰⁻⁹³. In this paradigm, prelaminar thinning results in a clinically shallow form of cupping^{94, 95} (being limited to the prelaminar tissues) that occurs in all forms of RGC axon loss (including aging) and is therefore non-specific.

“Laminar deformation” is that portion of cup enlargement that results from lamina cribrosa and peripapillary scleral connective tissue damage followed by permanent, IOP-induced deformation^{45, 46, 48, 49, 64}. Laminar deformation results in a clinically deeper form of cupping that occurs only in those optic neuropathies in which the ONH connective tissues have been damaged and have become susceptible to permanent, IOP-induced deformation. Whether the ONH connective tissues are primarily damaged by IOP or some other insult (ischemic, autoimmune, inflammatory, secondary astrocyte activation, or genetic predisposition⁶⁴) (Figure 5), if they deform, they do so under the effects of IOP (whether it is normal or elevated) in a predictable way and this deformation underlies “laminar” or “deep” or “glaucomatous” cupping (Figures 3 and 4). The previous sentence contains two important ideas. First, it is possible for the ONH to be primarily damaged by non-IOP-related processes and end up

looking and behaving in a manner we comfortably call “glaucomatous”. Second, even in this setting, IOP-related connective tissue stress and strain (at whatever level) still drive the processes that cause the damaged tissues to deform.

Thus “deep”, “laminar” or “glaucomatous” cupping are terms referring to the physical manifestation of ONH connective tissue damage: i.e. posterior deformation and excavation. It can only occur when IOP-related connective tissue stress and strain are actively involved (as either a 1° or 2° process) (Figure 4). Hayreh, et al^{96, 97} has argued that primary ischemia to the retrolaminar optic nerve could cause a fibrotic response that pulls the lamina posteriorly into a form that is indistinguishable from glaucomatous cupping. However, we see no evidence for this in early experimental glaucoma monkeys (16 – 30% axon loss) that demonstrate profound posterior deformation of the lamina and expansion of the scleral portion of the neural canal^{45, 46, 48-50}. These deformations occur after four to eight weeks of minimal to moderate IOP elevations. The retrolaminar septal connective tissues in these eyes, once quantified, may demonstrate an overall increase in volume. However, we believe this phenomenon, if present, occurs in response to RGC axonal loss and/or the redistribution of laminar load to the retrolaminar septa and pia. Understood as such, it is a response to, rather than a cause of, laminar, peripapillary scleral and scleral canal wall deformation.

Central tenets of structural engineering hold that the distribution of stress within any load-bearing structure is predictable based on its geometry and material properties. The structure will deform (generating strain within its constituent parts) according to its constituent material properties and the structure will mechanically yield (stretch beyond its elastic limit) and/or mechanically fail (pull apart) in a predictable manner based on this distribution of strain.

We have proposed that in “laminar” cupping, (Figures 3 and 4), individual connective tissue trabeculae of the anterior lamina cribrosa yield and then mechanically fail, thus transferring the force they were resisting to the immediately adjacent trabeculae, which increases their load for the same level of IOP. Thus, even under a constant level of IOP, the adjacent laminar trabeculae progressively yield and/or fail as the IOP-induced load is spread over a continually decreasing cross-sectional area of connective tissue. While new findings in early experimental glaucoma suggest that the lamina both deforms (yields) and thickens^{49, 98} in response to initial damage (Figure 6), we believe that the final pathway to profound deformation and excavation illustrated in Figure 4^{99, 100} still holds.

ONH Biomechanics, ONH Aging and Age-related Optic Nerve Axon Loss

Over a lifetime, the ONH connective tissues are exposed to substantial levels of IOP-related stress and strain at normal levels of IOP, which increase as IOP is elevated (Fig. 2)¹⁰¹⁻¹⁰⁵. Stresses and strains at a given level of IOP are physiologic or pathophysiologic depending upon the response of the tissues that experience them (Fig. 2). In this context, IOP is not so much “normal” as “physiologic” or “pathophysiologic” and what constitutes physiologic and pathophysiologic levels for IOP may change as they are influenced by associated systemic risks and aging.

Physiologic stress and strain induce a broad spectrum of changes in both the connective tissues and vasculature that are, over a lifetime, central to normal aging. While the concepts of age-related optic nerve axon loss^{53, 106-111} and an optic neuropathy of aging^{21, 68, 110, 112} remain controversial, we believe that the range of physiologic stress and strain within the ONH connective tissues experienced over a life-time are likely to be of central importance to both.

Pathophysiologic stress and strain induce pathologic changes in cell synthesis and tissue microarchitecture (Fig. 2) that exceed the effects of aging and underlie the two governing pathophysiologies in glaucoma: 1) mechanical yield and/or failure of the load-bearing

connective tissues of the ONH (Figures 3 and 4), and 2) progressive damage to the adjacent axons by a variety of mechanisms (Fig. 5).

The aged ONH is more likely to have stiff connective tissues¹¹³⁻¹²⁵ and a compromised blood supply^{126, 127}. However, age-related increases in laminar beam thickness^{114, 117, 119, 124, 128}, laminar astrocyte basement membrane thickness^{117, 128} and laminar extracellular matrix (ECM) hardening^{114, 117, 119, 128} should not only increase laminar beam stiffness, but should also diminish nutrient diffusion from the laminar capillaries through the laminar ECM, across the astrocyte BMs, and into the adjacent axons (Figure 1). Thus, for a given magnitude of IOP insult, the aged ONH should demonstrate: 1) less deformation due to the presence of a stiffer lamina and peripapillary sclera; and 2) more pallor for a given amount of deformation because a) the aged ONH may be more susceptible to axon loss and b) pallor precedes deformation in the aged eye, while deformation precedes (or supersedes) pallor in the young eye.

Connective Tissue Stiffness Underlies the Appearance and Behavior of the Aged ONH (Figure 5)

The clinical manifestation of glaucomatous damage at all ages should be variable depending upon ONH connective tissue stiffness^{21, 129}. Because aged connective tissues are most commonly stiffer than younger connective tissues¹¹³⁻¹²⁵, age should be a reasonable surrogate for ONH connective tissue stiffness. Stiffer ONH connective tissues lead to a shallower form of cupping in both the young and old patient²¹. While a stiff lamina will always be more resistant to deformation, in the aged patient the laminar trabeculae may also become brittle (i.e. deform less as stress increases, but fail at lower levels of strain). Thus, the aged lamina may be less likely to deform posteriorly due to its increased structural stiffness, but more susceptible to catastrophic failure (rather than yield).

