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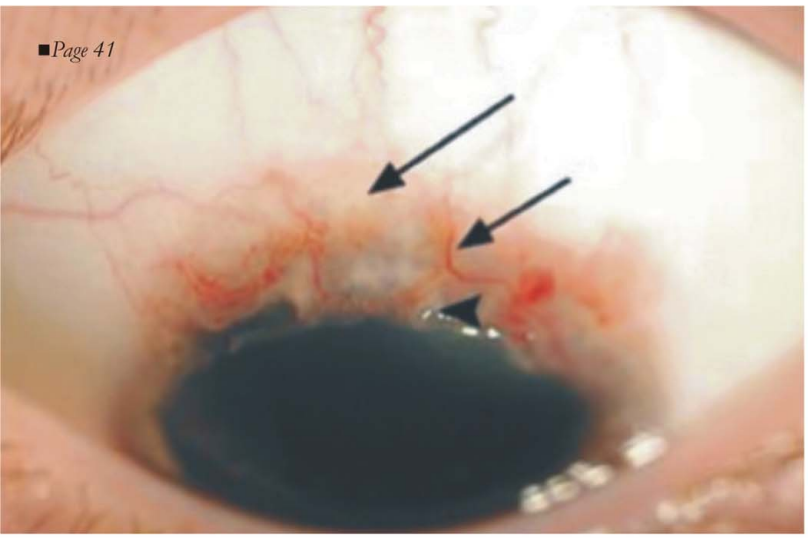
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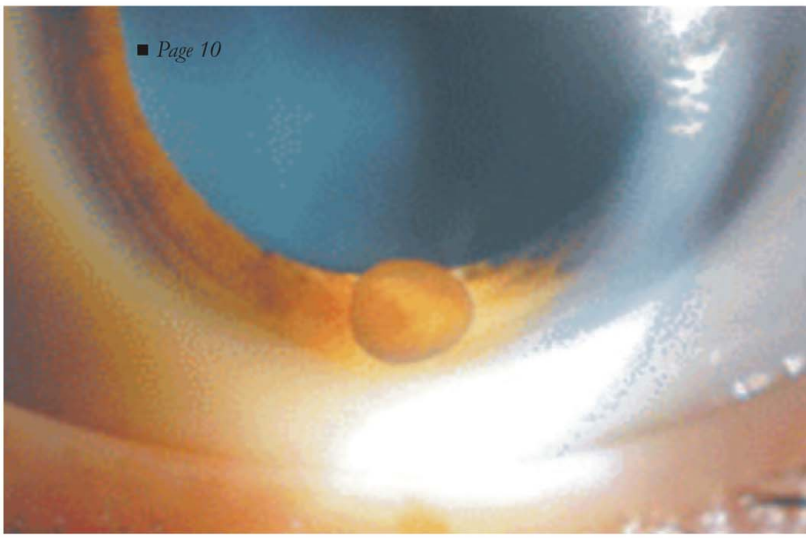
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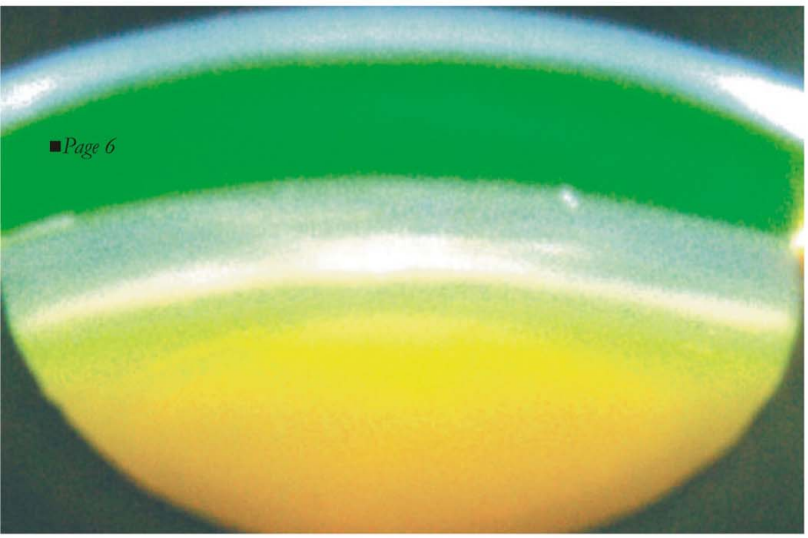
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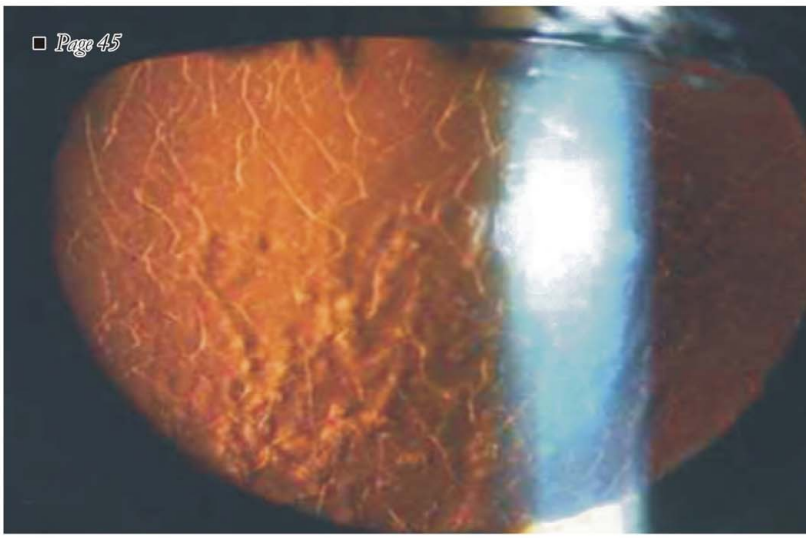
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Original

