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Structure and Function Relationship in Glaucoma- Historical Perspective to a Practical Approach

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1. Introduction

Physicians, by nature, seem to strive for more precise means to diagnose, quantify and manage chronic disease. It seems intuitive that doing so will help us diagnose earlier, have an increased understanding for the relative severity of disease in individual patients and, ultimately, through more timely diagnosis, mitigate morbidities associated with that disease. In the example of diabetes, we can now look at glycosylated hemoglobin levels (HbA1c) and derive a reasonable understanding of risk level and relative treatment success for individual patients. While the HbA1c value is not flawless as a metric, it has become an extremely robust and accepted tool in diabetes management. Our efforts to coalesce ocular physical measurements with functional values seem to point to our desire to define glaucoma in one simple value. While the effort itself has already shed great benefits to our understanding of this complex disease, it ultimately seems unlikely that we will ever be able to adequately define glaucoma in terms of a singular value.

During the past century, the metrics used to diagnose and manage glaucoma have varied and evolved. In the 1950's, using Schiotz tonometry, Leydecker showed that approximately 2.5% of the population had intraocular pressures greater than 21mm Hg. It was also determined that a similar number of people in that study had glaucoma. From that point forward, 21mm Hg became the empirical metric for determining who was at risk. More than fifty years has passed since the publication of Leydecker's study and a cornucopia of compelling scientific literature has been presented which has shed light on the diversity and complexity of glaucoma and clearly diminishes its relevance as a stand-alone diagnostic feature. Ironically, the vast body of evidence which clearly discourages reliance of the old 21 mm red flag in glaucoma diagnosis seems not to have been sufficient to clear it from the minds and hearts of too many

eye doctors in this century. It would appear that we have an inner need to strive for and adhere to simple answers to even the most complex problems.
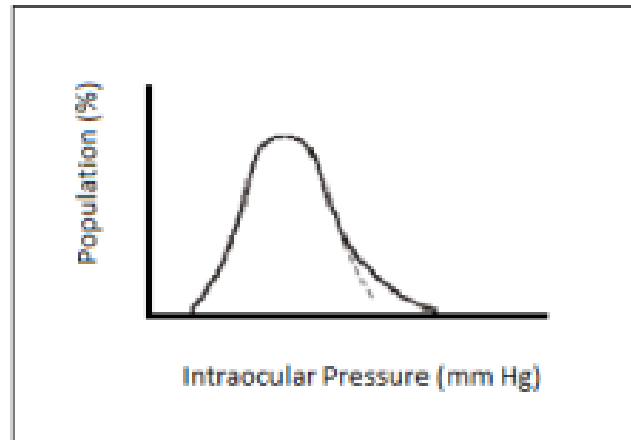

Figure 1. CURRENT SIGNIFICANCE OF 21 mmHg: The distribution of IOP in the general population as studied by Ley-decker (normal IOP was statistically defined two standard deviations above and below mean, as 11-21 mmHg) is not Gaussian, but is slightly skewed towards higher IOP's [1]

Beyond the early observation that glaucomatous vision loss is generally accompanied with high intraocular pressure, scientists began to observe the physical changes within the eye that seemed to occur in concert with that loss. In 1885, Priestley Smith elegantly defined glaucoma, stating that "The excavation of the disc in glaucoma is not a purely mechanical result of exalted pressure; it is, in part at least, an atrophic condition which, though primarily due to pressure, includes vascular changes and impaired nutrition of the substance of the optic disc… which may possibly progress even though all excessive pressure be removed". Given this understanding, eye doctors started to look for tools to study the eye and its function in greater detail.

Today, eye doctors are challenged with a new puzzle. In current clinical practive we can obtain physical and psychometric data that was previously unimaginable. We are still attempting to determine which of the vast data has the greatest utility and specificity in regard to the diagnosis, quantification and management of glaucoma.

2. Observation and measurement of structure

2.1. Ophthalmoscopy

Understandably, long before doctors could document the eye's interior contents with imaging techniques, observation and evaluation of the nerve was performed by ophthalmoscopy. Observations were recorded with drawings. Though others produced earlier versions of the ophthalmoscope, in 1851, Hermann von Helmholtz reported its usefulness and, therein, revolutionized ophthalmology.

Figure 2. Early Welsh Allyn ophthalmoscope

In 1915, Francis A. Welch and William Noah Allyn invented the world's first hand-held direct illuminating ophthalmoscope, precursor to the device now used by clinicians around the world. This refinement and updating of von Helmholtz's invention enabled ophthalmoscopy to become one of the most ubiquitous medical screening techniques in the world today. The company started as a result of this invention is Welch Allyn. [2]

The need for stereopsis arose soon after the discovery of the ophthalmoscope. Given the limitations of a two dimensional view, the glaucomatous cup was, at first, mistaken for a swelling. At that time, Brewster's popular stereoscope was introduced, and its theory and method were then applied to ophthalmoscopy by Giraud-Teulon. His was the first binocular instrument, subsequently much improved by Zachariah Laurence. Binocular indirect ophthalmoscopy was abandoned toward the end of the 19th century in favor of direct monocular ophthalmoscopy, until it was revived in the 1950s by Schepens. More recently, hand held biomicroscopic lenses, which were popularized in the late 1980's by Volk Optical, Inc., are now a clinical standard for indirect three dimensional observations and evaluation of the nerve. [3]

3. Disc documentation

3.1. Drawings

Having the ability to view the nerve in vivo, proper scientific method deemed it necessary to document of these observations. For the better part of the twentieth century, manual drawing of the disc remained the clinical standard.

While disc drawing and careful direct observation of the nerve still have significant benefits, our scientific curiosity and our frank understanding of the likelihood of human variability and error with manual drawings, has driven us to develop methods of observation and recording which yield information down to the cellular level and render documentation which is relatively free of the obvious variability in individual observer skill and methodology.