Whether a stiff lamina is also a brittle lamina, and whether a stiff or brittle lamina is more or less prone to axon loss for a given form of IOP insult, are core issues in the study of ONH susceptibility that are separate from the issue of clinical appearance. These factors can be studied in aged versus very young monkeys exposed to identically stable or identically fluctuating, telemetrically-controlled IOP elevations. These studies and the devices necessary to carry them out are under development in our laboratories.

Implications for Clinical ONH Imaging in Glaucoma

At present, all forms of clinical imaging in glaucoma assess either the thickness of the peripapillary retinal nerve fiber layer or the surface architecture of the prelaminar neural tissues for glaucomatous damage or progression. Our concept of ONH Biomechanics and its proposed links to ONH Aging and ONH appearance suggest that new, “subsurface” targets for clinical ONH imaging are necessary to predict ONH susceptibility and detect early glaucomatous damage. Our concepts of ONH aging additionally suggest that these deeper imaging strategies will also be necessary to characterize the differences in the neuropathy with age.

Predicting ONH Susceptibility

There is currently no science to predict what level of IOP will be safe for a given optic nerve head in glaucoma. Several groups are building engineering models of the neural and connective tissue of the ONH, in some cases based on digital, histologic reconstructions of human and monkey tissues^{98, 102-105, 130-132}. The purpose of these models is to predict the engineering stress and strain within the neural and connective tissues of individual ONHs at varying levels of IOP. Eventually these histology-based models will characterize the most important determinants of neural and connective tissue susceptibility to given level of IOP, and in so

doing, drive clinical imaging to capture these same sub-surface features of ONH neural and connective tissue architecture.

ONH Biomechanics suggests that the following features will be of central importance: 1) the 3D geometry and material properties of the lamina cribrosa, scleral flange and peripapillary sclera¹⁰¹⁻¹⁰⁵; 2) the difference in material properties between the scleral flange and the lamina cribrosa^{133, 134}; 3) the flow of blood and transport of nutrients across the BMs and ECM of the laminar beams; 4) the volume flow of blood through the intra-scleral branches of the posterior ciliary arteries¹³⁵; 5) the presence of peripapillary scleral posterior bowing and the distance between the anterior-most point of the subarachnoid space and the vitreous cavity¹³⁶

Early Detection of Sub-surface Structural Change in Ocular Hypertension (Figure 6)

We recently published three reports⁴⁸⁻⁵⁰ which utilize high resolution, digital, 3D histomorphometry to describe the following changes in the neural and connective tissues of the monkey ONH at the onset of Confocal Scanning Laser Tomographic (CSLT)-detected optic nerve head surface change in early experimental glaucoma: 1) prelaminar neural tissue thickening, 2) lamina cribrosa thickening, 3) posterior deformation of the lamina, the scleral flange and the peripapillary sclera; and 4) expansion of the scleral portion of the neural canal beneath Bruch's Membrane opening. All of these "sub-surface" structural changes may eventually be detectable with high-resolution OCT, or other next-generation technologies for clinical imaging^{137, 138}.

If true in humans, these data suggest that all ocular hypertensive patients might one day be followed to detect an increase in prelaminar neural tissue volume or thickening of the lamina cribrosa which precedes significant visual field and peripapillary nerve fiber layer (NFL) loss. Our concepts of ONH aging additionally suggest that the ratio of "prelaminar" to "laminar" alterations at the onset of glaucomatous ONH damage may be different in young versus old (compliant versus stiff) human eyes (Figure 6). The clinical importance of this difference is that ONH surface change may reflect more axon loss in the aged than in the young ONH. If true, visual field loss may precede clinically detectable ONH surface change more commonly in the aged (stiff) ONH.

Finally, beyond changes that are early in the neuropathy, clinical characterization of all stages of clinical cupping into laminar and prelaminar components⁵⁰ should provide quantitative definitions for common clinical descriptions such as "shallow", "deep", "senile sclerotic", "thinned", "tilted" and "excavated".

Summary

We propose that age-related alterations in ONH Biomechanics underlie the clinical behavior and likely increased susceptibility of the aged ONH. We further propose that the tools that are being developed to study ONH biomechanics will one day drive the outcome variables of a new generation of clinical ONH imaging. These new imaging techniques will be designed to gather the information necessary to model the ONH neural and connective tissues so as to determine individual ONH susceptibility to IOP. In so doing, a secondary benefit will be sub-surface structural change detection within the prelaminar and laminar tissues that may precede surface structural and functional change in ocular hypertension. A third benefit will be the clinical characterization of all forms of clinical cupping into prelaminar and laminar components. Such quantitative characterizations will add a precision to the discussion of clinical cupping which does not currently exist, and eventually aid in the assessment of etiology in all forms of optic neuropathy including those that may be age-related⁵⁰.

Acknowledgments

Supported in part by USPHS grant R01EY011610 (CFB) from the National Eye Institute, National Institutes of Health, Bethesda, Maryland; a grant from the American Health Assistance Foundation, Rockville, Maryland (CFB); a grant from The Whitaker Foundation, Arlington, Virginia (CFB); a Career Development Award (CFB) from Research to Prevent Blindness, Inc., New York, New York and unrestricted support from The Sears Trust, Mexico MO.