Optic Disc may be Sinking in Chronic Glaucoma

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Dr. S. S. Hasnain

"The author is a general ophthalmologist, practicing Ophthalmology in California , USA over a period of 35 years. Dr. Hasnain has suffered from raised intra-ocular pressure in both eyes ever since his early residency period about 40 years ago. He was advised anti-glaucoma therapy, but could not tolerate the eye drops due to their side effects and did not undergo surgery for fear of complications. He is still thriving with normal visual fields and the same IOP even after the passage of 40 years. The question arises, was it Glaucoma? or something else?

He rebuts the 150 year-old theory of cupped discs with solid arguments and postulates that the "Optic Discs may be sinking in Chronic Glaucoma". His first hypothesis, "Scleral edge, not Optic Disc or retina is the primary site of injury in Chronic Glaucoma" was given due recognition after being published in an indexed journal "Medical Hypothesis" in 2006 and was cited in a Text Book: GLAUCOMA: Medical Diagnosis & Therapy in a chaptered caption "New Horizon" by a renowned scientist Leonard A. Levin. His hypothesis received tremendous appreciation with a positive feedback in a conference "Envision '08" held in San Antonio, Texas and a poster presentation in ASCRS meeting 2009 in San Francisco with the highest views. He also conducted a poster presentation at the First World Congress on Controversies in Ophthalmology in Prague in March 2010.

Dr. Hasnain, thinks it to be an uphill task to change or challenge the well established paradigm of Cupping conformed 150 years ago. Yet, our readers will find the discussion very meaningful and argumentative.

— Chief Editor

INTRODUCTION

How did I get involved in glaucoma research?

In 1970, during my ophthalmology residency I was found to have a high intraocular pressure (IOP) of 30mm Hg in each eye on a routine examination. It was shocking news for me to have such high IOP especially when I was embarking on an ophthalmology career which required good vision. Statistically, the normal range IOP is between 10 to 22mm Hg. Although at time of discovery, I had 20/20 vision and normal visual fields in each eye, but I was afraid of becoming blind. I tried all sorts of eye drops to lower my IOP but could not tolerate them due to their side effects. I was reluctant to undergo glaucoma surgery for fear of complications therefore I never got treated. As time passed and 35 years later, I was still having a high IOP of about 30mm Hg, yet I have normal vision and visual fields in each eye. My CCT readings are normal at 550. It was very puzzling for me as to why I didn't become blind even after 35 years of having high IOP whereas my patients were becoming blind at normal range IOPs? My mind was occupied with this intriguing question and not finding the answer in textbooks, I resorted to my own glaucoma research which led me to a totally different pathogenesis of glaucoma - a **paradigm shift**.

I believe the term **'cupping'** was mistakenly given by scientists 150 years ago which has thrown us on a wrong path. Instead, I postulated that ***the optic disc may not be cupping but sinking in its entirety***. I had my professional obligation to share my views about glaucoma pathogenesis, whether my colleagues approve it or not. Since I had never written any article before, it was an adventurous task to write an article and then get it published. I managed to compile my thoughts in an article titled "***Scleral edge, not optic disc or retina is the primary site of injury in chronic glaucoma***" which was eventually published in *Medical Hypothesis*.

The retina is a very complex multi-layered structure consisting of rods, cones, ganglion cells and their axons also known as nerve fibers. For the sake of glaucoma, we will concentrate on the ganglion cells and their axons since they are the one destroyed in glaucoma. There are about one million axons originating from the ganglion cells at 360 degrees of the retina which converge to form an **optic disc** which is then continued as an optic nerve to the brain. We can only see the disc but not the nerve behind it with our ophthalmoscope. An analogy would be a road (retina) made of nerve fibers and converge to a manhole cover (optic disc) in the middle of the road. We can only see the manhole cover but not the structures underneath it. The optic disc is 1.5 mm in size in which about one million axons are densely packed and secured in the holes of the several sheets of the lamina cribrosa, whereas the optic disc itself is secured in the scleral opening by border tissue which lies between the scleral edge (rim) and the lamina containing axons. Since the lamina cribrosa is the integral part of disc, both are being discussed as one unit.