Before the mid 1970's, eye doctors, in training, could not yet see photographs of the live human retina. Ophthalmic texts traditionally included drawings of normal and pathological eyes, which were rendered by professional medical artists.
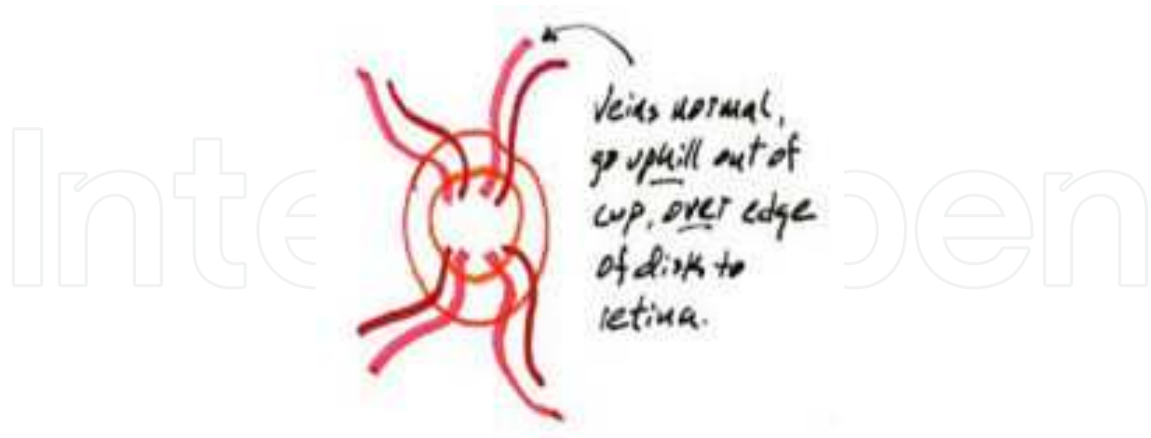
Veins normal, go uphill out of cup, over edge of disk to retina.

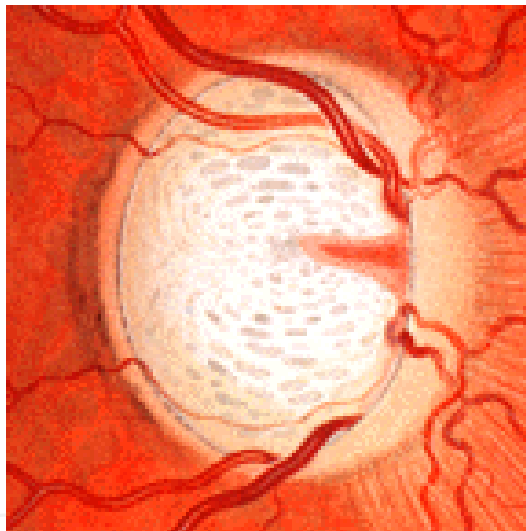**Figure 3.** Typical clinician's disc drawing

Figure 4. Medical artist's disc drawing of glaucomatous optic nerve

3.2. Photography

With fundus photography becoming commonplace by the early 1980's, stereo disc photography became possible and earned its place as the clinical gold standard in optic nerve documentation for the remainder of the twentieth century.

Recently, digital two and three dimensional photography have quickly outpaced conventional film photography of the nerve because of its obvious advantages in efficiency, economy and portability.
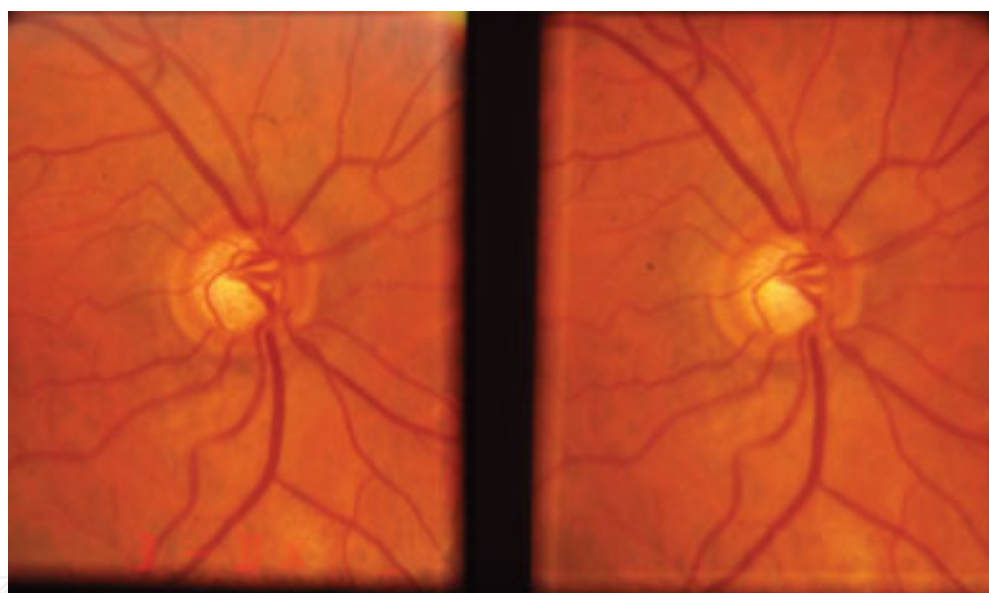
Figure 5. Optic nerve photograph

Figure 6. Simultaneous digital stereo disc photograph captured using the Nidek 3-DX system

3.3. Beyond photography

While photography had given us robust methodology for documentation of the appearance of the optic nerve head, it seemed natural to look for ways to numerically quantify various nerve attributes. An early attempt called the Glaucomascope, cast a series of infrared bars across the surface of the nerve. The variation in line contours signaled the instrument to make calculations regarding cup dimensions and, hopefully, track topographical change in concordance with glaucoma progression. The next generation of devices including the GDX (Carl Ziess) and the Heidelberg Retinal Tomograph (HRT) (Heidelberg Engineering), provided a

more comprehensive perspective of nerve attributes and, with GDX, added new measurements of the nerve fiber layer surrounding the papilla. The HRT was the first to incorporate nerve progression analysis.
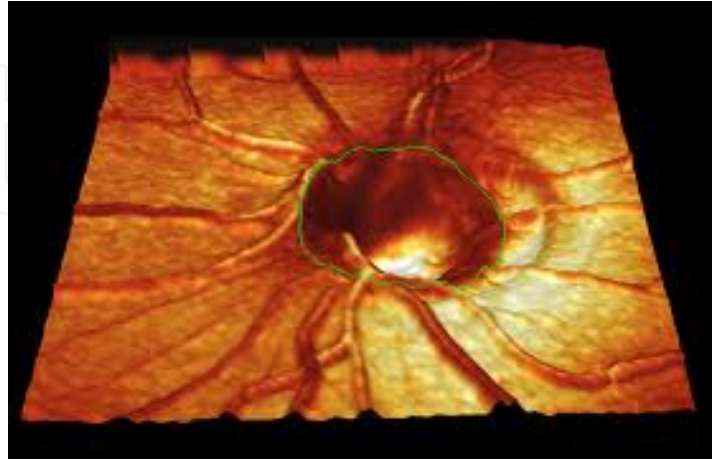

