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Review Article

Pathogenesis of Chronic Glaucoma: A Two-Stage Disease

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Abstract

Chronic glaucoma, also commonly known as glaucoma, is an unresolved mystery ever since it was given a separate entity in the 1850s [1]. There is a plethora of glaucoma theories such as the direct mechanical effect of elevated intraocular pressure (IOP) on the nerve fibers (NFs), posterior bowing of the lamina cribrosa (LC), lack of perfusion of the optic nerve head (ONH), increased sensitivity of the NFs to IOP, neurodegeneration, apoptosis, autoimmune disorder and others. However, none of these prevalent theories has addressed the issue of the orderly loss of NFs which is the crucial pathognomonic feature in chronic glaucoma.

In chronic glaucoma, the one million or so densely packed NFs in the ONH are being destroyed singly in an orderly tandem sequence from peripheral to central, never randomly. The orderly loss of NFs is perhaps the only lead we have in solving the mystery of glaucoma. Surprisingly, this pathognomonic feature has never been discussed while presenting various glaucoma theories. The orderly loss of NFs is the reason we do perimetry in chronic glaucoma. If the NFs were not being destroyed in a specific sequence in chronic glaucoma, the role of perimetry would be meaningless.

Although it is well recognized that elevated IOP is the established risk factor of chronic glaucoma, the elevated IOP acting directly on the densely packed NFs can't result in their individual orderly destruction. In fact, there is no biological mechanism acting directly on the NFs which could result in their orderly loss. Thus, there must be some mechanical scenario which will first separate the densely packed NFs individually for their orderly loss even though that mechanism may have resulted from the biological affect of elevated IOP on some important component of the ONH. In other words, the orderly loss of NFs can't be accomplished in one stage.

Therefore, it is hypothesized that chronic glaucoma is a two-stage disease. The first stage: a biological stage resulting in the degeneration of the border tissue of Elschnig (BT) induced by chronic ischemia due to elevated IOP or normal range IOP but 'acting as elevated IOP' in that particular subject. As a result of degeneration of the BT, the lamina cribrosa starts sinking in the scleral canal (initiation of the second mechanical stage) leading to stretching and severance of NFs at the scleral edge starting with the most peripheral NFs (being closest to the scleral edge) and ending with the most central NFs one-by-one in an orderly sequence. Chronic glaucoma may not be an optic neuropathy but an optic axotomy.

Keywords: *Chronic Glaucoma; Normal-Tension Glaucoma; Intraocular Pressure; Neurodegeneration; Optic Nerve Head; Optic Disc; Glaucomatous Field Loss*

Introduction and Discussion

There are two main events occurring in chronic glaucoma. First, there is the orderly loss of NFs from peripheral to central, never randomly. Second, elevated IOP, though an established risk factor in chronic glaucoma, can't destroy the densely packed NFs of the ONH in an orderly sequence by its direct action on the NFs. This is the mystery in glaucoma which can't be solved in one stage. Therefore, this presentation proposes that chronic glaucoma is a two-stage disease.

First stage (Biological): Degeneration of the border tissue of Elschnig

The border tissue of Elschnig (BT) lies between the sclera and lamina cribrosa (LC) and keeps the LC firmly in place acting as an 'O' ring seal.

The BT is supplied solely by the ciliary circulation which has a low-circulatory pressure (~25 mmHg) compared to the central retinal artery (CRA) pressure (~50 - 60 mmHg). Unfortunately, the CRA does not contribute to the BT. The systemic pressure supplying the BT and IOP are opposing forces. Normally, systemic blood pressure supplying the BT is higher than IOP for its proper perfusion and healthy maintenance.

This healthy relationship will be reversed either due to IOP becoming elevated from an ocular problem or normal IOP becoming relatively elevated due to a reduction in systemic ciliary pressure of the BT. Chronic ischemia and degeneration of the BT will ensue if the IOP becomes higher (due to an ocular problem) than the normal systemic pressure of the BT (~25 mmHg) in systemically healthy subjects resulting in high-tension glaucoma (HTG).

However, if the systemic pressure of the BT gets reduced (i.e. to 15 mmHg) due to systemic problems like chronic hypotension, then even a normal range IOP of 16 mmHg will 'act as elevated IOP' and start compressing the circulation of the BT in systemically compromised subjects resulting in normal-tension glaucoma (NTG).