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1. What is the physiological (original) cup of the optic disc?

The physiological or original cup of the optic disc is the remnant of the Bergmeister's papilla left over after its atrophy in fetal life. Bergmeister's papilla is mainly a tuft of the hyaloid vessels which supplies nutrition to the lens of the eyeball in fetal life. The physiological cup is a superficial depression in the center of an otherwise flat optic disc hence called a cup. It has been mentioned that the cup is devoid of axons and the axons are only concentrated in the rim area. This is not true because if we review the histology of the normal disc, these cups are identified as central connective tissue meniscus and underneath the entire lamina is full of axons and there is no empty space. The physiological cups are described as cup/disc ratio ranging from 0.1 to 0.9 which implies that 0.9 cup/disc ratio, cup is so large that it is occupying 90 % of the entire disc area.

2. What is the pathological cupping of the optic disc?

The term pathological cupping or simply known as 'cupping" implies the gradual enlargement concentrically or otherwise of the physiological cup. The term cupped disc was given in 1856 by Heinrich Muller (Duke-Elder, 1969) an ophthalmic pathologist. After the invention of the ophthalmoscope in 1851 by Helmholtz, ophthalmologists were able to see the glaucomatous optic discs of chronic glaucoma patients. The majority of the ophthalmologists at that time agreed with the phenomenon of cupping occurring in chronic glaucoma and since then the term ***cupping*** has become synonymous with glaucoma. Interestingly, there was one dissenter in 1864; Dr. Dixon disagreed that cupping was in response to high intraocular pressure. He argued that if high intraocular pressure has the mechanical force to induce the enlargement of the physiological cup, then it should have also displaced the lens and iris forward as well. But his opinion was turned down by another prominent ophthalmologist Sir William Bowman in favor of cupping. I will discuss later about cupping and whether it is truly occurring or not.

3. What is glaucoma?

Chronic glaucoma is a more common and was given a separate entity 150 years ago. The definition of chronic glaucoma is not yet fully established. In the past, all chronic glaucomas were believed to be associated with raised IOP. But after the invention of Goldmann applanation tonometry in 1955, the measurement of IOP became more accurate. As we started taking accurate measurements of IOP, we observed that many glaucoma patients had their IOPs consistently within the normal range. These patients are called having normal–tension glaucoma. Many ophthalmologists do not believe normal tension glaucoma as a separate entity. They believe that normal-tension glaucoma patients have unduly sensitive optic discs to IOP, therefore their optic discs atrophy despite normal IOP. I am not convinced because if someone is born with unduly sensitive discs to IOP, then that subject should have developed glaucoma in childhood rather than after age 50 or more. Chronic glaucomas having an elevated IOP are called high tension glaucoma (HTG) whereas those in which the untreated IOP is consistently within normal range are called normal tension glaucoma (NTG). Although both HTG and NTG have similar morphological changes in the optic disc and have identical course of disease, I believe both have a different etiology which I will discuss later in this presentation.

What happens to the eye in chronic glaucoma?

In both HTG and NTG, the optic disc is slowly destroyed over the time ranging from 10 to 20 years or more. Chronic glaucoma is defined as progressive optic neuropathy but we do not yet know how exactly the optic disc is being destroyed. There are several theories ranging from high IOP mechanically destroying the optic disc to the programmed death (apoptosis) of the ganglion cells of the retina but none of them satisfactorily explain some unsolved puzzling questions of glaucoma. I will discuss these puzzling questions which are the essence of my presentation.

METHODS:

This presentation is being conveyed in an unconventional approach. Instead of searching for various factors causing glaucoma, three puzzling questions and their answers based on deductive reasoning, morphology, and histology of the glaucomatous disc will be discussed and how I arrived at the conclusion that the optic disc may be sinking in its entirety in glaucoma.

4. Three puzzling questions of glaucoma:

- Puzzling question # 1. Why some ocular hypertension subjects (OHT) with high IOP such as 30mmHg never develop glaucoma whereas normal-tension subjects (NTG) develop glaucoma even at normal IOP (10-22 mmHg)?
- Puzzling question # 2. Why are the arcuate axons and peripheral axons destroyed in the early stages, whereas the macular axons last until the end-stage of glaucoma?
- Puzzling question # 3**.** Why can't glaucoma be halted despite maximally lowering of IOP?