Literature Cited

1. Rohtchina E, Mitchell P, Wang JJ. Relationship between age and intraocular pressure: the Blue Mountains Eye Study. *Clin Experiment Ophthalmol* 2002;30:173–175. [PubMed: 12010208]
2. Nomura H, Ando F, Niino N, et al. The relationship between age and intraocular pressure in a Japanese population: the influence of central corneal thickness. *Curr Eye Res* 2002;24:81–85. [PubMed: 12187477]
3. Nomura H, Shimokata H, Ando F, et al. Age-related changes in intraocular pressure in a large Japanese population: a cross-sectional and longitudinal study. *Ophthalmology* 1999;106:2016–2022. [PubMed: 10519601]
4. Klein BE, Klein R, Linton KL. Intraocular pressure in an American community. The Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci* 1992;33:2224–2228. [PubMed: 1607232]
5. Weih LM, Mukesh BN, McCarty CA, et al. Association of demographic, familial, medical, and ocular factors with intraocular pressure. *Arch Ophthalmol* 2001;119:875–880. [PubMed: 11405839]
6. Leske MC, Connell AM, Wu SY, et al. Distribution of intraocular pressure. The Barbados Eye Study. *Arch Ophthalmol* 1997;115:1051–1057. [PubMed: 9258228]
7. Wu SY, Leske MC. Associations with intraocular pressure in the Barbados Eye Study. *Arch Ophthalmol* 1997;115:1572–1576. [PubMed: 9400792]
8. Suzuki Y, Iwase A, Araie M, et al. Risk factors for open-angle glaucoma in a Japanese population: the Tajimi Study. *Ophthalmology* 2006;113:1613–1617. [PubMed: 16828504]
9. Geijssens, HC. Studies on Normal pressure Glaucoma. Amstelveen: Kugler; 1991.
10. Drance SM, Sweeney VP, Morgan RW, et al. Studies of factors involved in the production of low tension glaucoma. *Arch Ophthalmol* 1973;89:457–465. [PubMed: 4706442]
11. Levene RZ. Low tension glaucoma: a critical review and new material. *Surv Ophthalmol* 1980;24:621–664. [PubMed: 7414505]
12. Chumbley LC, Brubaker RF. Low-tension glaucoma. *Am J Ophthalmol* 1976;81:761–767. [PubMed: 937430]
13. Goldberg I, Hollows FC, Kass MA, et al. Systemic factors in patients with low-tension glaucoma. *Br J Ophthalmol* 1981;65:56–62. [PubMed: 7448157]
14. Klein BE, Klein R, Sponsel WE, et al. Prevalence of glaucoma. The Beaver Dam Eye Study. *Ophthalmology* 1992;99:1499–1504. [PubMed: 1454314]
15. Shiose, Y. Prevalence and clinical aspects of low-tension glaucoma. Philadelphia: Lippincott; 1983.
16. Tielsch JM, Sommer A, Katz J, et al. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey [see comments]. *Jama* 1991;266:369–374. [PubMed: 2056646]
17. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:714–720. [PubMed: 12049575]discussion 829-730
18. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology* 2004;111:1627–1635. [PubMed: 15350314]
19. Heijl A, Leske MC, Bengtsson B, et al. Measuring visual field progression in the Early Manifest Glaucoma Trial. *Acta Ophthalmol Scand* 2003;81:286–293. [PubMed: 12780410]
20. Broadway DC, Nicolela MT, Drance SM. Optic disk appearances in primary open-angle glaucoma. *Surv Ophthalmol* 1999;43:S223–243. [PubMed: 10416767]
21. Jonas JB, Grundler A. Optic disc morphology in “age-related atrophic glaucoma”. *Graefes Arch Clin Exp Ophthalmol* 1996;234:744–749. [PubMed: 8986446]

22. Nicolela MT, Drance SM, Broadway DC, et al. Agreement among clinicians in the recognition of patterns of optic disk damage in glaucoma. *Am J Ophthalmol* 2001;132:836–844. [PubMed: 11730646]
23. Nicolela MT, McCormick TA, Drance SM, et al. Visual field and optic disc progression in patients with different types of optic disc damage: a longitudinal prospective study. *Ophthalmology* 2003;110:2178–2184. [PubMed: 14597527]
24. May CA. The optic nerve head region of the aged rat: an immunohistochemical investigation. *Curr Eye Res* 2003;26:347–354. [PubMed: 12868015]
25. Nicolela MT, Walman BE, Buckley AR, et al. Various glaucomatous optic nerve appearances. A color Doppler imaging study of retrobulbar circulation. *Ophthalmology* 1996;103:1670–1679. [PubMed: 8874441]
26. Nicolela MT, Drance SM. Various glaucomatous optic nerve appearances: clinical correlations. *Ophthalmology* 1996;103:640–649. [PubMed: 8618765]
27. Asai T, Katsumori N, Mizokami K. Retinal ganglion cell damage in human glaucoma. 2. Studies on damage pattern. *Nippon Ganka Gakkai Zasshi* 1987;91:1204–1213. [PubMed: 3448905]
28. Garcia-Valenzuela E, Shareef S, Walsh J, et al. Programmed cell death of retinal ganglion cells during experimental glaucoma. *Exp Eye Res* 1995;61:33–44. [PubMed: 7556468]
29. Quigley HA, Nickells RW, Kerrigan LA, et al. Retinal ganglion cell death in experimental glaucoma and after axotomy occurs by apoptosis. *Invest Ophthalmol Vis Sci* 1995;36:774–786. [PubMed: 7706025]
30. Weber AJ, Kaufman PL, Hubbard WC. Morphology of single ganglion cells in the glaucomatous primate retina. *Invest Ophthalmol Vis Sci* 1998;39:2304–2320. [PubMed: 9804139]
31. Quigley HA, McKinnon SJ, Zack DJ, et al. Retrograde axonal transport of BDNF in retinal ganglion cells is blocked by acute IOP elevation in rats. *Invest Ophthalmol Vis Sci* 2000;41:3460–3466. [PubMed: 11006239]
32. Quigley HA. Ganglion cell death in glaucoma: pathology recapitulates ontogeny. *Aust N Z J Ophthalmol* 1995;23:85–91. [PubMed: 7546696]
33. Wygnanski T, Desatnik H, Quigley HA, et al. Comparison of ganglion cell loss and cone loss in experimental glaucoma. *Am J Ophthalmol* 1995;120:184–189. [PubMed: 7639302]
34. Panda S, Jonas JB. Decreased photoreceptor count in human eyes with secondary angle-closure glaucoma. *Invest Ophthalmol Vis Sci* 1992;33:2532–2536. [PubMed: 1634350]
35. Kendell KR, Quigley HA, Kerrigan LA, et al. Primary open-angle glaucoma is not associated with photoreceptor loss. *Invest Ophthalmol Vis Sci* 1995;36:200–205. [PubMed: 7822147]
36. Nork TM, Ver Hoeve JN, Poulsen GL, et al. Swelling and loss of photoreceptors in chronic human and experimental glaucomas. *Arch Ophthalmol* 2000;118:235–245. [PubMed: 10676789]
37. Janssen P, Naskar R, Moore S, et al. Evidence for glaucoma-induced horizontal cell alterations in the human retina. *Ger J Ophthalmol* 1996;5:378–385. [PubMed: 9479522]
38. Yucel YH, Zhang Q, Gupta N, et al. Loss of neurons in magnocellular and parvocellular layers of the lateral geniculate nucleus in glaucoma. *Arch Ophthalmol* 2000;118:378–384. [PubMed: 10721961]
39. Yucel YH, Zhang Q, Weinreb RN, et al. Atrophy of relay neurons in magno- and parvocellular layers in the lateral geniculate nucleus in experimental glaucoma. *Invest Ophthalmol Vis Sci* 2001;42:3216–3222. [PubMed: 11726625]
40. Yucel YH, Zhang Q, Weinreb RN, et al. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. *Prog Retin Eye Res* 2003;22:465–481. [PubMed: 12742392]
41. Gaasterland D, Tanishima T, Kuwabara T. Axoplasmic flow during chronic experimental glaucoma. 1. Light and electron microscopic studies of the monkey optic nervehead during development of glaucomatous cupping. *Invest Ophthalmol Vis Sci* 1978;17:838–846. [PubMed: 81192]
42. Minckler DS, Bunt AH, Johanson GW. Orthograde and retrograde axoplasmic transport during acute ocular hypertension in the monkey. *Invest Ophthalmol Vis Sci* 1977;16:426–441. [PubMed: 67096]
43. Quigley HA, Addicks EM, Green WR, et al. Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. *Arch Ophthalmol* 1981;99:635–649. [PubMed: 6164357]

