Evaluation of the optic nerve head includes both observational and functional studies. Direct study of the optic disc often employs the hand held ophthalmoscope with the accessory use of a green light to allow improved visualization of the nerve fiber layer. Comprehensive analysis of the optic disc is better achieved using a stereoscopic view, which can be obtained directly through the use of various lenses at the slit lamp, by analysis of stereo disc photos, or through computerized tools such as the laser confocal ophthalmoscope. Photographic analysis of the nerve fiber layer is best performed using a wide angle, red-free study. Functional studies of the optic disc employ peripheral vision testing to carefully plot defects in the visual field. Taken together, the disc appearance in conjunction with visual field analysis, help the clinician make a definitive diagnosis or determine if other tests are required.

Direct measurement of optic disc parameters can be made at the slit lamp. Absolute measurements of the disk or cup size depend on the viewing instrument and the use of mathematical formulas. Correction factors for the Goldmann lens are well documented in the literature. Interestingly, photographic measurements are approximately 1.27 times larger than those obtained with the Goldmann three mirror lens at the slit lamp. Hand held lenses such as the Volk 60D or the Volk Superfield noncontact lens require alternate equations that have been published. The neuroretinal rim size is a measurement that has been used in multiple studies of glaucomatous optic nerve damage. As compared with photographic measures, computerized tomography of the optic nerve, using the Heidelberg retinal tomograph, produce larger estimates of the neuroretinal rim size as a percentage of the optic disc. Furthermore, the discrepancy between these types of measurement increase with advanced glaucomatous insult. These studies reveal that absolute measurements are complex and longitudinal studies of individual optic nerves should be performed carefully with similar instruments. Direct comparisons between different evaluation strategies, for example photography, computerized imaging, and slit lamp biomicroscopy, may be misleading.

**OPTIC NERVE PARAMETERS**

**Optic disc**

The normal optic disc ranges in size from 2.1 – 2.8 mm² in adult, non-highly myopic whites. The adult size is reached by age 3. Significant changes in disc area are primarily obvious in eyes that are greater than 5 diopters ametropic, increased size in myopes and decreased size in hyperopes. The myopia-associated increase in disc area is estimated to be about 1.2% for each diopter of myopia. Multiple investigations of the normal size variability of the optic disc have been performed. One large study reveals an increased disc size in blacks. This investigation used 3387 photographic images taken with the Topcon instrument and determined that the average optic disc size in the black population measured 2.92 mm², whereas the disc size in the white population averaged 2.63 mm². This study also revealed larger cups and cup to disc ratios (C/D) in blacks than in whites, 0.04 vs. 0.71 mm² and 0.56 vs. 0.49, respectively. The neuroretinal rim measurements were similar in the two populations. The authors noted an increased disc size in males as compared to females (about 2-3% difference) but failed to consider whether this observation correlated with body mass or height. No age-related differences were noted in the subjects, all older than 40 years of age.

Other large population studies have been performed in Australia and Europe. A study of 3358 phakic subjects older than 49 was performed in the Australia Blue Mountains region. This study revealed an increased C/D ratio in association with age, 0.01 for each decade, and IOP, 0.04 for each 10 mm Hg. A study of 5114 subjects older than 55, performed in Rotterdam, revealed a mean disc area of 2.42 mm² with a normal variability of about 2 fold. The mean C/D ratio was 0.49. This study did not reveal any disc-age correlation. Increased disc area was associated with gender (male), increasing myopia (disc area increase of 0.033 mm² per diopter of myopia), and increased height (0.02 mm² per 10 cm in increased height).

Large discs or macrodiscs may be congenital or acquired and are either functionally normal or associated with visual abnormalities. Congenital or primary macrodisc may occur in the setting of developmental anomalies such as optic pits or the morning glory syndrome or may be subject to hereditary factors. Megalopapilla is described in the Marshall islands where asymptomatic patients were noted to have large discs (greater than 2.1 mm in diameter) with high C/D ratios (greater than 0.6), normal IOP, normal nerve fiber layer, and no interval change over an 18 year observation in 3 individuals. Primary enlargement of the disc correlates positively with the size of the cornea.
disc may show an oblique orientation \(^\text{13}\). Increasing corneal astigmatism also positively correlates with an increasing and elongated optic disc, with the axis of the corneal astigmatism \(^\text{14}\).