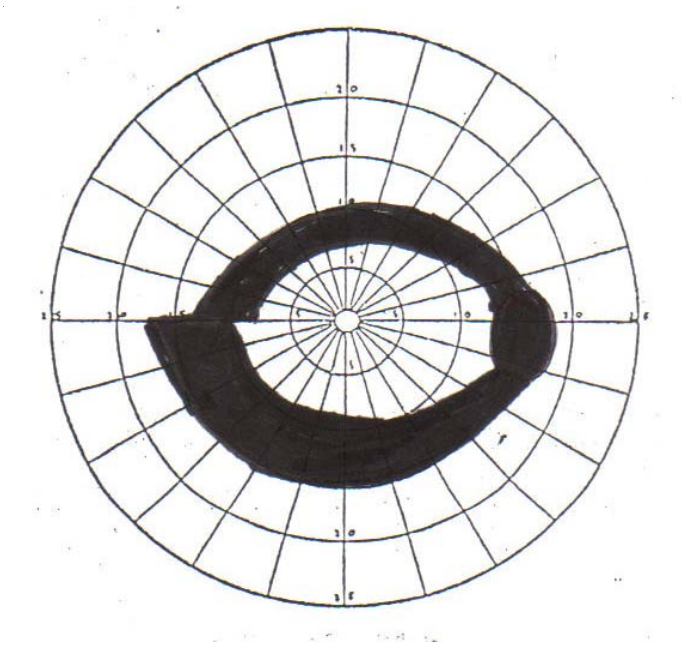
DISCUSSION

Puzzling question # 1. **Why some ocular hypertension subjects (OHT) with high IOP such as 30mmHg never develop glaucoma whereas normal-tension subjects (NTG) develop glaucoma even at normal IOP (10-22 mmHg)?**

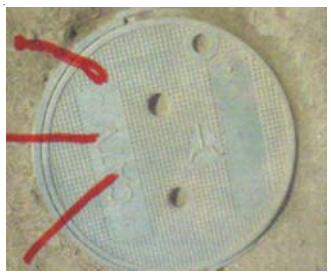
For answers to the above question, I resorted to the detailed medical history of hundreds of glaucoma patients. Medical history revealed that pure high-tension glaucoma subjects were usually in good health, whereas normal–tension glaucoma subjects had cardio-pulmonary and circulatory problems. Interesting, about 70% of the NTG patients were long-term smokers. Many female NTG patients had the only history of long term exposure to second-hand smoke from their husbands who had passed away several years ago due to smoking-related diseases. These findings suggest that NTG may be a systemic disease and HTG an ocular disease and thus glaucoma construed as a multi-factorial disease.

Circular Border tissue (green) lies between the optic disc and the scleral edge (rim). Border tissue acts as a cushion and also secures the optic disc in the scleral opening

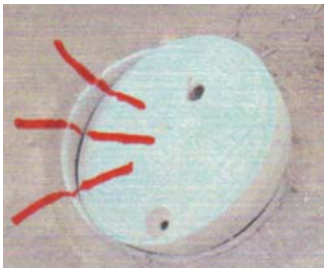
Analogy: Sinking Manhole Cover to glaucomatous optic disc



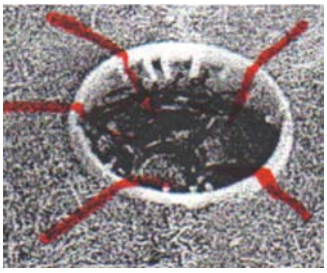
Double arcuate field defects. This may be the answer to the puzzling question number 2. Why are the arcuate fibers selectively destroyed first in glaucoma?

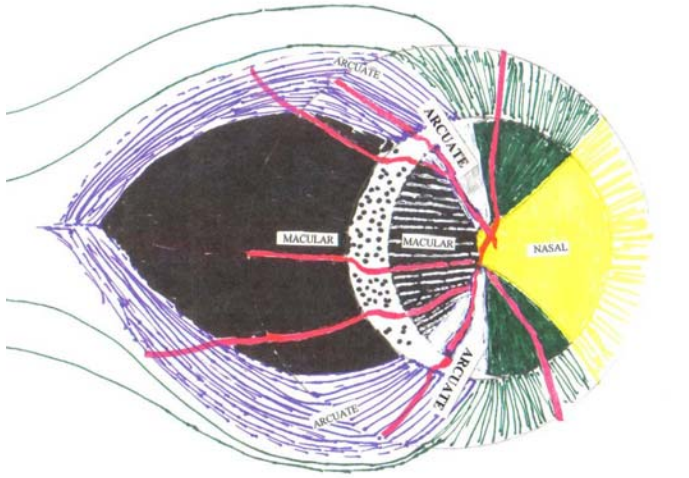


Normal: If course is blood veseels crossing the disc margin is straight there there is no sinking or no glaucoma.



Early stage glaucoma: Kinking of the blood vessels at the margin due to sinking.





Due to temporal sinking all the temporal fibers which include sup. and inf. arcuate and macular fibers would be severed simultaneously. However, arcuate fibers being fewer in number, therefore they would be depleted earlier giving rise to double arcuate field defects whereas the macular fibers being abundant would last till the end stage of glaucoma. Concurrent severing of the macular fibers is revealed by loss of ganglion cells of the macular area by OCT.