In both ocular and systemic circumstances, IOP becoming higher than the systemic pressure of the BT will compress the ciliary circulation of the BT. The slow and prolonged compression of the ciliary circulation of the BT will result in chronic ischemia and its degeneration. Thus, the degeneration of the BT can develop either due to an ocular problem in healthy subjects (HTG) or due to poor systemic circulatory conditions (NTG). Of course, many subjects will be having elevated IOP due to an ocular problem and also having poor systemic circulatory conditions. In such cases, degeneration of the BT will be accelerated (Figure 1).

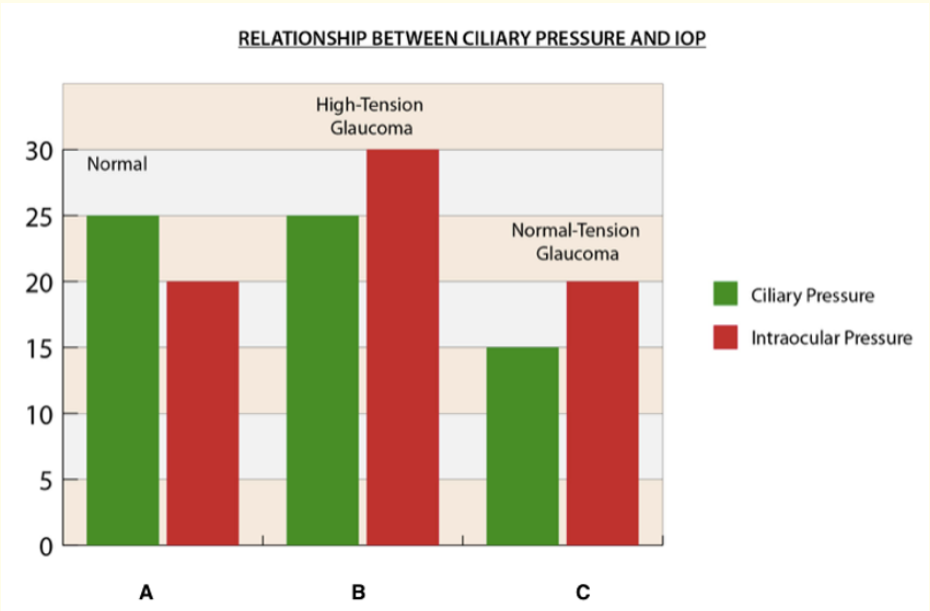

Figure 1: *Graphic Diagram- The Interaction Between Ciliary Systemic Pressure and IOP. Normally, the ciliary systemic pressure supplying the border tissue should be higher than IOP for its good perfusion and healthy maintenance as in column (A). In column (B), the IOP is increased to 30mmHg due to an ocular problem whereas the ciliary pressure is still the same at 25, resulting in high-tension glaucoma. In column C, due to decrease of the ciliary pressure to 15 resulting from systemic problems such as hypotension, the normal IOP at 20 mmHg is now 'acting as an elevated IOP', resulting in normal-tension glaucoma. Note: In (B) and (C) the situation is reversed - IOP becomes higher than the ciliary pressure. HTG appears to be an ocular problem whereas NTG as a systemic problem.*

It may take several years for the degeneration of the BT to occur. The latent period will vary due to several factors. The higher the IOP compared to systemic pressure of the BT, the shorter the latent period. Moreover, if the BT is inherently structurally weak, as in high myopia, the latent period will also be short. Other factors like sleep apnea and long-term smoking resulting in systemic chronic hypoxia will also lead to early degeneration of the BT. The more risk factors present, the shorter the latent period for the degeneration of the BT to occur. However, IOP becoming higher than the systemic pressure of the BT is the main risk factor for degeneration of the border tissue. Other factors will be secondary. Degeneration of the BT (biological stage) will then lead to the sinking of the LC (mechanical stage).

Second stage (Mechanical): Sinking of the lamina cribrosa and initiation of the orderly loss of nerve fibers

Before we discuss the orderly loss of NFs in glaucoma, it is imperative to study the arrangement of NFs in the retina and ONH. First, the one million or so nerve fibers in the retina are arranged in layers from superficial to deep. Second, the most central vision fibers originate closest to the disc, lie most superficial (closest to vitreous) and exit from the most central part of the disc. In contrast, the most peripheral nerve fibers originate from the most distant retina or farthest from the optic disc, lie deepest (closest to the sclera) and exit closest to the edge of the scleral opening (Figure 2).