Figure 7. HRT 3-D image of the optic nerve and retinal nerve fiber layer (RNFL)

The Heidelberg Retina Tomograph (HRT) is a confocal scanning laser ophthalmoscope. A laser light scans the retina in 24 millisecond sequential scans, starting above the retinal surface, then capturing parallel images at increasing depths. The stacks of images can be combined to create a three-dimensional (3-D) topographic image of the retina. Images are aligned and compared using TruTrack™ software for both individual examinations and for detecting change between examinations.

When applying the technology to glaucoma, the HRT takes data from a 3-D stack of tomographic images of the optic nerve and retinal nerve fiber layer (RNFL), aligns the images and computes a 3-D topographic map of the surface of the retina. This 3-D topographic map is analyzed for signs of glaucomatous damage and the results are displayed on either a single eye examination report or on an OU examination report.

The GDx nerve fiber analyzers measures the retinal nerve fiber layer (RNFL) thickness with a scanning laser polarimeter based on the birefringent properties of the RNFL. Measurement is obtained from a band 1.75 disc diameters concentric to the disc.

The GDx projects a polarized beam of a light into the eye. As this light passes through the NFL tissue, it changes in speed. The detectors measure the change and convert it into thickness units that are graphically displayed. The GDx measures modulation around an ellipse just outside the optics disc and ratios of the thickest points either superiorly or inferiorly to the temporal or nasal regions.

The state of polarization of the light is change (retardation) as it passes through birefringent tissue (cornea and RNFL). Corneal birefringence is eliminated (in part) by a propriety 'corneal compensator'. The amount of retardation of light reflected from the fundus is converted to RNFL thickness.
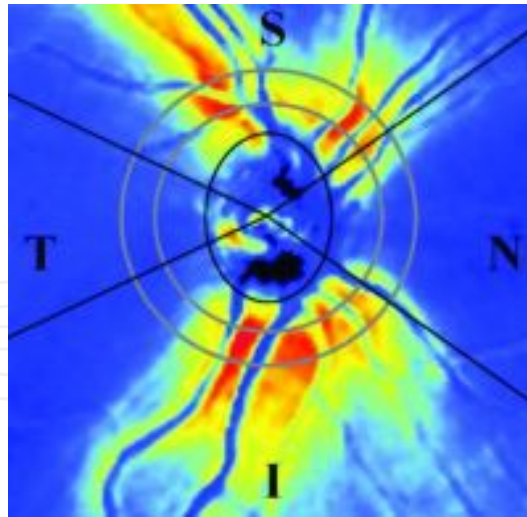
Figure 8. GDX ONH image

A Dutch study found that while there is a correlation between standard automated perimetry and GDx, variable corneal compensation (VCC) measurements in patients with glaucoma, suggesting that GDx VCC measurements relate well with functional loss in glaucoma. In healthy subjects, they found virtually no correlation between perimetry and GDx VCC measurements. This would cast doubt on its predictive value and suggests false positives. [4]

4. Ocular Coherence Tomography (OCT) – the new gold standard

Optical coherence tomography (OCT) has advanced considerably since it was first applied to the eye. It is an extension of a technique called low-coherence interferometry, which was initially applied to ophthalmology for in vivo measurements of eye axial length. OCT cross sections are used to evaluate the optic disc and retinal layers such as the retinal nerve fiber layer (RNFL). Scan patterns that enabled reproducible measurements were developed, and these eventually became incorporated into commercial systems. In 2000 Zangwill et al published a study comparing OCT nerve fiber thickness values against stereo photography and threshold visual field results showing that the OCT shows promise for providing quantitative measures of RNFL thickness for diagnosing and monitoring glaucoma. [5]

With these improvements in speed and sensitivity as seen in spectral domain OCT, it is now feasible to collect volumetric (three-dimensional; 3D) scans of tissue, whereas in the past, the amount of time required to do this would have been prohibitive. Broadband volumetric retinal imaging with SD-OCT have demonstrated speeds of up to 312,500. To date, most clinical systems operate at an acquisition rate of ~27,000 A-scans/s and an axial resolution of 5 to 6 μm.

The unprecedented speed and versatility of current forms of OCT have given us a new and vast data set, allowing us to seek out specific retinal measurements that are most highly specific for the diagnosis and observation of glaucomatous progression. Having the capacity to observe tissue at a cellular level, we now can more aptly compare between individuals and with specific

individuals over time. The additional information at hand also allows us to emerge from cup/disc ratio, the age old and weather beaten descriptive of the nerve in the context of glaucoma. It is now possible to look far deeper into retinal and nerve attributes and across a wider diameter of retina, to look for structural changes that are most highly pathognomonic of glaucoma and its progression. [6]
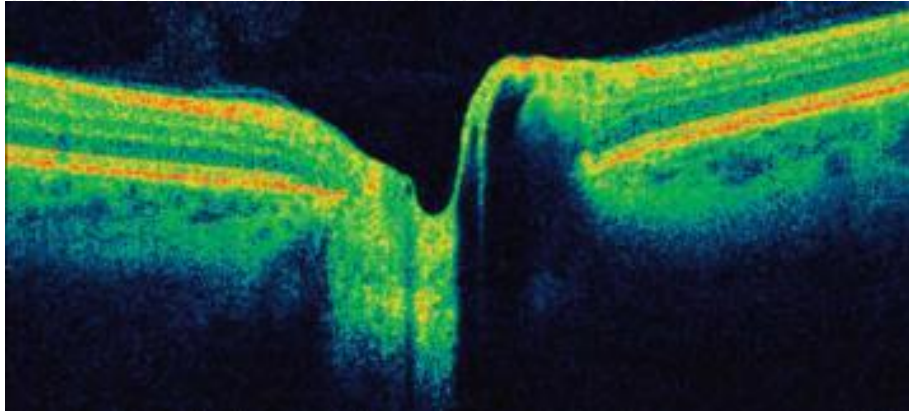