44. Quigley HA, Green WR. The histology of human glaucoma cupping and optic nerve damage: clinicopathologic correlation in 21 eyes. *Ophthalmology* 1979;86:1803–1830. [PubMed: 553256]
45. Bellezza AJ, Rintalan CJ, Thompson HW, et al. Deformation of the lamina cribrosa and anterior scleral canal wall in early experimental glaucoma. *Invest Ophthalmol Vis Sci* 2003;44:623–637. [PubMed: 12556392]
46. Burgoyne CF, Downs JC, Bellezza AJ, et al. Three-dimensional reconstruction of normal and early glaucoma monkey optic nerve head connective tissues. *Invest Ophthalmol Vis Sci* 2004;45:4388–4399. [PubMed: 15557447]
47. Downs JC, Suh JK, Thomas KA, et al. Viscoelastic material properties of the peripapillary sclera in normal and early-glaucoma monkey eyes. *Invest Ophthalmol Vis Sci* 2005;46:540–546. [PubMed: 15671280]
48. Downs JC, Yang H, Girkin C, et al. Three Dimensional Histomorphometry of the Normal and Early Glaucomatous Monkey Optic Nerve Head: Neural Canal and Subarachnoid Space Architecture. *Invest Ophthalmol Vis Sci* 2007;48:3195–3208. [PubMed: 17591889]
49. Yang H, Downs JC, Girkin C, et al. 3-D Histomorphometry of the Normal and Early Glaucomatous Monkey Optic Nerve Head: Lamina Cribrosa and Peripapillary Scleral Position and Thickness. *Invest Ophthalmol Vis Sci* 2007;48:4597–4607. [PubMed: 17898283]
50. Yang H, Downs JC, Bellezza AJ, et al. 3-D Histomorphometry of the Normal and Early Glaucomatous Monkey Optic Nerve Head: Prelaminar Neural Tissues and Cupping. *Invest Ophthalmol Vis Sci* 2007;48:5068–5084. [PubMed: 17962459]
51. Johnson EC, Morrison JC, Farrell S, et al. The effect of chronically elevated intraocular pressure on the rat optic nerve head extracellular matrix. *Exp Eye Res* 1996;62:663–674. [PubMed: 8983948]
52. Johnson EC, Deppmeier LM, Wentzien SK, et al. Chronology of optic nerve head and retinal responses to elevated intraocular pressure. *Invest Ophthalmol Vis Sci* 2000;41:431–442. [PubMed: 10670473]
53. Cepurna WO, Kayton RJ, Johnson EC, et al. Age related optic nerve axonal loss in adult Brown Norway rats. *Exp Eye Res* 2005;80:877–884. [PubMed: 15939045]
54. Anderson DR. Ultrastructure of human and monkey lamina cribrosa and optic nerve head. *Arch Ophthalmol* 1969;82:800–814. [PubMed: 4982225]
55. Morrison J, L'Hernault N, Jerdan J, et al. Ultrastructural localization of extracellular matrix components in the monkey optic nerve head. *Uvest Iogtgaknik Vus Scu* 1988;29:353.
56. Quigley HA, Dorman-Pease ME, Brown AE. Quantitative study of collagen and elastin of the optic nerve head and sclera in human and experimental monkey glaucoma. *Curr Eye Res* 1991;10:877–888. [PubMed: 1790718]
57. Hernandez MR. Ultrastructural immunocytochemical analysis of elastin in the human lamina cribrosa. Changes in elastic fibers in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 1992;33:2891–2903. [PubMed: 1526740]
58. Investigators TA. The advanced glaucoma intervention study (AGIS): 7. the relationship between control of intraocular pressure and visual field deterioration [In Process Citation]. *Am J Ophthalmol* 2000;130:429–440. [PubMed: 11024415]
59. Kass MA, Heuer DK, Higginbotham EJM, et al. The Ocular Hypertension Treatment Study (A Randomized Trial Determines that Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open-Angle Glaucoma). *Arch Ophthalmol* 2002;120:701–713. [PubMed: 12049574]
60. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003;121:48–56. [PubMed: 12523884]
61. Anderson DR, Drance SM, Schulzer M. Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. *Am J Ophthalmol* 2003;136:820–829. [PubMed: 14597032]
62. Fechtner RD, Weinreb RN. Mechanisms of optic nerve damage in primary open angle glaucoma. *Surv Ophthalmol* 1994;39:23–42. [PubMed: 7974188]
63. Burgoyne CF, Morrison JC. The Anatomy and Pathophysiology of the Optic Nerve Head in Glaucoma. *J Glaucoma* 2001;10:S16–S18. [PubMed: 11890263]
64. Burgoyne CF, Downs JC, Bellezza AJ, et al. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. *Prog Retin Eye Res* 2005;24:39–73. [PubMed: 15555526]