Differentiation between a congenitally or acquired enlarged disc may be challenging in light of the wide variability in the normal range. One clue lies in the observation of cilioretinal arteries. The prevalence of cilioretinal arteries is about 0% in small discs (< 2.0 mm\(^2\)) and up to 50% in large discs (> 4.1 mm\(^2\)) \(^\text{15}\). It has been suggested that the presence of two cilioretinal arteries help differentiate a congenitally large disc in a normal eye from an acquired macrodisc.

### Neuroretinal rim

The normal neuroretinal rim is broadest inferiorly with the most obvious nerve fiber bundles, and decreases in thickness first superiorly followed by the nasal and temporal rims \(^\text{2,16,17}\). In glaucoma, loss of rim tissue usually starts in the inferotemporal and superotemporal regions. In advanced glaucoma, prominent loss in the temporal disc is apparent. This pattern of loss of neuroretinal rim tissue correlates positively with perimetric data. Pallor of the disc, in glaucoma, is commonly associated with cup enlargement. Focal or diffuse absence of the rim is more consistent with a diagnosis of glaucoma. In contrast, a pale rim raises the suspicion of a non-glaucomatous optic neuropathy.

One hypothesis is that large pores in the lamina cribosa and alterations in the interpore connective tissue may predispose to glaucomatous fiber loss \(^\text{2}\). Bowing of the lamina cribosa outward is a typical feature of glaucoma and the pathophysiology of this structural change is uncertain. Experimental studies of the lamina cribosa reveal an age-related decreased mechanical compliance \(^\text{18,19}\). Biochemical studies show an age-related increase in elastin and concomitant decrease in fibronectin and glial fibrillary acidic protein (GFAP) \(^\text{19}\).

### Optic cup

The optic cup is defined as the central depression in the optic nerve head, observed by contour, not color. On physical examination the cup is best defined using slit lamp biomicroscopy with a high power view or by analysis of stereo photography. Kinking of the vasculature on the optic disc may help serve as a guide. Abnormality of the cup is often defined as outside of 2 standard deviations from the population mean. However, there is significant challenge in differentiating the normal, but enlarged cup, from the pathologically altered cup. Digital optic nerve imaging

Computerized evaluation of the optic disc, cup, and rim has been of increasing interest particularly in the area of glaucoma screening and diagnosis \(^\text{20-22}\). Controversy exists as to whether this modality is an effective tool to evaluate and diagnose optic nerve damage. The confocal laser scanning tomography was used to evaluate nerves of 161 subjects with glaucoma, defined by an open anterior chamber angle and typical glaucomatous visual field defects, and compared the findings to those obtained from 194 normal subjects \(^\text{23}\). Multiple different mathematical formulas were assessed to determine the predictive power of the test for the diagnosis of glaucoma. The sensitivity and specificity of the formulas ranged from 50-94%, with the sector based formula providing the most precise diagnostic score. However this strategy was less accurate in the analysis of small optic discs. From a practical standpoint the ophthalmoscopic observation in the early detection of glaucomatous change was more precise than any combination of computerized analysis.

A large study was performed of the use of scanning laser ophthalmoscopy in the evaluation of four types of glaucomatous disc appearances in 2,388 subjects \(^\text{24}\). The categories of discs studied included focal ischemia, myopic glaucomatous, senile sclerotic, and generalized cup enlargement. Scanning laser ophthalmoscopy was able to accurately detect nerves with visual field damage in 92.3% of focal ischemia, 81.6% of myopic, 66.7% of senile sclerotic, and 78.6% of discs with generalized cup enlargement. The conclusion from this large study was that the clinical evaluation remains the gold standard in the evaluation of the optic disc.

Utility of digital imaging in the preperimetric diagnosis of glaucoma was tested in 102 glaucoma suspects with increased IOP and a normal visual field. The Heidelberg retinal tomograph was used to obtain the data in order to compare values from the glaucoma suspect group to those of 50 normal controls and 61 known glaucoma patients \(^\text{25}\). Although differences were observed between the groups a high interindividual variability limited the power to differentiate between normals and preperimetric glaucoma. The use of digital images in the diagnosis of glaucomatous optic nerve changes may have better utility in the longitudinal study of individuals rather than as a screening tool in a large population \(^\text{26}\).