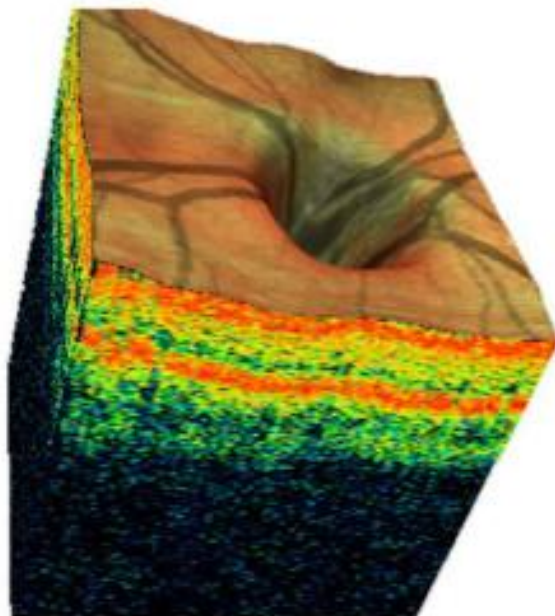**Figure 9.** OCT crossectional view of the optic nerve

Figure 10. OCT three dimensional optic nerve scan

5. Measuring the nerve

5.1. Cup Disc Ratio (C/D)

In quantifying glaucoma risk and severity, the C/D ratio of the optic nerve has been the standard bearer during the past one hundred years. An eye with a low ratio was considered less apt to be glaucomatous and, if glaucoma was diagnosed, was known to be less advanced. High ratios implied high risk and or advanced disease. Some investigators noted that that the significance of a specific C/D value would vary widely depending on the diameter of the nerve itself. Investigators also began to note that nerve attributes such as rim thickness can be quite meaningful. For example, given two nerves with C/D=.50, one may have a well centered cup and no glaucomatous visual field loss, while another,.50 nerve, with loss if the inferior margin may show a severe superior nasal field defect. To further confuse the notion of C/D, more recent attention has been given to disc diameter and its implications on the significance of C/D in individual patients. Our current understanding is that nerve diameter plays a large role in the relative value of C/D. A C/D of.60 with a relatively small nerve is likely to have far greater implications with regard to glaucoma than the same C/D in a large nerve.

Given the additional perspective of the influence of cup position and nerve diameter, it should be easy to understand the now diminished value of C/D as a singular descriptive value of the state of disease. Reminiscent of the loss of relevance of the age old "21 mm Hg" standard, our current understanding of the scope of changes that occur within the nerve, surrounding the nerve and, more recently, those changes in the axonal bed and the peri papillary ganglion cell layer, further disenfranchises C/D and the meaningful descriptive of structural change in glaucoma.

5.2. Retinal nerve fiber layer

Technologies such as GDX and, more recently, OCT provide nerve fiber measurements outside of the boundaries of the disc and it has become evident that axonal changes in the area surrounding the nerve are important in understanding the nature and severity of glaucoma. [7, 8]

In a study performed by Bowd et al, clearly revealed that OCT revealed statistically significant quantitative differences in RNFL thickness between OHT and normal eyes within their study population. [9]

Additional studies such as those performed by Garas (2009), Sehi (2009) and Savini (2009) (table 1) have helped develop greater confidence in our ability to clinically determine RNFL thickness and to evaluate those findings in comparison to a reasonable field of normative data. [10-12]

Similar investigations in the following years helped give confidence that there was finally a method of determining RNFL thickness that was reliable enough so that meaningful compar‐ isons could be made between normal and glaucomatous subjects. Beyond that general comparison, investigators could search for specific nerve and other retinal attributes which are more specific to the diagnosis and management of glaucoma. In 2010, Mansoori et al

showed that SD-OCT identified differences in most parameters between eyes with glaucoma and normal eyes and also between eyes with glaucoma and OHT. It was important to note that they also observed that there was overlap of RNFL thickness between normal and OHT eyes, which somewhat limits the ability of this instrument to differentiate between normal and OHT subjects.[13]

	Garas			Sehi			Savini		
	Mean	**Std. Dev.**	**95% Normal Range**	**Mean**	**Std.**	**95% Normal Range**	**Mean**	**Std. Dev.**	**95% Normal Range**
Average RNFL	106.7	7.5	91.7 to 121.7	103.3	12.6	78.1 to 128.5	105.8	14.9	76.7 to 135.6
Superior	128.8	12.8	103.2 to 154.4	134.5	18.6	97.3 to 171.1	128.44	24.48	83.48 to 173.4
Inferior	136.6	12.7	111.2 to 162	129.7	16.9	95.9 to 163.5	137.15	21.99	93.17 to 181.13
S/I Ratio	0.943			1.037			0.936		

Table 1. Retinal nerve fiber layer thickness averages in normal patients. Garas et al 2009 (14 normals), Sehi et al (20 normals) and Savini et al (23 normals)

5.3. Ganglion cell layer

Most recently, the new abundant source of data rendered via spectral domain OCT measurements, allow us to document structural changes in the axonal bed as well as other retinal layers which were thought to, possibly, have close association with some types of glaucomatous progression. It seems intuitive that failing nerves might show changes at their endpoints before doing so in their mid-sections. Additionally, it seemed likely that axonal ganglia might show changes in concert with various types of axonal demise. Studies such as those conducted Desatnik et al and Ziemer et al in the 1990's helped point us to our new appreciation of the value of perimacular measurements. [14, 15]

Determining the extent of retinal ganglion cell loss may prove to be a superior method for identifying glaucomatous progression. The loss of these cells leads to functional deficits and structural changes in the retinal nerve fiber layer (RNFL). In their efforts to correlate structural and functional loss in glaucoma, Harwerth and associates showed that the number of retinal ganglion cells can be reliably estimated from either visual field sensitivity data or from OCT RNFL analysis. [16]