65. Pederson JE, Anderson DR. The mode of progressive disc cupping in ocular hypertension and glaucoma. *Arch Ophthalmol* 1980;98:490–495. [PubMed: 7362506]
66. Pederson JE, Gaasterland DE. Laser-induced primate glaucoma. I. Progression of cupping. *Arch Ophthalmol* 1984;102:1689–1692. [PubMed: 6541902]
67. Johns KJ, Leonard-Martin T, Feman SS. The effect of panretinal photocoagulation on optic nerve cupping. *Ophthalmology* 1989;96:211–216. [PubMed: 2704541]
68. Klein BE, Klein R, Lee KE, et al. Does the intraocular pressure effect on optic disc cupping differ by age? *Trans Am Ophthalmol Soc* 2006;104:143–148. [PubMed: 17471334]
69. Sponsel WE, Shoemaker J, Trigo Y, et al. Frequency of sustained glaucomatous-type visual field loss and associated optic nerve cupping in Beaver Dam, Wisconsin. *Clin Experiment Ophthalmol* 2001;29:352–358. [PubMed: 11778803]
70. Greenfield DS, Siatkowski RM, Glaser JS, et al. The cupped disc. Who needs neuroimaging? *Ophthalmology* 1998;105:1866–1874. [PubMed: 9787356]
71. Bianchi-Marzoli S, Rizzo JF 3rd, Brancato R, et al. Quantitative analysis of optic disc cupping in compressive optic neuropathy. *Ophthalmology* 1995;102:436–440. [PubMed: 7891982]
72. Schwartz JT, Reuling FH, Garrison RJ. Acquired cupping of the optic nerve head in normotensive eyes. *Br J Ophthalmol* 1975;59:216–222. [PubMed: 1138847]
73. Kalvin NH, Hamasaki DI, Gass JD. Experimental glaucoma in monkeys. I. Relationship between intraocular pressure and cupping of the optic disc and cavernous atrophy of the optic nerve. *Arch Ophthalmol* 1966;76:82–93. [PubMed: 4957379]
74. Vrabec F. Glaucomatous cupping of the human optic disk: a neuro-histologic study. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1976;198:223–234. [PubMed: 1083166]
75. Anderson DR, Cynader MS. Glaucomatous optic nerve cupping as an optic neuropathy. *Clin Neurosci* 1997;4:274–278. [PubMed: 9292255]
76. Quigley H, Anderson DR. Cupping of the optic disc in ischemic optic neuropathy. *Trans Am Acad Ophthalmol Otolaryngol* 1977;83:755–762.
77. Trobe JD, Glaser JS, Cassady J, et al. Nonglaucomatous excavation of the optic disc. *Arch Ophthalmol* 1980;98:1046–1050. [PubMed: 7387507]
78. Hayreh SS, Jonas JB. Optic disc morphology after arteritic anterior ischemic optic neuropathy. *Ophthalmology* 2001;108:1586–1594. [PubMed: 11535455]
79. Hall ER, Klein BE, Knudtson MD, et al. Age-related macular degeneration and optic disk cupping: the Beaver Dam Eye Study. *Am J Ophthalmol* 2006;141:494–497. [PubMed: 16490495]
80. Piette SD, Sergott RC. Pathological optic-disc cupping. *Curr Opin Ophthalmol* 2006;17:1–6. [PubMed: 16436917]
81. Alward WL. Macular degeneration and glaucoma-like optic nerve head cupping. *Am J Ophthalmol* 2004;138:135–136. [PubMed: 15234293]
82. Danesh-Meyer HV, Savino PJ, Sergott RC. The prevalence of cupping in end-stage arteritic and nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2001;108:593–598. [PubMed: 11237915]
83. Ambati BK, Rizzo JF 3rd. Nonglaucomatous cupping of the optic disc. *Int Ophthalmol Clin* 2001;41:139–149. [PubMed: 11198141]
84. Greenfield DS. Glaucomatous versus nonglaucomatous optic disc cupping: clinical differentiation. *Semin Ophthalmol* 1999;14:95–108. [PubMed: 10758217]
85. Sharma M, Volpe NJ, Dreyer EB. Methanol-induced optic nerve cupping. *Arch Ophthalmol* 1999;117:286. [PubMed: 10037587]
86. Manor RS. Documented optic disc cupping in compressive optic neuropathy. *Ophthalmology* 1995;102:1577–1578. [PubMed: 9098243]
87. Orgul S, Gass A, Flammer J. Optic disc cupping in arteritic anterior ischemic optic neuropathy. *Ophthalmologica* 1994;208:336–338. [PubMed: 7845652]
88. Sonty S, Schwartz B. Development of cupping and pallor in posterior ischemic optic neuropathy. *Int Ophthalmol* 1983;6:213–220. [PubMed: 6885256]
89. Votruba M, Thiselton D, Bhattacharya SS. Optic disc morphology of patients with OPA1 autosomal dominant optic atrophy. *Br J Ophthalmol* 2003;87:48–53. [PubMed: 12488262]

