Clinical & Refractive Optometry is pleased to present this continuing education (CE) article by Dr. Shawn L. Cohen entitled **New Advances in the Management of Glaucoma.** In order to obtain a 1-hour Council of Optometric Practitioner Education (COPE) approved CE credit, please refer to page 127 for complete instructions.

New Advances in the Management of Glaucoma

Shawn L. Cohen, MDCM, FRCSC

ABSTRACT

As our understanding of the pathophysiological mechanisms of primary open-angle glaucoma continues to expand and improve, new approaches to detection and medical and surgical management of this disease continue to emerge. This review highlights recent advances in glaucoma detection, with emphasis on new devices such as optic nerve head and blood flow analyzers. Medical management advances have been made possible with the introduction of new ocular hypotensive agents and pressure-independent therapies. Surgical intervention has evolved with the introduction of new approaches to combined glaucoma and cataract surgery, angle surgery and glaucoma implants. These new advances in diagnosis and the medical and surgical management of open-angle glaucoma are designed to achieve earlier awareness of disease onset, new treatment endpoints, more sensitive markers of disease progression, as well as safer, more effective and better-targeted therapeutic interventions.

INTRODUCTION

Currently, we define primary open-angle glaucoma (POAG) as a multifactorial optic neuropathy in which there is a characteristic acquired loss of optic nerve fibers.[1] While the diagnosis of POAG once required a characteristic visual-field change, such damage is not required to establish a diagnosis, as we now know that optic nerve and nerve-fiber layer changes precede visual-field changes.[2] Furthermore, open-angle glaucoma (OAG) may occur as a primary condition with intraocular pressure (IOP) within the "normal" range of 10 to 21 mm Hg. In this case, the terms "normal" or "low-tension" glaucoma apply. In short, the current diagnosis of OAG rests on the appearance of both the optic nerve head and the gonioscopic angle, to the observing physician. Yet, as our understanding of the pathophysiology of glaucoma continues to expand and improve, our definition, classification, detection methods, and therapeutic options are being modified accordingly.[3] This review highlights new advances in our understanding of POAG, and the impact of these advances on detection and medical and surgical therapeutic approaches.

S.L. Cohen — Department of Ophthalmology, Jewish General Hospital, McGill University, Montreal, Quebec

Correspondence to: Dr. Shawn Cohen, Drummond Medical Building, 1414 Drummond, Suite 222, Montreal, Quebec H3G 1W1

DISCUSSION

The Impact of Corneal Pachymetry

The concept that central corneal thickness could affect IOP readings has forced us to cross a barrier in our definition of high-pressure and low-pressure OAG. The corneal ultrasound pachymeter is a portable unit that uses ultrasound (A-scan) or optical (doubling prism) technology to determine the thickness of the human cornea. Intuitively, a thick cornea produces a higher apparent eye pressure, much as a flat tire, with its thick wall, feels firm and is hard to digital compression. Conversely, a thin-walled eye produces a lower apparent eye pressure, much as a filled balloon that is ready to burst, and feels soft to compression. The correction of eye pressure measurements makes predictions of glaucoma more accurate and also allows for better differentiation of normal-tension from high-tension glaucoma.[4-6]

After corneal surface refractive procedures, central corneal thickness may be greatly reduced, with consequent implications for IOP estimations and measurements. Pneumotonometry appears more reliable than Goldmann applanation, if applied to the peripheral cornea.[7,8] Discrepancy exists between various IOP correction factors after laser in situ keratomileusis (LASIK) surgery, although values ranging from 1.85 to 3.5 mm Hg measured IOP reduction per 70 microns of corneal tissue ablated are usually reported.[9,10] This discrepancy results from a multitude of variables that may affect pachymetry results,[8] including the effect of mechanical stretch,[11] as induced by suction ring used during LASIK surgery to

transiently raise the IOP. Consequently, the "true" value of IOP for a given refractive surgery patient remains, at best, an estimate. In short, post-LASIK IOP readings may represent gross underestimations and falsely low values of IOP are subsequently measured for life. Perhaps providing patients with their preoperative and postoperative data following refractive surgery may better protect them in the future.

Advances in Glaucoma Diagnosis

From diurnal IOP variations[12] to new advances in automated perimetry,[13-17] various technologies are being tested for their predictive accuracy. The Swedish Interactive Threshold Algorithm (SITA) represents a great advance in algorithms as it significantly reduces visual field test time and thus patient fatigue, compared with the full threshold algorithm.[13,14] Frequency Doubling Technology (FDT) emerges as a new portable and rapid screening device, and blue-yellow or Short Wavelength Automated Perimetry (SWAP) has demonstrated a limited ability to detect glaucoma at earlier stages of disease.[15-17]

Many other newer technologies demonstrate impressive early glaucomatous diagnostic and monitoring capabilities.[18-23] Yet, important practical limitations — including cost, susceptibility to artifact,[24] reduced reproducibility,[25] sensitivity that varies with the extent of the disease[26] and other factors — limit their generalizability and widespread use.[20,26-28] For the general ophthalmologist, such tools often seem out of reach. For the ophthalmologists working in a tertiary care institution, selecting the best tool remains a challenge. These devices include optic nerve head and nerve fiber layer analyzers, such as the Scanning Laser Ophthalmoscope (Carl Zeiss, Thornwood, New York), Confocal Scanning Laser Tomograph (HRT: Heidelberg Engineering, Heidelberg, Germany) and TopSS: Laser Diagnostic Technologies, San Diego, California), Ocular Coherence Tomograph (Humphrey Instruments, San Leandro, California), Nerve Fiber Analyzer I and Nerve Fiber Analyzer GDx (Laser Diagnostic Technologies, San Diego, California) and Retinal Thickness Analyzer (Talia Technology Ltd., Mevaseret Zion, Israel). Non-invasive blood flow analysis can be obtained from ultrasound color Doppler imaging (ADT 3000, Advanced Data Technology, USA) and laser Doppler velocimetry (HRF: Heidelberg Engineering, Heidelberg, Germany).