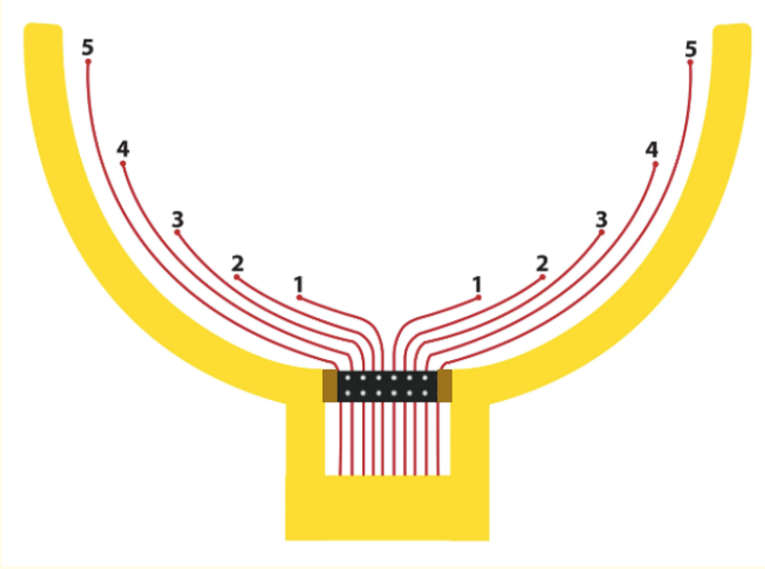

Figure 2: *Schematic Diagram. Normal Arrangement of Nerve Fibers in the Retina and ONH. The most peripheral nerve fibers (5) originate farthest from the optic disc, lie deepest (closest to the sclera) and exist nearest to the scleral edge. The most central fibers (1) originate closest to the disc, lie most superficial (closest to the vitreous) and exit from the most central part of the disc.*

Third, the NFs originating from the nasal retina proceed directly to the nasal part of the optic disc. However, the situation is different in the temporal retina because of the presence of the macular fibers. The NFs originating from the nasal aspect of the macular area proceed directly to the temporal part of the disc as the papillomacular bundle. The fibers originating from the temporal macular and temporal retina arch above and below the macular fibers to reach the superior and inferior poles of the optic disc respectively. They are hence known as the arcuate fibers (Figure 3).

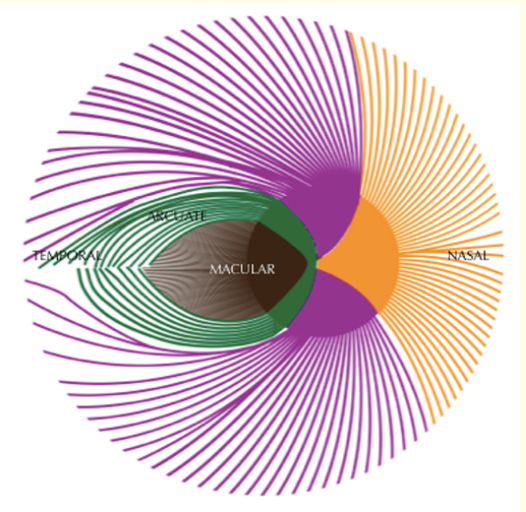

Figure 3: *Schematic Diagram. Normal Arrangement of Nerve Fibers in the Retina and Optic Disc. The arcuate fibers arch above and below the macular fibers to reach the poles of the optic disc.*

As the LC sinks due to degeneration of the BT, the peripheral NFs being closest to the scleral edge are stretched and severed first against the scleral edge creating an empty space. As a result, the next-in-line fiber will move peripherally towards the scleral edge and get severed. The peripheral NFs are destroyed first but as the disease progresses to the paracentral region (10 to 20 degrees), there is initial occurrence of isolated scotomas in the paracentral area.

As more of the arcuate fibers become severed, the isolated scotomas become enlarged and ultimately coalesce to form superior and inferior arcuate scotomas - together known as the ring scotoma. After the peripheral and paracentral visual field (VF) is lost, about 10 degrees of central VF is retained due to abundance of macular NFs even though they are also being severed from day one.