90. Quigley HA, Addicks EM. Chronic experimental glaucoma in primates. II. Effect of extended intraocular pressure elevation on optic nerve head and axonal transport. *Invest Ophthalmol Vis Sci* 1980;19:137–152. [PubMed: 6153173]
91. Hernandez MR. The optic nerve head in glaucoma: role of astrocytes in tissue remodeling. *Prog Retin Eye Res* 2000;19:297–321. [PubMed: 10749379]
92. Agapova OA, Kaufman PL, Lucarelli MJ, et al. Differential expression of matrix metalloproteinases in monkey eyes with experimental glaucoma or optic nerve transection. *Brain Res* 2003;967:132–143. [PubMed: 12650974]
93. Johnson EC, Jia L, Cepurna WO, et al. Global Changes in Optic Nerve Head Gene Expression after Exposure to Elevated Intraocular Pressure in a Rat Glaucoma Model. *Invest Ophthalmol Vis Sci* 2007;48:3161–3177. [PubMed: 17591886]
94. Jonas JB, Dichtl A. Optic disc morphology in myopic primary open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1997;235:627–633. [PubMed: 9349946]
95. Fernandez MC, Jonas JB, Naumann GO. Para-papillary chorioretinal atrophy in eyes with shallow glaucomatous optic disk cupping. *Fortschr Ophthalmol* 1990;87:457–460. [PubMed: 2272573]
96. Hayreh SS. Pathogenesis of cupping of the optic disc. *Br J Ophthalmol* 1974;58:863–876. [PubMed: 4375487]
97. Hayreh SS, Pe'er J, Zimmerman MB. Morphologic changes in chronic high-pressure experimental glaucoma in rhesus monkeys. *J Glaucoma* 1999;8:56–71. [PubMed: 10084276]
98. Roberts, MD.; Hart, RT.; Liang, Y., et al. Continuum-level finite element modeling of the optic nerve head using a fabric tensor based description of the lamina cribrosa. *ASME Summer Bioengineering Conference*; Keystone, CO: American Society of Mechanical Engineers; 2007.
99. Emery JM, Landis D, Paton D, et al. The lamina cribrosa in normal and glaucomatous human eyes. *Trans Am Acad Ophthalmol Otolaryngol* 1974;78:OP290–297. [PubMed: 4825057]
100. Quigley HA, Hohman RM, Addicks EM, et al. Morphologic changes in the lamina cribrosa correlated with neural loss in open-angle glaucoma. *Am J Ophthalmol* 1983;95:673–691. [PubMed: 6846459]
101. Greene PR. Mechanical considerations in myopia: relative effects of accommodation, convergence, intraocular pressure, and the extraocular muscles. *Am J Optom Physiol Opt* 1980;57:902–914. [PubMed: 7223834]
102. Bellezza AJ, Hart RT, Burgoyne CF. The optic nerve head as a biomechanical structure: initial finite element modeling. *Invest Ophthalmol Vis Sci* 2000;41:2991–3000. [PubMed: 10967056]
103. Sigal IA, Flanagan JG, Ethier CR. Factors influencing optic nerve head biomechanics. *Invest Ophthalmol Vis Sci* 2005;46:4189–4199. [PubMed: 16249498]
104. Sigal IA, Flanagan JG, Tertinegg I, et al. Reconstruction of human optic nerve heads for finite element modeling. *Technol Health Care* 2005;13:313–329. [PubMed: 16055979]
105. Sigal IA, Flanagan JG, Tertinegg I, et al. Finite element modeling of optic nerve head biomechanics. *Invest Ophthalmol Vis Sci* 2004;45:4378–4387. [PubMed: 15557446]
106. Repka MX, Quigley HA. The effect of age on normal human optic nerve fiber number and diameter. *Ophthalmology* 1989;96:26–32. [PubMed: 2919049]
107. Balazsi AG, Rootman J, Drance SM, et al. The effect of age on the nerve fiber population of the human optic nerve. *Am J Ophthalmol* 1984;97:760–766. [PubMed: 6731540]
108. Morrison JC, Cork LC, Dunkelberger GR, et al. Aging changes of the rhesus monkey optic nerve. *Invest Ophthalmol Vis Sci* 1990;31:1623–1627. [PubMed: 2387691]
109. Cull G, Cioffi GA, Dong J, et al. Estimating normal optic nerve axon numbers in non-human primate eyes. *J Glaucoma* 2003;12:301–306. [PubMed: 12897574]
110. Sandell JH, Peters A. Effects of age on the glial cells in the rhesus monkey optic nerve. *J Comp Neurol* 2002;445:13–28. [PubMed: 11891651]
111. Sandell JH, Peters A. Effects of age on nerve fibers in the rhesus monkey optic nerve. *J Comp Neurol* 2001;429:541–553. [PubMed: 11135234]
112. Frisen L. High-pass resolution perimetry and age-related loss of visual pathway neurons. *Acta Ophthalmol (Copenh)* 1991;69:511–515. [PubMed: 1750320]
113. Albon J, Purslow PP, Karwatowski WS, et al. Age related compliance of the lamina cribrosa in human eyes. *Br J Ophthalmol* 2000;84:318–323. [PubMed: 10684845]

114. Morrison JC, Jerdan JA, Dorman ME, et al. Structural proteins of the neonatal and adult lamina cribrosa. *Arch Ophthalmol* 1989;107:1220–1224. [PubMed: 2757553]
115. Pena JD, Roy S, Hernandez MR. Tropoelastin gene expression in optic nerve heads of normal and glaucomatous subjects. *Matrix Biol* 1996;15:323–330. [PubMed: 8981328]
116. Quigley HA. Childhood glaucoma: results with trabeculotomy and study of reversible cupping. *Ophthalmology* 1982;89:219–226. [PubMed: 7088505]
117. Hernandez MR, Luo XX, Andrzejewska W, et al. Age-related changes in the extracellular matrix of the human optic nerve head. *Am J Ophthalmol* 1989;107:476–484. [PubMed: 2653045]
118. Jeffery G, Evans A, Albon J, et al. The human optic nerve: fascicular organisation and connective tissue types along the extra-fascicular matrix. *Anat Embryol (Berl)* 1995;191:491–502. [PubMed: 7677257]
119. Albon J, Karwatowski WS, Easty DL, et al. Age related changes in the non-collagenous components of the extracellular matrix of the human lamina cribrosa. *Br J Ophthalmol* 2000;84:311–317. [PubMed: 10684844]
120. Bailey AJ, Paul RG, Knott L. Mechanisms of maturation and ageing of collagen. *Mech Ageing Dev* 1998;106:1–56. [PubMed: 9883973]
121. Brown CT, Vural M, Johnson M, et al. Age-related changes of scleral hydration and sulfated glycosaminoglycans. *Mech Ageing Dev* 1994;77:97–107. [PubMed: 7745995]
122. Albon J, Karwatowski WS, Avery N, et al. Changes in the collagenous matrix of the aging human lamina cribrosa. *Br J Ophthalmol* 1995;79:368–375. [PubMed: 7742286]
123. Friedenwald J. It is evident that an increasing rigidity of the ocular coats is characteristic of advancing age. *AJO* 1937;20:985–1024.
124. Kotecha A, Izadi S, Jeffrey G. Age related changes in the thickness of the human lamina cribrosa. *Br J Ophthalmol* 2006;90:1531–1534. [PubMed: 16943226]
125. Albon J, Farrant S, Akhtar S, et al. Connective Tissue Structure of the Tree Shrew Optic Nerve and Associated Ageing Changes. *Invest Ophthalmol Vis Sci* 2007;48:2134–2144. [PubMed: 17460272]
126. Grunwald JE, Piltz J, Patel N, et al. Effect of aging on retinal macular microcirculation: a blue field simulation study. *Invest Ophthalmol Vis Sci* 1993;34:3609–3613. [PubMed: 8258519]
127. Harris A, Harris M, Biller J, et al. Aging affects the retrobulbar circulation differently in women and men. *Arch Ophthalmol* 2000;118:1076–1080. [PubMed: 10922201]
128. Hernandez MR, Wang N, Hanley NM, et al. Localization of collagen types I and IV mRNAs in human optic nerve head by in situ hybridization. *Invest Ophthalmol Vis Sci* 1991;32:2169–2177. [PubMed: 2071331]
129. Jonas JB, Grundler A. Optic disc morphology in juvenile primary open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1996;234:750–754. [PubMed: 8986447]
130. Roberts MD, Burgoyne CF, Hart RT, et al. Continuum-Level Finite Element Modeling of the Optic Nerve Head: Influence of Microstructure on Biomechanics in Normal and Early Glaucoma Eyes. *Invest Ophthalmol Vis Sci*. 2007
131. Downs J, Roberts MD, Burgoyne CF, et al. Finite Element Modeling of the Lamina Cribrosa Microstructure in Normal and Early Glaucoma Monkey Eyes. *Invest Ophthalmol Vis Sci* 2007;48:3301. [PubMed: 17591902]
132. Downs, JC.; Roberts, MD.; Burgoyne, CF., et al. Finite Element Modeling of the Lamina Cribrosa Microarchitecture in the Normal and Early Glaucoma Monkey Optic Nerve Head. *ASME Summer Bioengineering Conference*; Keystone, CO: American Society of Mechanical Engineers; 2007.
133. Zeimer R. Could glaucoma damage be due to a viscoelastic mismatch between the sclera and the lamina cribrosa? *Journal of Japan Glaucoma Society* 1992;2:17–20.
134. Zeimer, R. Biomechanical Properties of the Optic Nerve Head. In: Drance, SM., editor. *Optic Nerve in Glaucoma*. Amsterdam/New York: Kugler Publications; 1995. p. 107-121.
135. Langham M. The temporal relation between intraocular pressure and loss of vision in chronic simple glaucoma. *Glaucoma* 1980;2:427–435.
136. Jonas JB, Berenshtein E, Holbach L. Lamina cribrosa thickness and spatial relationships between intraocular space and cerebrospinal fluid space in highly myopic eyes. *Invest Ophthalmol Vis Sci* 2004;45:2660–2665. [PubMed: 15277489]