### The optic disc in prematurity

Prematurity alone, studied in a group of infants with an average of 27 weeks gestation, is associated with smaller discs and smaller rims but no change in cup area, giving an increased C/D appearance \(^\text{27}\). In contrast, optic nerve hypoplasia exhibits a small cup, small rim, and small disc with retinal vascular anomalies \(^\text{28}\). Optic nerve hypoplasia has been associated with the fetal alcohol syndrome and with periventricular leukomalacia \(^\text{29}\).

Alteration in the cerebral circulation in the preterm infant prior to 34 weeks gestation may result in a variety of optic disc abnormalities. Difficulties in tissue...
oxygenation and impairment of autoregulatory mechanisms of cerebral blood flow, in combination with a low perfusion pressure, may result in tissue hypoxia in a watershed type of distribution. This hypoxia may result in damage to the actively proliferating and differentiating oligodendrocytes precursors. Alternatively, impaired venous drainage with edema and subsequent hemorrhage may result in hypoxia. Gestational timing of the hypoxic insult may cause optic disc hypoplasia or may produce large cups in normal discs with small neuroretinal rims.

THE LARGE CUP
An enlarged C/D ratio may indicate a pseudoglaucomatous condition or may be associated with glaucoma, chronic ischemia, retinal degenerations, inflammation, trauma, or compression. Pseudoglaucomatous large cups
A series of optic discs with pseudoglaucomatous cupping (N=21) were compared to 571 normal optic discs and 706 glaucomatous optic discs. The optic discs with pseudoglaucomatous cupping typically had larger disc areas (4.49 mm²), larger cup to disc ratios with an increased horizontal ratio, increased incidence of cilioretinal arteries, normal neuroretinal rim area, normal configuration of the neuroretinal rim, and a normal nerve fiber layer. In this study the increased incidence of cilioretinal arteries was also noted in conjunction with a normal rim area and normal rim configuration. Reversibility of the enlarged cup
Evidence for plasticity the C/D size is demonstrated in short-term studies. A prospective study of 13 adults with open angle glaucoma and elevated IOP was performed over a 3-4 month time period. This study used a computer-facilitated analysis to quantitate the cup volume and the C/D ratio. The initial IOP in these patients was 33 mm Hg (+/- 8 mm Hg) and the final IOP averaged 16.9 mm Hg (+/- 6 mm Hg). The C/D ratio showed a significant decrease from 0.573 to 0.499 over the course of this study with an accompanying increase in the mean neuroretinal rim area. The change in the C/D ratio was proportional the decrease in IOP.
A more recent study used a computerized optic nerve head analyzer to determine the C/D ratio in 17 patients with chronic open angle glaucoma over the course of therapy. This group of patients were evaluated at times of low IOP (therapeutic success), increased IOP (therapy failure or medication noncompliance), and with resumed IOP control (additional of medication or improved compliance). A positive association between the C/D ratio and IOP was noted and associated with an average increase or decrease of 10 mm Hg.
Experimental observations of the relationship between IOP and optic cup was performed in volunteers. A total of 10 myopic (mean refractive error was –5.7 D) and 10 emmetropic individuals were studied with the Heidelberg retinal tomography unit to determine optic disc parameters at a normal IOP and following the transient elevation of the IOP by 20-25 mm Hg. Elevation of IOP for approximately 2-3 minutes was achieved through use of a suction cup applied to the conjunctiva with ascertainment of IOP by tonopen. The cup area and volume significantly increased in both emmetropic and myopic subjects in association with increased IOP.
Glucoma
The increased C/D ratio in associated with glaucoma is well characterized. Rim pallor should not occur with glaucomatous damage and implies the need for further diagnostic testing in the setting of suspected normal tension glaucoma. Morphologically, juvenile onset chronic glaucoma is similar to chronic open angle glaucoma in the increase in the C/D ratio, steepness of cupping, and neuroretinal rim abnormalities. Pseudoxefoliation may be associated with an increased C/D ratio. A study of 66 patients with unilateral exfoliation observed an average increase of 1.6 mm Hg in IOP in the exfoliative eye but no significant difference in the C/D ratio, disc area, or neuroretinal rim. Prospective study of 22 patients with unilateral pseudoxefoliation over a 3 year period demonstrated equal IOP measurements with unilateral changes in the C/D appearance in the exfoliative eye. Careful slit lamp analysis for pseudoxefoliation should be performed in the setting of a unilateral increased C/D ratio.
Optic disc hemorrhage has been observed in association with glaucoma and may be helpful in the differential diagnosis of an enlarged C/D ratio. This large study analyzed photographs of 3654 optic nerves from individuals older than 49 years for the presence of disc hemorrhage. The overall prevalence of hemorrhage was 1.4%. Patients with known glaucoma had a disc hemorrhage prevalence of 13.8%. The individuals with normal tension glaucoma had the highest incidence of hemorrhage (25%) whereas the rate for individuals with ocular hypertension was low (1.5%). Other associations with the presence of disc hemorrhage included increased IOP, pseudoxefoliation, diabetes, and increased systolic blood pressure. Disc hemorrhages in patients without glaucoma were associated with a large vertical C/D ratio or a history of typical migraine. Interestingly, no association was found between the presence of disc hemorrhage and a history of vascular events or the use of aspirin or tobacco.
Concern about the possible relationship between panretinal photocoagulation (PRP) and subsequent disc appearance prompted formal analysis of the C/D ratios in these patients. Photographs of individuals from the
Wisconsin Epidemiologic Study of Diabetic Retinopathy were evaluated. No correlation between changing C/D ratios and PRP was noted; however, a larger C/D ratio was noted in patients with a history of glaucoma. Retrospective analysis of photographs of eyes prior to and 1 year following PRP also demonstrated stability in the C/D ratio.