6. Functional measurement

6.1. Subjective testing

The first record of a visual field defect is found in Hippocrates description of a hemianopia from the late fifth century B.C. Ptolemy (150 B.C.) first attempted to quantify the visual field
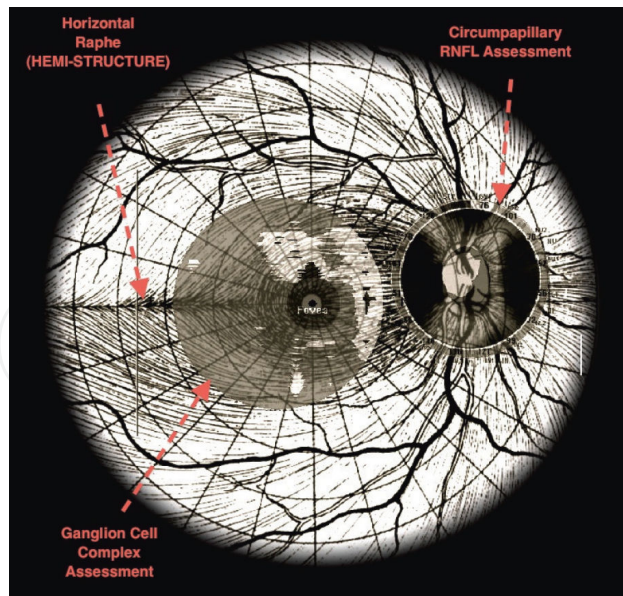
Figure 11. The RTVue scanning zones for assessment of the peripapillary retinal nerve fiber layer (RNFL) and the gan‐glion cell complex (GCC)
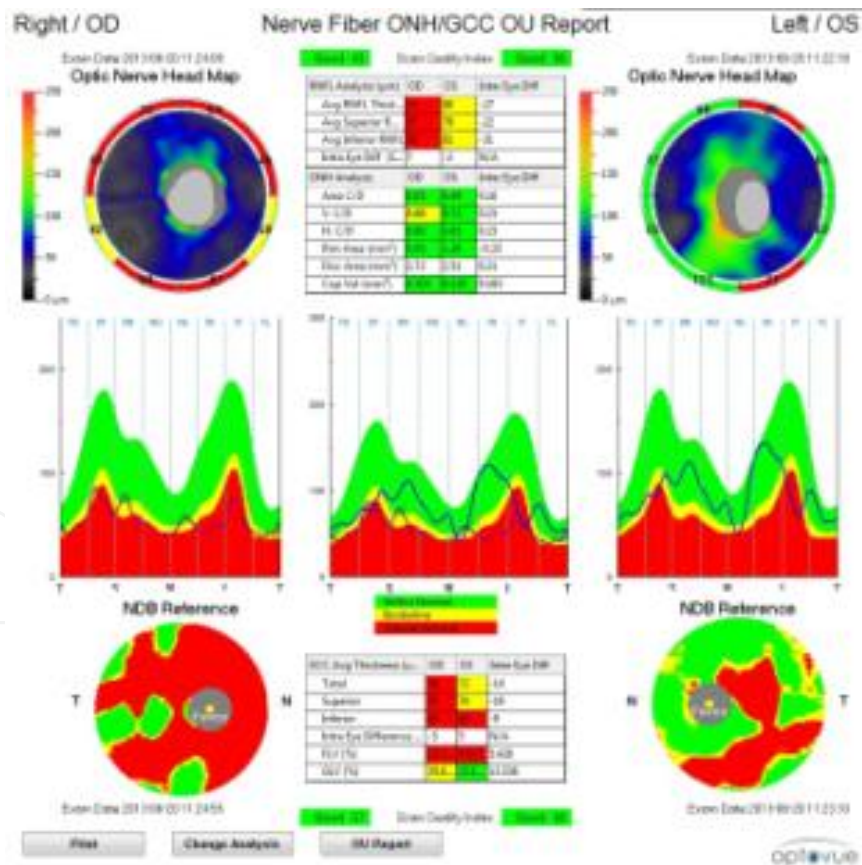

Figure 12. Optovue OCT report showing RNFL and GCC thickness. Colors green, yellow and red indicate normal, bor‐derline and abnormal (low) findings.

and noted its circular form. According to Lloyd, Galen was the first physician "to record a recognition of Extramacular fields." He suggests the first illustration of the visual field was published in an article by Ulmus of Padua in 1602.

Early in the sixteenth century (about 1510) Leonardo da Vinci recognized that temporally the visual field reaches around more than 90 degrees from fixation. He said (Manuscript D. folio 8 verso), "the eye sees those objects behind it that are placed in lateral areas." He suggested that the cornea and the aqueous served to bend the light rays into the eye.
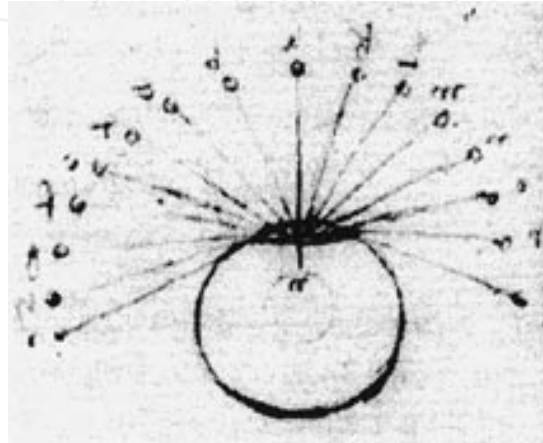

Figure 13. DaVinci's Illustration of rays approaching the cornea from different directions

Von Graefe (below) is credited with introducing perimetry into clinical medicine. In 1855, at the age of 28, he published "Examination of the Visual Functions in Amblyopic Affections." Von Graefe built on the work of Helmholtz. Helmholtz had recommended that, in order to keep one's bearing during the examination of the ocular fundus, a numbered grid be placed in front of the patient to direct the patient's eye into certain known directions of gaze. It was a piece of blackboard marked in this way that von Graefe used as a tangent screen. He worked at a distance of 18 inches and used as a test object a piece of white chalk, about 1 cm across, held in a wire. He made use of various symbols and dots as a fixation point so that the patient could recognize his deficits more easily. [17]

It was not until the late 1980's, when automated perimetry became widely available, that manual methods of visual field assessment were finally outpaced as the clinical standard. With the newfound ability to determine the relative depth of defect of a given point, clinicians had the ability to appreciate a three dimensional plot of one's visual status.