137. Guo L, Tsatourian V, Luong V, et al. En face optical coherence tomography: a new method to analyse structural changes of the optic nerve head in rat glaucoma. *Br J Ophthalmol* 2005;89:1210–1216. [PubMed: 16113384]
138. Van Velthoven ME, Faber DJ, Verbraak FD, et al. Recent developments in optical coherence tomography for imaging the retina. *Prog Retin Eye Res* 2007;26:57–77. [PubMed: 17158086]
139. Cioffi, GA.; Van Buskirk, EM. Vasculature of the anterior optic nerve and peripapillary choroid. In: Ritch, R.; Shields, MB.; Krupin, T., editors. *The Glaucomas*. Mosby St. Louis: Basic Sciences; 1996. p. 177-197.
140. Quigley, HA. Overview and introduction to session on connective tissue of the optic nerve in glaucoma. In: Drance, SM.; Anderson, DR., editors. *Optic Nerve in Glaucoma*. Amsterdam/New York: Kugler Publications; 1995. p. 15-36. Chapter 2
141. Quigley HA, Brown AE, Morrison JD, et al. The size and shape of the optic disc in normal human eyes. *Arch Ophthalmol* 1990;108:51–57. [PubMed: 2297333]
142. Morrison JC, L'Hernault NL, Jerdan JA, et al. Ultrastructural location of extracellular matrix components in the optic nerve head. *Arch Ophthalmol* 1989;107:123–129. [PubMed: 2910271]

Figure 1. The Optic Nerve Head (ONH) is Centrally Influenced by IOP-related Stress and Strain

The ONH is made up of prelaminar, laminar and retrolaminar regions (A). Within the clinically visible surface of the Normal ONH (referred to as the optic disc) (B), central retinal vessels enter the eye and RGC axons appear pink due to their capillaries (which are principally supplied by branches from the posterior ciliary arteries (PCA) in (C)). The primary site of RGC axon insult in glaucoma is within the lamina cribrosa (schematically depicted with axon bundles in (D)), isolated by trypsin digest in a scanning electron micrograph in (E) and drawn with stippled extracellular matrix (ECM), central capillary (red) and surrounding astrocytes (yellow with basement membranes in black) (F). Blood flow within the ONH, while controlled by autoregulation, can be affected by non-IOP-related effects such as systemic blood pressure fluctuation and vasospasm within the retrobulbar portion of the PCAs. Additional IOP-induced effects may include compression of PCA branches within the peripapillary sclera (due to scleral stress and strain) and compression of laminar beam capillaries reducing laminar capillary volume flow (C and F)¹³⁵. There is no direct blood supply to the axons within the laminar region. Axonal nutrition within the lamina (F) requires diffusion of nutrients from the laminar capillaries, across the endothelial and pericyte basement membranes, through the ECM of the laminar beam, across the basement membranes of the astrocytes, into the astrocytes, and across their processes to the adjacent axons (vertical lines). Chronic age-related changes in the endothelial cell and astrocyte basement membranes, as well as IOP-induced changes in the laminar ECM and astrocyte basement membranes may diminish nutrient diffusion to the axons in the presence of a stable level of laminar capillary volume flow. The clinical manifestation of IOP-induced damage to the ONH is most commonly “deep cupping” (G) but in some eyes cupping can be shallower accompanied by pallor (H). Z-H = circle of Zinn-Haller; PCA= posterior ciliary arteries; NFL = nerve fiber layer; PLC = prelaminar region; LC = lamina cribrosa; RLC = retrolaminar region; ON = optic nerve; CRA = central retinal artery. (A) Reprinted with permission from *Arch Ophthalmol*⁵⁴; (C) reprinted with permission from *The Glaucomas*. St. Louis: Mosby; 1996:177–97¹³⁹; (D) reprinted with permission from *Optic Nerve in Glaucoma*. Amsterdam: Kugler Publications; 1995:15–36¹⁴⁰; (E) reprinted with permission from *Arch Ophthalmol*¹⁴¹; (F) reprinted with permission from *Arch Ophthalmol*¹⁴²

Figure 2. Whether, Over the Course of a Lifetime, an Eye Demonstrates the “Neuropathy of Aging” or the Neuropathy of Glaucoma Lies in ONH Susceptibility