There were also HTG subjects who also had NTG related systemic problems as well. Systemic blood pressure and intraocular pressure are opposing forces and their interaction plays a big role in circulation of the optic disc area. Although chronic glaucoma is now accepted as a multifactorial disease, it all eventually depends upon how IOP and systemic ciliary circulation interact with each other. I believe retinal circulation is not involved in chronic glaucoma. Normally, the IOP should be lower than the systemic ciliary pressure for the healthy maintenance of the optic disc and its surrounding area.

5. The reason some OHT subjects do not develop glaucoma despite having a high IOP may be due to the fact that they may be in good health and have good circulation to the optic disc area and are thus less prone to the adverse effects of high IOP.

Glaucoma, being a multifactorial disease may answer puzzling question # 1.

The more risk factors present, the more the likelihood of developing glaucoma akin to ischemic heart disease.

Here, I hypothesize that the reason I didn't develop glaucoma, may be due to my good health. My good ciliary circulatory pressure to the optic disc fought back the high IOP and thus my optic disc survived. If I had cardio-pulmonary or circulatory problems or had been a smoker, then most likely I would have been blind by now because of my high IOP of 30mmHg for almost four decades. We will discuss more in detail about the interaction between IOP and systemic circulation in puzzling question # 2.

Puzzling question # 2.

Why are the arcuate and peripheral axons destroyed in early stages of glaucoma whereas the macular axons last until the end-stage of glaucoma? What are the arcuate axons?

Axons originating from the ganglion cells of the nasal retina usually proceed directly to the optic disc. However, the situation is different in the temporal part because of the presence of the macular area. Since the axons originating from the nasal macular area go horizontally to the optic disc, the axons originating from the temporal macular and paramacular area have to arch above and below the horizontal nasal macular fibers in order to reach the optic disc hence known as arcuate axons. Arcuate axons lie within 10 to 20 degrees from the point of fixation known as the paracentral region. Arcuate axons are destroyed in the early stages of glaucoma producing characteristic arcuate (arch-shaped) field defects in the paracentral visual field area. Although arcuate field defects were documented more than one hundred years ago by Bjerrum and Ronnie, we have no consensus as to why the arcuate axons are selectively destroyed in the early stages of glaucoma. In this presentation, I have greatly emphasized about the selective destruction of the arcuate axons, because I believe the early arcuate field defects are perhaps the only lead we have in discovering the pathogenesis of glaucoma.

Another point to note here is about the arrangement of the axons in the retina and the optic disc. The axons originating from the most peripheral part of the retina lie deepest (closest to the sclera) and exit from the most peripheral part of the optic disc (closest to the scleral rim/edge), whereas the axons originating closest to the optic disc lie most superficial (closest to the vitreous) and exit from the most central part of the optic disc. Arcuate axons and the peripheral axons are lost early in glaucoma whereas the central fibers belonging to 10 degrees central vision last until the end-stage of glaucoma. It will be important to keep the above arrangement of the axons in mind during this presentation.

6. Now we proceed to puzzling question #2. Since the arcuate axons are destroyed in both HTG and NTG, we have to find out not only the cause of selective destruction of the arcuate axons but also the common ground of injury for both HTG and NTG if these are two different types of glaucoma**.**

The arcuate axons can possibly be destroyed at one of three sites: **the optic disc including the lamina cribrosa, the retina, or the junctional area. Can the arcuate axons be selectively destroyed if the primary site of injury is the optic disc including lamina cribrosa?**

Not likely, due to the following reasons:

- There are about one million axons including superior and inferior arcuate axons densely packed in the intricate meshwork of the lamina cribrosa in the 1.5mm size optic disc. It is not possible that the mechanical force of high IOP could selectively destroy just only the arcuate axons and leave others unaffected.
- It is hypothesized that raised IOP results in backward bowing of the lamina cribrosa which in turn causes the pinching of the arcuate axons due to presence of different size holes in the lamina. If the bowing of the lamina is occurring due to high IOP, then why are the arcuate axons being destroyed in NTG in which we should not expect any bowing due to its normal IOP? It is difficult to comprehend that the optic disc, with a density of one million axons in the 1.5 mm size disc, will still have any room left for the movement of the laminal sheets.
- It is very unlikely that alterations of architecture of the connective tissue of the lamina, impediment of the axoplasmic transport by any cause or the reduction of the blood flow can be so selective as to specifically target only the arcuate axons and not the rest. It is unlikely that any mechanism within the complex and intricate meshwork of the lamina cribrosa can be as precise and selective as to destroy only the arcuate axons as though they have been cut with a pair of scissors.
- In view of the above reasons the lamina cribrosa may not be the primary site of injury in chronic glaucoma.

7. Can the arcuate axons be selectively destroyed while within the retina?

Not likely, similar to the case of the lamina cribrosa, the arcuate fibers cannot be selectively destroyed within the retina. There are about one million axons including arcuate axons spread out around 360 degrees within the retina. It is not possible that raised intraocular pressure could selectively and accurately destroy only the arcuate fibers within the retina in the early stages of glaucoma. It is unlikely any pathology could selectively destroy only the arcuate axons within the retina or the ganglion cells serving the arcuate axons in the early stages of glaucoma.