Compressive optic neuropathy

Optic nerve compression may result in an increased C/D ratio but is usually associated with neuroretinal rim pallor. One study used magnified stereophotographs to analyze the optic discs of 29 patients with intracranial lesions producing compressive optic neuropathy. Age-matched controls were used as comparisons. The intracranial lesions included pituitary adenomas (n=14), meningiomas (n=7), aneurysms (n=2), and craniofaryngiomas (n=6). Stereo disc photographs were analyzed in a masked fashion and the cup and disc areas were determined. The mean C area/D area ratio of all compromised eyes was 0.37 and controls was 0.10; this demonstrated statistical significance. In particular, cases with unilateral optic neuropathy and compression revealed significant intereye differences, suggesting clinical utility of this observation.

Abnormalities of the carotid artery, either aneurysmal dilatation or ectasia of the carotid artery, may cause slow progressive nerve fiber layer abnormalities and optic atrophy with increased cupping of the optic nerve. However, radiologic evidence for contact between the carotid artery and optic nerve is common and may not indicate pathologic compression. Common causes of optic neuropathy should always be considered in cases of suspected arterial compression of the optic nerve and careful evaluations should be performed prior to neurosurgical intervention for this condition.

Chronic Ischemia

Endothelins are vasoconstrictive peptides (21 amino acids in length) that are produce by endothelial cells and are implicated in the regulation of blood flow and have been associated with vasospastic disease. Several studies have observed either increased plasma levels of endothelin-1 (ET-1) or altered production of ET-1 in normal tension glaucoma patients. These observations are consistent with a potential ischemic etiology in some cases of normal tension glaucoma.

Experimental evidence supports the potential mechanism of endothelin induced chronic ischemia causing an increased C/D ratios with loss of neuroretinal rim tissue. Chronic ischemia at the optic nerve head was induced unilaterally in rabbits by intravitreal injection of endothelin-1. Animals were monitored for capillary blood flow and a decrease of blood flow at the optic nerve head was documented at below 80% of baseline. The C/D ratio was significantly increased in the endothelin treated eye in comparison to the control; this was independent of intraocular pressure. Histologic evaluation of the endothelin-1 treated eyes showed axonal loss and demyelination in the prelaminar region of the optic nerve. This study supports the hypothesis that ischemia alone, without increased IOP, can cause excavation and enlargement of the cup.

CONCLUSIONS

The differential diagnosis of an enlarged optic cup ranges from normal variant to glaucomatous damage to compressive optic neuropathy from an intracranial process. The diagnostic challenge is in the careful history and physical examination that directs the subsequent evaluation.

References