The introduction of computers and automation heralded a new era in perimetric testing. Static testing can be performed in an objective and standardized fashion with minimal perimetrist bias. A quantitative representation of the visual field can be obtained more rapidly than with manual testing. The computer allows stimuli to be presented in a pseudorandom, unpredictable fashion. Patients do not know where the next stimulus will appear, so fixation is improved, thereby increasing the reliability of the test. Random presentations also increase the speed with

which perimetry can be performed by bypassing the problem of local retinal adaptation, which requires a 2-second interval between stimuli if adjacent locations are tested.

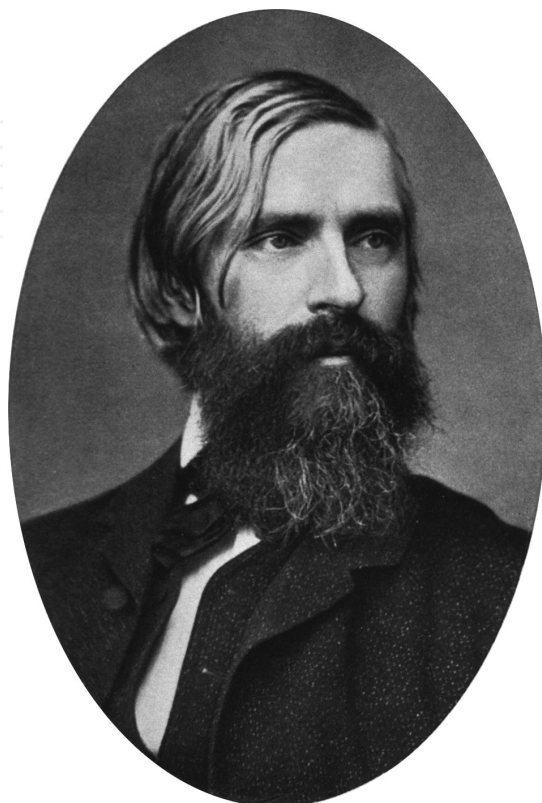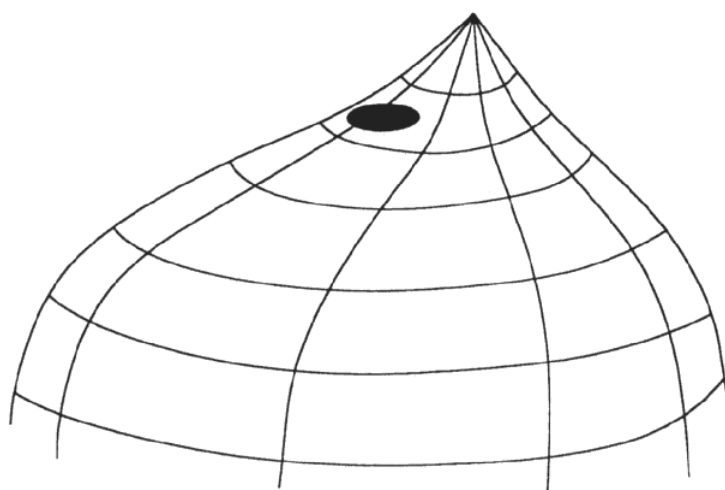**Figure 14.** Albrecht von Graefe

Figure 15. The normal island of vision. The hill is highest at fixation, where visual sensitivity is greatest. The height of the hill of vision declines toward the periphery as visual sensitivity diminishes.

Any clinically or statistically significant deviation from the normal shape of the hill of vision can be considered a visual field defect. In glaucoma, these defects are either diffuse depressions of the visual field or localized defects that conform to nerve fiber bundle patterns. [18]

6.2. Current choices in subjective functional testing

The addition of computerization to assessment of the eyes functional performance led the way to the development of several testing alternatives. Early white on white threshold testing strategies were followed with faster and more efficient programs such as Humphries Swedish Interactive Testing Algorithm (SITA) and the Haag-Streit Tendency Oriented Perimetry (TOP), Along with unenhanced test specificity, both strategies significantly reduce testing times by over 70%. The TOP strategy requires less than three minutes per eye per test.

A daunting point of frustration with the limits of threshold analysis came from the under-standing that significant axonal loss had to have occurred before a repeatable threshold could be demonstrated. In 1982, Quigley reported that as much as 40% of optic nerve fibers may be lost before significant threshold visual field loss. [19]

Alternatives more recent methods in subjective field analysis, such as short wavelength (blue – yellow) and flicker strategies, were developed with the goal of reliably eliciting subject glaucomatous defects at an earlier point the progression of the disease. It is now shown that the flicker type tests such as Frequency Doubling Technology will have a role to play as a glaucoma screening tests, where as the the blue-yellow tests may not be as predictive as once throught. 20 Recently, there has been increased inteest in 10 degree white on white threshold fields because of its greater test point density and its apparent structure relationship to new OCT ganglion cell complex (GCC) imaging analyses. 14, 15

6.3. Objective testing

Objective methods such as Visual Evoked Potential (VEP), pattern electroretinography (pERG) (Diopsys, Inc.), and Relative Afferent Pupillary Defect (RAPDx) (Konan, USA) offer the potential of earlier and more specific functional testing but here continues to be a need to more reliably access functional loss at an earlier point in glaucomagenesis. While VEP and pERG measure the relative integrity of the electrical signal that passes through the nerve during the visual process,

RAPDx expands on the notion of diminished afferent pupillary reflex that may occur as nerve integrity is lost and glaucoma progresses.

With newer imaging methods such as OCT, we have made significant strides in earlier detection of structural loss, while our ability to detect functional loss earlier than what we achieve via white on white threshold field analysis remains a challenge. Given early evidence that VEP, pERG and RAPDx may offer some reliable evidence of early functional change, one can only hope that robust scientific evidence paired with more technical advancement of these types of tools may help us get a bit closer. [21-23]

Figure 16. Visual Evoked Potential (VEP), pattern electroretinography (pERG) (Diopsys, Inc.)