Can the arcuate axons be selectively destroyed if the apoptosis of the ganglion cells of the retina is occurring?

- In order for the arcuate axons to be selectively destroyed by genetically controlled apoptosis in the early stages of glaucoma, it has to fulfill two requirements. First, our genes should predict the impending chronic glaucoma and then to initiate apoptosis starting specifically with those ganglion cells which serve the arcuate axons. I do not believe our genes are so smartly programmed to meet the above prerequisites.

- If apoptosis is triggered in response to high IOP, then why is apoptosis occurringin NTG where the trigger factor of high IOP is missing? How can we explain the arcuate field defects occurring in a young person with chronic traumatic or chronic secondary glaucoma in which genetically controlled apoptosis should not be occurring?
- If the primary pathology lies in the ganglion cells of the retina then why is there excavation of the disc occurring remotely? Tay-Sachs, which is a classic genetic disease of the ganglion cells of the retina neither results in arcuate field defects nor in the excavation of the optic disc.
- Apoptosis may occur randomly or generalized, but to initiate selectively and precisely with those ganglion cells which serve the arcuate axons, appears very unlikely.

If the lamina cribrosa or the retina cannot be the primary site of injury of the arcuate axons then what may be site of injury in both HTG and NTG? We are then left with the junctional area where the retinal axons leave the retina and cross over the border tissue of Elschnig to become prelaminar fibers.

8. Can the border tissue of Elschnig be the common site of injury for both HTG and NTG?

To answer the above question, we have to study the border tissue and its circulation. The border tissue of Elschnig is composed of dense collagenous tissue lying between the lamina cribrosa and the sclera and secures the disc in the scleral canal like an 'O' ring seal. The border tissue is exclusively supplied by low-pressure short posterior ciliary arteries and unfortunately does not receive any contribution from high-pressure central retinal artery. Ciliary circulation is a low-pressure system due to its multiple branches compared to the central retinal artery which has high-pressure since it remains solitary from its origin from the ophthalmic until its emergence from the disc for the supply of the retina. Low-pressure ciliary circulation can be easily compressed (compromised) by high IOP or reduced due to poor systemic circulatory problems. An analogy will be a garden hose whose water output would be reduced either by external squeeze or due to reduced water supply from its source. As discussed earlier, the ciliary circulatory pressure and intraocular pressure are opposing forces and normally the intraocular pressure should remain lower than the ciliary circulatory pressure for the healthy maintenance of the border tissue. But if this status is reversed either due to an increase in IOP or due to a decrease in ciliary pressure resulting from poor systemic circulation, the oxygenation and nutrition of the border tissue will suffer. If the pressure of the inherently low-pressure ciliary circulation is further reduced due to systemic conditions like chronic hypotension then even normal range IOP would become too high for the weakened ciliary circulation of that subject, resulting in chronic ischemia and atrophy of the border tissue. Thus, the ciliary circulatory pressure should always remain higher than the IOP to prevent the atrophy of the border tissue. **Chronic glaucoma may be called as an "O" ring disease.**

I would like to emphasize the role of chronic ischemia in the causation of the atrophy of the border tissue. It will require a long and slow deprivation of oxygenation and nutrition for the tough collagenous border tissue to atrophy. That is why we do not observe the sinking of the disc in acute glaucoma as there is no time for the border tissue to atrophy. Chronicity is the key to the atrophy of the border tissue therefore chronic glaucoma is really a chronic disease as it will take time to develop. An analogy would be that it would take a long period of slow starvation for an obese person to become emaciated.

Systemic problems which result in chronic hypoxic state like obstructive respiratory conditions/sleep apnea and long-term smoking may also lead to the atrophy of the border tissue. This may be the reason that about 70% of the NTG subjects were found to be long term smokers in this study. In evaluating chronic glaucoma, we may have to take into considerations all the factors which can jeopardize the nutrition of the border tissue.

9. Having hypothesized that the optic disc may be sinking, it will be meaningless unless it can answer puzzling question # 2 as to why the arcuate axons are selectively destroyed in the early stages of glaucoma.

Returning to puzzling question #2:

Can the arcuate axons be selectively destroyed if the optic disc is sinking?

Likely. As the border tissue of Elschnig which lies between the lamina cribrosa and the sclera atrophies, the lamina cribrosa becomes loose and begins to **sink** in the scleral canal. Since the disc is usually temporally tilted, the temporal lamina would sink below the scleral edge first. As the lamina sinks below the scleral edge, the prelaminar axons prior to their entry into lamina cribrosa will be stretched and then axotomized against the scleral edge since one end of the axon is attached to the ganglion cell body of the retina, the other in the sinking lamina.

All the temporal axons consisting of superior and inferior arcuate and centrally located macular axons will be axotomized *simultaneously*. However, the arcuate axons being fewer in number, compared to the macular axons, will be depleted earlier resulting in production of arcuate field defects.