The severance of NFs accelerates further sinking of LC due to loss of anchorage provided by the NFs as roots anchor a tree. The cascade of severance of NFs and sinking of the LC will become self-propagated and continue until all the NFs have moved in an orderly tandem fashion to the scleral edge and become severed. This may explain the unstoppable nature of glaucoma despite the maximum lowering of IOP. The severed segments undergo phagocytosis, thus creating excavation (empty spaces) that we are mistakenly interpreting as cupping of the ONH. The sinking of the LC and severance of nerve fibers can explain the orderly loss of NFs in glaucoma as supported by glaucomatous visual field defects (Figure 4).

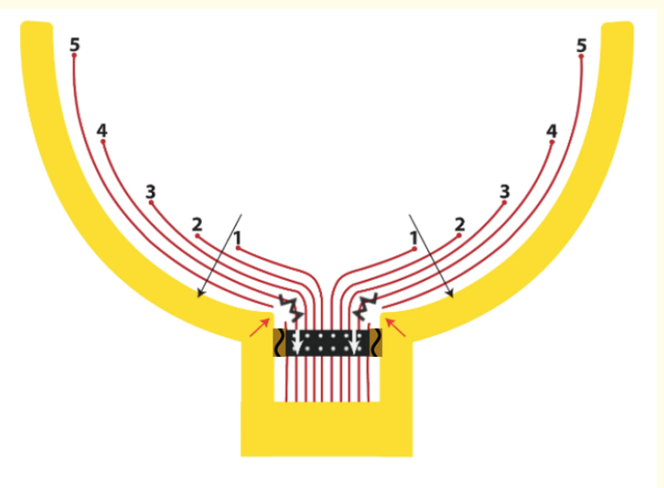

Figure 4: *Schematic Diagram. Sinking of the Lamina Cribrosa and Severance of Nerve Fibers. Due to sinking of the LC, the most peripheral and deepest prelaminar nerve fibers (5) are stretched and severed against the scleral edge (red arrow). The next-in-line fiber (4) will move towards the scleral edge to occupy the space vacated by the preceding severed fiber will also get stretched and severed. This process will continue in an orderly sequence until the most central fiber (1) has moved towards the scleral edge and gets severed (black arrow). Note: atrophy of the border tissue (brown) and sinking of the LC.*

Glaucomatous field loss do not support the lamina cribrosa as the primary site of injury in chronic glaucoma

It is widely believed that the LC is the primary site of injury in chronic glaucoma. However, there are several arguments against this conception. First, the glaucomatous field defects do not support the characteristic field loss with respect to the arrangement of NFs in the LC. The glaucomatous field defects such as arcuate field defects and Ronnie's nasal step produced due to the horizontal temporal raphe correspond fully with the arrangement of NFs while they are in the retina or in the ONH prior to their 90 degree turn. After the NFs make their 90 degree turn into the prelaminar area, they become vertically oriented and thus lose their retinal arrangement and also the horizontal raphe.

Moreover, in the prelaminar region, the loose NFs begin to arrange in bundles and the macular NFs begin to move to the central position. The arcuate NFs combine with the rest of the NFs and lose their distinctive arcuate appearance. Therefore, the arrangement of NFs in the prelaminar and laminar region changes drastically compared to when the NFs were in the retina (Figure 5).

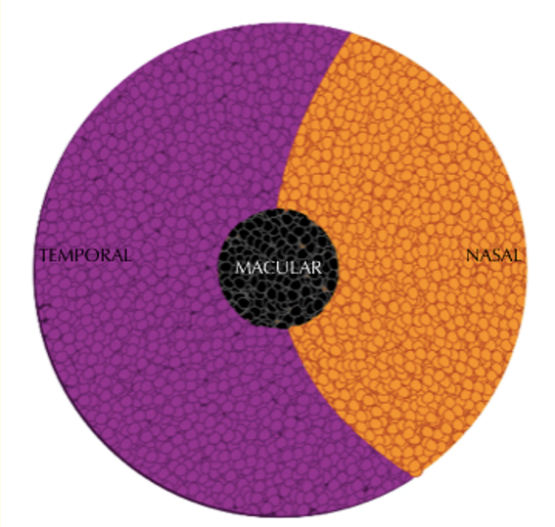

Figure 5: *Schematic Diagram. Cross-section of Nerve Fibers in the Lamina Cribrosa. A substantial change in the arrangement of NFs compared to while they were in the retina (Figure 3). Note the absence of the horizontal temporal raphe and of the arcuate NFs. Damage to NFs in the LC can't produce Ronnie's nasal step and the arcuate scotoma.*

The hallmark glaucomatous field defects such as the arcuate scotoma and Ronnie's horizontal nasal step can't be produced due to injury to the NFs after their 90 degree turn because neither the isolated arcuate nerve fibers nor the horizontal raphe is present in the prelaminar area and in the LC.