Figure 17. RAPDx (Konan, USA) measures Relative Afferent Pupillary Defect

7. Combining structural and functional data to optimize specificity in diagnosis

Along with our better understanding of the various limitations of either structural or functional analysis as a singular metric for glaucoma management, the obvious question has become can we, somehow, fortuitously coalesce both data sets? By combining the two, can we apprehend glaucoma earlier in its progression and develop better methods of dividing glaucoma into more meaningful subtypes? Will doing so allow us to treat more promptly, effectively and more specifically? Finally, is there a way to combine structural tests with functional tests to give us some type of unified glaucoma value?

Several investigators pioneered early structure function studies with the goal of establishing a better understanding of the relationships between various structural and functional values. In 1976, Stephen Drance described optic disc changes as they correlated to visual field defects in chronic open-angle glaucoma. Drance's studies were followed by Hoskins et al and Hitchings et al who also observed the nature of optic changes which occurred in concert with glaucomatous visual field changes (ref's). [24-26] These investigations were conducted with the goal of pairing specific anatomical changes commonly associated with glaucoma with associated functional (visual field) changes. Others tried to find a common more useful value in combining structural and functional data in different ways. [24-26]

Perhaps, the most renowned investigations which have established the foundations of our current understanding of the structure function relationship were performed by Quigley et al during the 1980's. Glaucomatous eyes were studied posthumously to determine how the number and distribution of human optic nerve axons compared with clinical measurements available the same eyes, including visual acuity, disc appearance, and visual field studies. Quigley reported that definite loss of axons occurs prior to reproducible visual field defects in some patients suspected of having glaucoma. In glaucoma, the superior and inferior poles of the nerve lose nerve fibers at a selectively greater rate, leading to an hourglass-shaped atrophy. He also reported that the pattern of atrophy in examples of toxic amblyopia, ischemic optic neuropathy and chronic papilledema differ from that of glaucoma, suggesting different mechanisms of damage in these conditions.

In later investigations, Harwerth et al described relationships between field loss and retinal ganglion cells. The data were analyzed by a model that predicted ganglion cell densities from standard clinical perimetry, which were then compared to histologic cell counts. Their work became part of the foundation for our current interest and understanding of functional loss in the context of retinal tissue changes beyond the losses previously described in retinal axons. [27-30]

In 2005, Gardiner et al produced a topographical map to demonstrate how sectors of the optic nerve head (ONH) are related to locations in the visual field, using empiric cross-sectional patient data. They observed one hundred nine subjects with healthy eyes and 166 subjects with diagnosed or suspected glaucoma (one test per patient) were evaluated using a Heidelberg Retina tomograph (HRT) and white-on-white standard automated perimetry (SAP). The

Tomograph ONH images were divided into 36 sectors; and the sector rim areas normalized to account for changes in the total rim area. These were then correlated with SAP thresholds. For each visual field location, a map was produced indicating the strength of correlation between the normalized sector rim areas and thresholds. Their efforts resulted in a map relating regions of the ONH to SAP test locations. This map may be useful in elucidating the structure-function relationship, particularly for cases of localized glaucomatous loss.

Their results also indicate that narrowing of the neuroretinal rim in some areas appeared to be more significant than in others, in terms of predicting functional loss; in particular in the polar areas of the ONH. This may account for some of the limitations of predictive power that has been shown of global HRT indices. [31]

In 2010, Harwerth et al attempted to build a model of these linking propositions using data from investigations of the relationships between losses of visual sensitivity and thinning of retinal nerve fiber layer over progressive stages of glaucoma severity. A foundation for the model was laid through the pointwise relationships between visual sensitivities (behavioral perimetry in monkeys with experimental glaucoma) and histological analyses of retinal ganglion cell densities in corresponding retinal locations. The subsequent blocks of the model were constructed from clinical studies of aging in normal human subjects and of clinical glaucoma in patients to provide a direct comparison of the results from standard clinical perimetry and optical coherence tomography. The final formulation is a nonlinear structure-function model that was evaluated by the accuracy and precision of translating visual sensitivities in a region of the visual field to produce a predicted thickness of the retinal nerve fiber layer in the peripapillary sector that corresponded to the region of reduced visual sensitivity. The model was tested on two independent patient populations, with results that confirmed the predictive relationship between the retinal nerve fiber layer thickness and visual sensitivities from clinical perimetry. Thus, the proposed model for linking structure and function in glaucoma has provided information that is important in understanding the results of standard clinical testing and the neuronal losses caused by glaucoma, which may have clinical application for inter-test comparisons of the stage of disease. The model was tested on two independent patient populations, with results that confirmed the predictive relationship between the retinal nerve fiber layer thickness and visual sensitivities from clinical perimetry. Thus, the proposed model for linking structure and function in glaucoma has provided information that is important in understanding the results of standard clinical testing and the neuronal losses caused by glaucoma, which may have clinical application for inter-test comparisons of the stage of disease. [16]

In 2012, Medeiros et al confirmed that an index combining structure and function performed better than isolated structural and functional measures for detection of perimetric and preperimetric glaucoma as well as for discriminating different stages of the disease. Observational study included 333 glaucomatous eyes (295 with perimetric glaucoma and 38 with preperimetric glaucoma) and 330 eyes of healthy subjects. All the eyes were tested with standard automated perimetry and spectral domain optical coherence tomography within 6 months. Estimates of the number of retinal ganglion cells (RGCs) were obtained from standard automated perimetry and spectral domain optical coherence tomography and a weighted