Initially, there would be isolated scotomas in the paracentral region due to depletion of the arcuate axons, but once all the arcuate axons are axotomized and depleted there would be sharply defined arcuate field defect whereas the macular axons will last until the end-stage due to their abundance.

This may answer puzzling question # 2 as to why the arcuate axons are being selectively destroyed in the early stages of chronic glaucoma whereas the macular axons (central vision) last until the end stage of glaucoma. The question arises as to why the peripheral fields are lost early in glaucoma?

As mentioned earlier, the peripheral axons (for the peripheral vision) lie deeper and exit closer to the scleral edge. Therefore as the sinking of the optic disc occurs the

deeper axons will be axotomized against the scleral edge first. If cupping was occurring, then the central and superficial axons (closer to the vitreous) should have been destroyed first, but this not the case since peripheral axons are being destroyed first, consistent with the sinking disc.

10. What happens as the sinking of the disc continues?

The optic disc is secured in the scleral foramen by two factors, one is the border tissue of Elschnig which acts as an 'O' ring seal and other is the 360 degrees of the axons themselves which anchor the optic disc in place as roots anchor a tree. As the optic disc becomes more loose and sinks further, it results in severing of additional axons. As the deeply located peripheral axons are being axotomized, the disc will sink further therefore the central axons will move towards the peripheral part of the disc and come closer to the scleral edge and thus also axotomized. The movement of the central axons towards the periphery breaks the physiological cup and thus the so called enlargement of the cup. It is not a true enlargement but rather breaking up of the physiological cup which I would prefer to describe as an excavation or de-cupping rather than cupping. Loss of anchorage of the disc as a result of severed axons will create a self propagated cascade of loosening and sinking of the disc which would continue until all the axons are axotomized at the scleral edge. Thus, the sinking of the disc would become unstoppable akin to a sinking ship. Histology of the end-stage glaucomatous disc reveals an empty crater devoid of the lamina and the axons. Where did they go? Most likely the lamina after becoming empty of axons is lying at the bottom of the crater akin to a sunken ship.

This may answer puzzling question #3 as to why glaucoma can't be halted despite maximally lowering of IOP.

Points against the cupping of the optic disc

- The physiological cup of an optic disc is a superficial depression in the center of an otherwise flat optic disc which is produced by the atrophy of the Bergmeister's papilla in fetal life. Histology of the normal optic disc identifies this cup as a central connective tissue meniscus. It is difficult to believe that the physiological cup made of fibrous tissue would enlarge in response to high IOP and then reverse in size when the IOP is lowered. If the cup is being affected by raised IOP, then the mechanical force of high IOP should have deepened rather than concentrically enlarged the cup. If the high IOP is concentrically enlarging instead of deepening the cup, then it may be defying the laws of physics.
- If there is a true concentric enlargement of the physiological cup, then it would imply that the subjects born with small cups such as 0.2 cup/disc ratio would take a longer time to become 100% cupped or totally blind, whereas subjects born with large cups like 0.8 cup/disc ratio would become totally blind sooner as they are already 80% cupped to begin with. But this is not the case. If cupping is produced due to high IOP, then why is it not occurring in acute glaucoma where the IOP goes very high whereas cupping is occurring in NTG in which the IOP is within normal range?
- True concentric enlargement of the physiological cup cannot selectively destroy the arcuate fibers as it should be involving the entire 360 degrees of axons and not only the arcuate.
- Axons for the central vision are located in the central part of the disc and also superficial (closer to the vitreous). If the cupping were occurring, then the central axons should have been destroyed first but instead the peripheral axons which are located deeper are being destroyed first in glaucoma.
- Ophthalmic literature and textbooks describe the phenomenon of reversal of cupping when the IOP is lowered. This may be a fallacy. The cases described are usually those in which the IOP has been suddenly and drastically lowered by glaucoma surgery. Due to too much lowering of the IOP, there is rebound hyperemia or papilledema of the optic disc resulting in reduction in the size of cups. If there is a true reversal of cupping, then we should also have witnessed the reversal of lost vision and of visual fields and also regaining of the lost axons. But this is not occurring.
- If the original cup was enlarging concentrically, then the central blood vessels should have remained centrally and not had displaced nasally.

Points favoring sinking of the optic disc.

- Sinking of the optic disc may explain the excavation of the optic disc since the axons are being severed and depleted unlike flat disc atrophy in which the axons are being atrophied and not severed. Arcuate or wedge shaped defect in the retina pertaining to total disappearance of the arcuate axons as seen on red-free ophthalmoscopy can only be explained that the axons are being axotomized and not atrophied in glaucoma. Arcuate shaped defects in the retina are not present in non-glaucomatous optic atrophy because in these cases the axons are being atrophied and not axotomized. End –stage glaucomatous disc is an empty crater due to axotomy of all the axons.

Axotomy of the axons resulting in excavation of the disc and ultimately the area becoming an empty area is a unique feature of glaucoma.