Second, the earliest field defect in glaucoma would be a central scotoma since the macular NFs will be damaged first if bowing of the LC was indeed taking place. But in actuality, the peripheral NFs are being destroyed first, and the central at the end-stage. Third, for the orderly loss of NFs to occur, the NFs should be lying loose so they can be easily separated individually, not when the NFs are firmly anchored in the meshwork of the laminar pores. In view of the aforementioned, the LC itself can't be the primary site of injury in glaucoma.

Evidence of sinking lamina cribrosa and severance of nerve fibers

It has been well documented that the LC starts migrating posteriorly from the early stages of glaucoma [2]. The kinking and sloping of the blood vessels at the disc margin and on the surface of the glaucomatous disc is due to sinking of the LC. The notching at the poles in

early glaucomatous ONH is due to severance and depletion of the arcuate fibers at the point of their entry. The empty arcuate spaces in the retina are due to depletion of arcuate NFs after their severance.

The arcuate field defects in chronic glaucoma are produced due to severance of NFs. The entire temporal NFs (superior arcuate, inferior arcuate and macular NFs) are being severed simultaneously. However, the arcuate fibers, being fewer in number compared to macular fibers, are depleted earlier resulting in superior and inferior arcuate scotomas. The arcuate scotomas are not due to their increased susceptibility to elevated IOP. The sharply defined arcuate scotomas can only be produced by their severance and total depletion of NFs, not due to atrophy of the NFs (Figure 6).

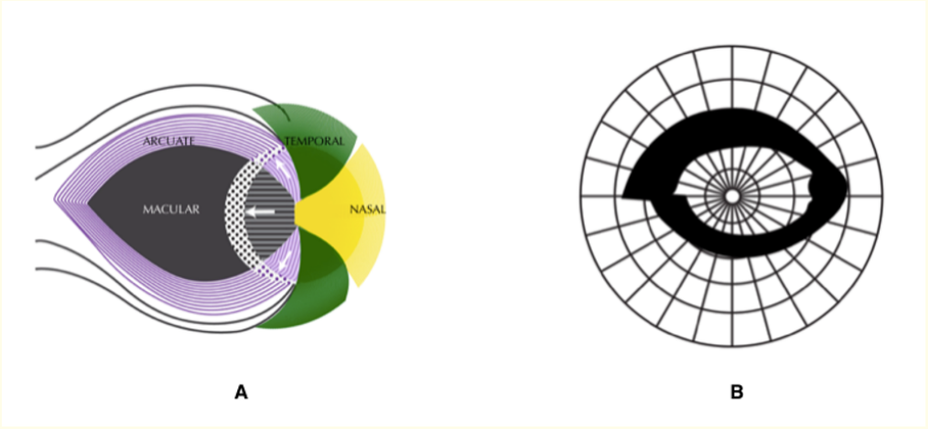

Figure 6: *Schematic Diagram. Production of Arcuate Scotomas. Due to sinking of LC, all the temporal NFs - macular, superior and inferior arcuate - are being severed simultaneously (A). However, the arcuate NFs being fewer in number compared to the macular NFs are depleted earlier, resulting in sharply defined arcuate field defects (B).*

Progressive thinning of the retinal nerve fiber layer (RNFL) is the salient feature of glaucoma which can only be explained by their severance. The atrophy of the NFs will not result in progressive thinning of the RNFL since atrophied tissue do not totally disappear. We do not observe progressive thinning of the RNFL in cases of optic atrophy such as due to multiple sclerosis in which the NFs are truly being atrophied.

The 'floor effect' when OCT cannot measure any further thinning of the RNFL in glaucoma subjects is due to the fact that the entire RNFL has been severed and depleted to the point of no further thinning. The end-stage glaucomatous disc is not a 100% cupped LC, but an empty crater left over after the severance and phagocytosis of NFs (Figure 7) [3]. The splinter hemorrhages at the margin of the ONH are due to severance of vasculature, meeting the same fate as of the NFs. The sinking of LC and severance of NFs and vasculature are supportive of the morphological changes occurring in the glaucomatous disc.