For a given ONH, IOP generates low or high levels of stress depending upon the 3D architecture (geometry) of the ONH connective tissues (size and shape of the canal, thickness of the lamina and sclera) - (**Susceptibility 1**). Some ONHs will have relatively low stress at high IOP (d). Others will have high stress at low IOP (e). Whether a given level of IOP-related stress is physiologic or patho-physiologic depends upon the ONH's microenvironment (**Susceptibility 2**). Strong connective tissues, a robust blood supply and stable astrocytes and glia increase the chance of Normal ONH Aging (right – bottom). While the existence of a neuropathy of aging is controversial, the difference between “normal” age-related axon loss (if it is shown to exist) and the development of glaucomatous damage is a matter of ONH susceptibility. *Reprinted with permission from Burgoyne, et al⁶⁴.*

Figure 3. All Clinical Cupping, Regardless of Etiology, is a Manifestation of Underlying “Prelaminar” and “Laminar” Pathophysiologic Components

A. Normal ONH. To understand the two pathophysiologic components of clinical cupping, start with **(B)** a representative digital central horizontal section image from a post-mortem 3D reconstruction of this same eye (white section line in **(A)**) - vitreous top, orbital optic nerve bottom, lamina cribrosa between the sclera and internal limiting membrane (ILM) delineated with green dots. **(C)** The same section is delineated into principle surfaces and volumes (Black – ILM; purple - prelaminar neural and vascular tissue; cyan blue line – Bruch's Membrane Opening (BMO)-zero reference plane cut in section; green outline – Post-BMO Total Prelaminar area or a measure of the space below BMO and the anterior laminar surface). **(D)**

Regardless of the etiology, clinical cupping can be “shallow” (E) or “deep” (F) (these clinical photos are representative and are not of the eye in (A)). A prelaminar or “shallow” form of cupping (G, black arrows) is primarily due to loss (thinning) of prelaminar neural tissues without important laminar or ONH connective tissue involvement. Laminar or “deep” cupping (H, small white arrows depict expansion of the green shaded space) follows ONH connective tissue damage and deformation that manifests as expansion of the total area beneath BMO, but above the lamina. Notice in (H) that while a laminar component of cupping predominates (white arrows) there is a prelaminar component as well (black arrows). While prelaminar thinning is a manifestation of neural tissue damage alone, we propose that laminar deformation can only occur in the setting of ONH connective tissue damage followed by permanent (fixed) IOP-induced deformation. Reprinted with permission from Yang, et al.⁵⁰).

Figure 4. Our Central Hypothesis Regarding ONH Connective Tissue Damage In “Laminar” Cupping

“Deep”, “laminar” or “glaucomatous” cupping is a manifestation of ONH connective tissue damage which can be caused by either IOP-related or non-IOP related insults (See Figure 5). However, regardless of the primary insult to the ONH connective tissues, their deformation (if present) is driven by IOP-related connective tissue stress and strain. Thus the presence of ONH connective tissue deformation in any optic neuropathy is evidence that the level of IOP at which it occurred, (whether normal or elevated) is too high for the connective tissues in their present condition. (A) Schematic of normal laminar thickness (x) within the scleral canal with scleral tensile forces acting on the scleral canal wall. (B) Early IOP-related damage in the monkey

eye (Figure 6)⁴⁵⁻⁵⁰ includes posterior bowing of the lamina and peripapillary sclera accompanied by neural canal expansion (mostly within the posterior (outer) scleral portion) and thickening (not thinning) of the lamina (y). In our studies to date this appears to represent mechanical yield (permanent stretching) rather than mechanical failure (physical disruption) of the laminar beams (C) Progression to end-stage damage includes profound scleral canal wall expansion (clinical excavation) and posterior deformation and thinning of the lamina (z) by mechanisms that are as yet uncharacterized^{99, 100}. If all other aspects of the neuropathy are identical, the stiffer the lamina, the more resistant it will be to deformation. Whether this is better or worse for the adjacent axons is a separate question that remains to be determined.

Figure 5. While damage to the neural and connective tissues of the ONH is multifactorial, ONH appearance in the neuropathy is importantly influenced by connective tissue stiffness
 In our biomechanical paradigm, IOP-related strain influences the ONH connective tissues and the volume flow of blood (primarily) and the delivery of nutrients (secondarily), through chronic alterations in connective tissue stiffness and diffusion properties (explained in Figures 1 and 2). Non-IOP related effects such as auto-immune or inflammatory insults (yellow) and retrobulbar determinants of ocular blood flow (red) can primarily damage the ONH connective tissues and/or axons, leaving them vulnerable to secondary damage by IOP-related mechanisms at normal or elevated levels of IOP. Once damaged, the ONH connective tissues can become more or less rigid depending upon lamina cribrosa astrocyte and glial response. If weakened, ONH connective tissues deform in a predictable manner (Figure 4) which underlies a laminar component of clinical cupping (Figure 3).

Figure 6. Profound Subsurface Structural Change Accompanies the Onset of CSLT-Detected Clinical Cupping in the Young Adult Monkey Eye but this May be Different in the Old Monkey Eye

Upper: Normal lamina cribrosa (unhatched), scleral flange (hatched), prelaminar tissue (beneath the internal limiting membrane - brown line), Bruch's membrane (solid orange line), Bruch's Membrane Opening (BMO) zero reference plane (dotted orange line), Border tissue of Elschnig (purple line), choroid (black circles) are schematically represented in the upper illustration. **Lower:** Overall changes in the ONH surface and subsurface architecture at the onset of CSLT-detected ONH surface change in experimental ocular hypertension in young adult monkey eyes are depicted below. Posterior bowing of the lamina and peripapillary scleral flange, thickening of the lamina and thickening (arrows) not thinning of the prelaminar neural tissues (brown shading) underlie posterior deformation of the ONH and peripapillary retinal surface (dotted brown to solid brown ILM). Thus, while expansion of the clinical cup and deformation of the surface are clinically detectable at this early stage of the neuropathy, because they occur in the setting of prelaminar tissue thickening, (not thinning), clinical cupping in experimental ocular hypertension in these young adult eyes is "laminar" in origin, without a significant "prelaminar" component (Figure 3). Because aged eyes will have (on average) stiffer connective tissues, we predict they will demonstrate less laminar and more prelaminar cupping at the onset of clinically detectable ONH surface change. (*Adapted from Yang, et al*⁵⁰)