averaging scheme was used to obtain a final estimate of the number of RGCs for each eye. The CSFI was calculated as the percent loss of RGCs obtained by subtracting estimated from expected RGC numbers. The performance of the CSFI for discriminating glaucoma from normal eyes and the different stages of disease was evaluated by receiver operating characteristic curves. [32, 33]
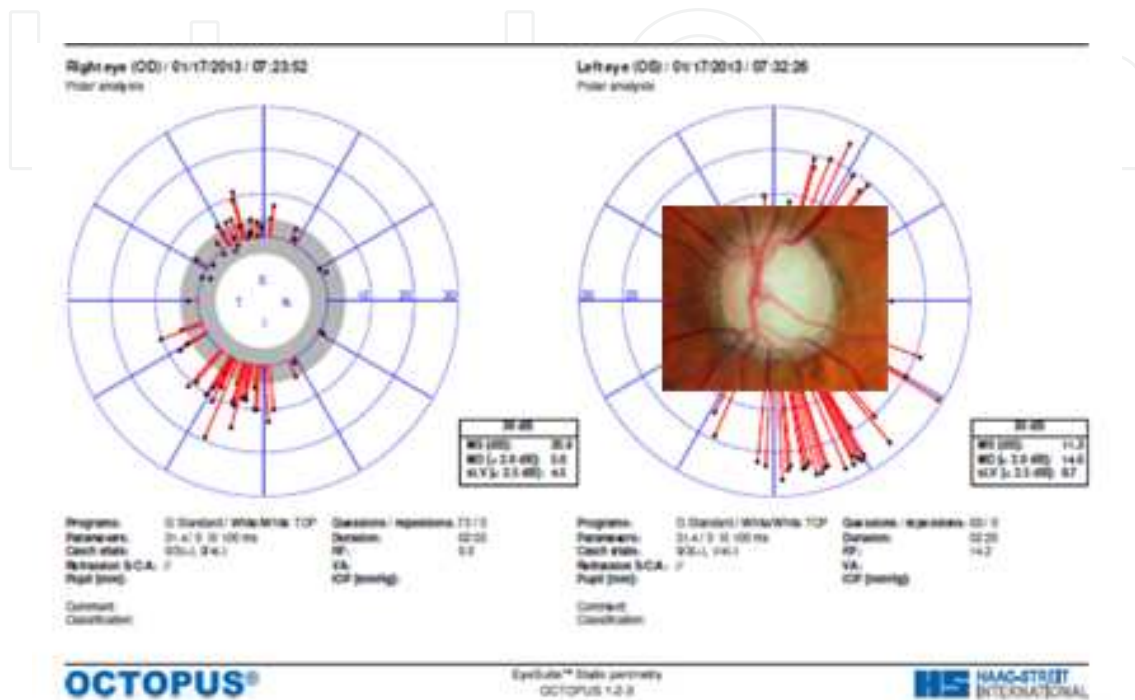

Figure 18. Polar analysis of a threshold visual field showing severity of the defect in concert with nerve anatomy. While traditional graphical reports of field analysis show projected (inverted) findings, the polar analysis is anatomically correct.

In 2013, Meira-Freitas et al demonstrated that baseline and longitudinal estimates of retinal ganglion cell counts based on combined structure and function tests may be helpful in predicting progression, and performed significantly better than conventional approaches for risk stratification of glaucoma suspects. The study included 288 glaucoma suspect eyes of 288 patients followed for an average of 3.8 ± 1.0 years. Estimates of RGC counts were obtained by combining data from SAP and OCT according to previously described method. Joint longitudinal survival models were used to evaluate the ability of baseline and rates of change in estimated RGC counts for predicting progression over time, adjusting for confounding variables. [34]

Also, in 2013, Le et al implemented fourier-domain optical coherence tomography (FD-OCT) system to map the macula and peripapillary regions of the retina in 56 eyes of 38 patients with perimetric glaucoma. The macular GCC and peripapillary NFL thicknesses were mapped and standard automated perimetry (SAP) was performed. Loss of GCC and NFL were correlated with the VF map on both a point-by-point and regional basis, showing that there are significant point-specific and regional correlations between GCC loss, NFL loss, and deficits on SAP. Their

findings suggest that using these different data sources together may improve our understanding of glaucomatous damage and aid in the management of patients with glaucoma. [35]

In 2013, Hye-Young Shin et al Two hundred and thirteen eyes of 213 patients with glaucoma were observed to explore and compare the relationships between the visual field (VF) sensitivities assessed by standard automated perimetry (SAP) and the ganglion cell inner plexiform layer (GCIPL) and peripapillary retinal nerve fiber layer (pRNFL) thicknesses as measured by Cirrus high-definition optical coherence tomography (HD-OCT) in glaucomatous eyes.

The average and sectorial GCIPL thicknesses determined by Cirrus HD-OCT were significantly associated with global and regional VF sensitivity in patients with glaucoma. They concluded that the macular GCIPL thickness values may provide more valuable information than temporal profile thickness values for understanding the structure–function relationships of the macular region. [35]

In 2013, Marín-Franch et al reported their comparison structural and functional damage from glaucoma often using statistical methods such as linear regression, which was agreed to have limitations that can lead to inadequate clinical recommendations. These limitations were analyzed, using examples from the literature. Inferences from linear regression are model dependent. They concluded that tests of linear relations between structure and function in glaucoma may be improved by the use of Deming regression, although its application requires knowledge about test-retest variability of measures of glaucomatous damage. [37, 38]

8. Summary

It has been said that in Einstein's Grand Quest for a Unified Theory "He failed, of course, but he didn't exactly waste his time." Similarly, our search for a simplified common denominator to describe glaucoma in a simple way is likely to fail. Our methods of documenting the optic nerve and various ocular structures related to the genesis of glaucoma have evolved from direct observation paired with hand drawings to ocular corherance tomographic devices, which render elegant cross sectional views with as little as 5 microns of resolution. Quantification of the visual field has also evolved to sophisticated threshold subjective analyses and promising new objective strategies. In spite of this impressive technical evolution, we have yet to agree upon a practical combination of structural and functional data that can provide a single metric for risk of glaucoma and the level of its progression.

Perhaps, the solution to this conundrum can be derived from our acceptance that glaucoma does not appear to be one simple disease, but rather one that is the result of a litany of risk factors that commonly result in the untimely deterioration of the optic nerve. As investigators have and continue to examine the many structural and functional changes that may occur in the process of glaucoma, the field of clinical variables ironically seems to expand rather than contract. Physical changes may be observed at the neural retinal rim first, while in other patients changes in the peri macular ganglion cell layer may be the first signal of glaucomatous

change. Some patients might show degradation in their peripheral visual fields while others seem to start with central changes. Recent investigators have even suggested that early changes, in glaucoma, may occur within the brain.

As with Einstein's Grand Quest, it can be argued that the efforts of researchers to find a "unified glaucoma value" have not been a waste of time. While there seems to be no simple solution to this puzzle in sight, we have been given a far better understanding of glaucoma's multivariate etiology which should enable more specific and prompt diagnosis and, ultimately, more specific and effective glaucoma therapies.

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