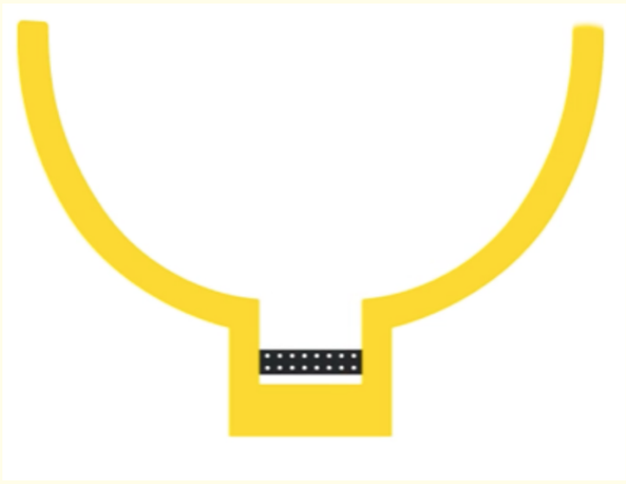

Figure 7: *Schematic Diagram. End-Stage Glaucomatous Disc. Note the absence of NFs and vasculature resulting from their severance. The sunken LC devoid of nerve fibers lying at the bottom of the crater.*

Conclusion

Based on the orderly loss of NFs in chronic glaucoma, the prevalent glaucoma theories such as the direct role of IOP on NFs, posterior bowing of the lamina cribrosa, neurodegeneration and others become invalid since none of them can explain the orderly loss of NFs. In fact, there is no biological mechanism which can cause the orderly loss of NFs in glaucoma.

The orderly loss of NFs can't be accomplished in one stage. Therefore, chronic glaucoma may be a two-stage disease. The first, biological stage in which there is degeneration of the BT resulting from chronic ischemia due to elevated IOP or normal IOP 'acting as elevated IOP' in that particular subject. The degeneration of the BT initiates sinking of the LC (the second, mechanical stage).

The sinking of the LC results in stretching and breakage of NFs starting with the most peripheral and ending with the most central NFs in an orderly tandem sequence. The histology of the end-stage glaucomatous disc reveals an empty crater suggesting that severance of NFs and vasculature has occurred. The severance of NFs is a unique feature of glaucoma as no other ONH disease results in severance of nerve fibers. In summary, chronic glaucoma may not be an optic neuropathy, but an optic axotomy [4-10].

Bibliography

1. Duke-Elder S and Barrie J. "Diseases of the lens and vitreous, glaucoma and hypotony, System". Volume X1. London: Henry Kimpton (1969): 385.

2. Yang H., *et al*. "Posterior (outward) migration of the lamina cribrosa and early cupping in monkey experimental glaucoma". *Investigative Ophthalmology and Visual Science* 52.10 (2011): 7109-7121.

3. Yanoff and Fine. "Ocular Pathology". Harper & Row (1975): 496, 615.

4. Hasnain SS. "Arcuate Field Defects in Glaucoma". *Ophthalmology Update* 11.1 (2013): 67-73.

5. Hasnain SS. "Scleral edge, not optic disc or retina is the primary site of injury in chronic glaucoma". *Medical Hypothesis* 67.6 (2006): 1320-1325.

6. Hasnain SS. "The Missing Piece in Glaucoma?" *Open Journal Of Ophthalmology* 6.1 (2016): 56-62.

7. Hasnain SS. "Pathogenesis of Orderly Loss of Nerve Fibers in Glaucoma". *Optometry: Open Access* 1.2 (2016): 110.

8. Faiq MA and Sofi RA. "A Glimpse into the Mysteries of Glaucoma: From Theories to Clinics". *Oman Journal of Ophthalmology* 12.1 (2019): 1-3.

9. Zeried FM and Osuagwu UL. "Changes in retinal nerve fiber layer and optic disc algorithms by optical coherence tomography in glaucomatous Arab subjects". *Clinical Ophthalmology (Auckland, N.Z.)* 7 (2013): 1941-1949.

10. Faiq MA. "The Dark Matter of Vision: In Search of a Grand Unifying Theory for Glaucoma". *Oman Journal of Ophthalmology* 11.2 (2018): 101-102.

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