- Sinking of the disc may explain as to why glaucoma cannot be halted despite maximally lowering of IOP. Once the disc begins sinking, the cascade of loosening and sinking of the disc will ensue until all the axons are axotomized.
- Sinking of the optic disc may explain loss of peripheral field first since the peripheral axons because of their deeper and closer to the scleral edge location will be axotomized first and the central axons at the end.
- Sinking of the optic disc may explain the manifestation of single or double arcuate field defects in the earlier stages of glaucoma.
- Sinking of the optic disc may explain the nasal shifting of the blood vessels due to loss of anchorage created

by the severance of the temporal fibers more so than the nasal fibers due to usually temporally tilted optic disc.

- Sinking may explain the occurrence of splinter hemorrhage which may be due to severing of the smaller blood vessels, a fate similar to that of axons.
- Sinking may explain progressive thinning of RNF layer as revealed by OCT due to continuous severing and depletion of the axons.
- Sinking of the disc may explain the thinning of the ganglion cell complex of the macular area in early stages of glaucoma because the macular fibers are also being axotomized along with the arcuate fibers.
- Severing of the axons in glaucoma may explain the retrograde degeneration of ganglion cells of the retina proximally and also of the neurons in the lateral geniculate nucleus and of the occipital cortex distally.
- Sinking of the optic disc may explain sloping and kinking of the blood vessels at the entire disc margin occurring prior to any change in the contour of the physiological cup.
- Sinking of the optic disc may explain the higher incidence of chronic glaucoma in myopia due to inherent thinning and weakness of the border tissue making the 'O' ring seal weaker thus myopic discs are more prone to sinking.

CONCLUSIONS:

There are two main points in my hypothesis. **First, the optic disc may be sinking in its entirety and secondly, the axons are being severed, not atrophied in glaucoma**. **Lamina cribrosa may not be the primary site of injury in glaucoma, the prelaminar axons prior to their entry into lamina cribrosa are being severed against the scleral edge**.

End-stage histology of the glaucomatous disc reveals an empty crater, which can only be explained if the axons are being severed, whereas the histology of non-glaucomatous flat disc atrophy reveals shrunken and collapsed axons but no empty crater since no severing of the axons is occurring in such cases.

Axotomy of the axons resulting in excavation of the disc is the unique feature of chronic glaucoma.

I believe the term cupping was mistakenly given 150 years ago. About 40 years ago another term 'cup-to-disc ratio' was introduced which instead of facilitating, has made glaucoma diagnosis even more complicated. With the concept of cup-to-disc ratio, subjects born with large cups but normal IOP and normal fields may be treated as NTG whereas those born with small cups but high IOP may be ignored treatment as an OHT.

13. Ironically, nowhere else in medicine the same phenomenon or parameters are being used to describe both healthy and the diseased state of an organ as is the use of term *cupping* describing both the physiological and pathological cupping. No wonder there is a great inter-clinician variance in glaucoma diagnosis despite the invention of OCT and other high-tech instruments. If we see a new patient with large cups with normal visual fields, then how can we know if these large cups are physiological pathological if the previous photographs are not available?

The sinking optic disc will be a paradigm shift to the cupping theory. Cupping of the optic disc implies that the problem starts from the center of the disc end extends towards the peripheral part or in other words the central axons (for central vision) should be destroyed first and the peripheral axons (for the peripheral vision) at the end, but this is not occurring in glaucoma. Sinking of the disc will imply that the peripheral axons will be destroyed first and the central axons at the end and this is exactly what is revealed by visual field examination in glaucoma.

All I ask my colleagues is to view the glaucomatous discs as sinking rather than cupping (gestalt switch), and then they for themselves can decide if the disc is cupping or sinking in glaucoma.

My colleague ophthalmologists weigh all pros and cons in the light of above arguments.

Finally a quote from Albert Einstein " ***The significant problems we face cannot be solved at the same level of thinking we were at when we created them."***

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CHANGE OF PARADIGM

Dr. Husnain thinks that we are working under a wrong paradigm of "Cupping of the Disc" mistakenly given to us 150 years ago. He considers ' why RNFL thins out in glaucomatous disc only? How and Why? ' Scientists fail to answer this vital question. He claims that such changes can occur in non-glaucomatous flat disc atrophy as well. Though it is difficult to change the old established paradigm, yet we think that the young generation may take up this challenge and convert the old paradigm in the light of new concepts based on modern thinking '**Sinking Disc Hypothesis**'

The World Glaucoma Congress in Boston has turned down his changing paradigm without explaining any scientific reason which appears ***unethical.*** In the world of emerging scientific advancement, we must ascertain on scientific lines which is the mainstay of our searching methodology in the New World Order.

Thomas Kuhn writes in his famous book **"*Structure of Scientific Revolution"*** that **Almost every significant breakthrough in the field of scientific endeavor is first a break with the tradition, with old ways of thinking, with old paradigms**" .

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