Glaucomatous Progression:
A Physiological Approach to Detection and Monitoring

Vascular phenomena are considered important in the evolution of optic nerve and visual field progression in OAG.[29-32] Many studies center on the arteriolar microvascular findings in OAG.[33-37] These changes in arteriolar geometry can be linked directly to ocular blood perfusion changes by the Pressure Attenuation Index (PAI).[38] The PAI is measured directly from optic disc photos and can distinguish normal subjects from those with axial ametropia or with a pathophysiological change in their retinal arterioles.[38] The PAI predicts, independent of the extent of optic atrophy, which patients with ocular hypertension will progress to OAG, over a follow-up interval of 5 to 18 years.[39] The index also provides a more sensitive and reproducible marker of ocular hypertension progression than stereo photographic analysis, visual field changes and clinical impression of progression.[39] The masked intra-observer percent variation of 0.5% and an inter-observer variance of 1.1%[39] allows for shortened study follow-up, since clinical endpoints are more reliably determined. Since the changes in arteriolar diameters and nerve-fiber layer thicknesses may reverse after glaucoma therapy,[40,41] it is possible that the PAI may serve as a physiological treatment end-point or target variable. Overall, a physiological approach to glaucoma may allow us to test newer forms of glaucoma therapy, possibly involving ocular blood flow considerations in the daily management of glaucoma.

New Studies Modify Glaucoma Management

Not only is glaucoma detection changing, the approach to glaucoma management is changing as the results of large trials emerge. The Normal Tension Glaucoma Study clarified the natural history of NTG progression; 65% of randomized non-treated patients did not show progression during 5 years of follow-up; IOP reduction of a specific magnitude (30%) can have a favorable outcome on glaucoma progression.[42,43] No correction for pachymetry was required in this study, and an IOP of up to 24 mm Hg was permitted, potentially biasing the results. Also, when progression did occur, rates were highly variable and as high as 10% per year.[42,43] From the Advanced Glaucoma Intervention Study, subpart 7, we learned that IOP perturbations across the target level can have a very negative impact on glaucoma progression, reinforcing the need for stricter, more reproducible and sustained control.[44] The study also reinforced the concern that our target IOP thresholds may need to be lower than commonly or previously thought.[44]

Ongoing trials include the Collaborative Initial Glaucoma Treatment Study (CIGTS), which will evaluate the role of primary trabeculectomy versus medical management as the initial treatment of OAG.[45] The Ocular Hypertension Treatment Study (OHTS) seeks to evaluate the safety and efficacy of topical anti-glaucoma medication in preventing or delaying the onset of optic nerve and/or visual field damage in subjects with ocular hypertension.[46] The Early Manifest Glaucoma Trial seeks to evaluate the role of immediate pressure reduction, as compared to

no initial reduction, in patients with early glaucoma and normal or moderately elevated IOP.[47] Such studies may better allow us to select more appropriate and rational "target intraocular pressure" goals for glaucoma patients — a very important concept, which is gaining popularity.[48] Again, we learned from the Advanced Glaucoma Intervention Study (AGIS) that more sustained control of IOP at a given level better protects against glaucomatous progression.[44]

Perhaps the most encouraging of all findings is the observation that glaucomatous changes may be reversible in adults.[40,41-49] Reversal of the mechanical effect of laminar bowing and the increase in reperfusion or hyperemia after significant IOP reduction may explain the ONH cupping reversal observed after a large IOP reduction. Yet, the optic nerve head improvement may remain as a stable, non-transient event in some cases (Fig. 1 A-D). While the AGIS demonstrated the effects of IOP reduction to 14 mm Hg on the stabilization of glaucoma progression, it has been suggested that technology may have reached a level of sensitivity where subtle improvement in disc morphology can now be reliably detected.[44,49]

New Advances in the Medical Treatment of Glaucoma

The introduction of new ocular-hypotensive agents raises some concern. Long-term use of a select group of anti-glaucoma agents increases the number of conjunctival and tenon's inflammatory cells.[50] Some of this enhanced the risk of external bleb scarring and filtration surgery failure may be reversed with topical preoperative corticosteroid therapy.[51] Also, the delay inherent in multiple trials of ocular-hypotensive medications may further delay more definitive IOP control that could be achieved surgically.[52] Yet, while compliance would be expected to decrease as the number of medications increases, newer agents demonstrate fewer side effects, and combination therapies may increase the compliance rate.[53-57] Furthermore, as newer agents act at varying sites, the potential for medical control increases. The neuroprotective aspect of glaucoma medication research may even allow for retinal ganglion cell protection, irrespective of the level of intraocular pressure.[58] Perhaps for these reasons, surgical intervention still retains its place behind medical therapy in the therapeutic regimen for glaucoma treatment in North America.

New ocular-hypotensive agents continue to be developed. Latanoprost (Xalatan, Pharmacia) is a prostaglandin F2α analog that lowers IOP by way of increased uveoscleral outflow. There are reports of uveitis, cystoid macular edema, hypertrichosis, iris pigmentation and exacerbation of ocular herpetic disease associated with the use of this agent.[59,60] Isopropyl unoprostone (Rescula, Novartis), unlike latanoprost, does not bind strongly to the prostaglandin receptor, does not appear to increase the severity or recurrence rate of herpes simplex virus keratitis, appears to have a greater effect on trabecular outflow than uveoscleral outflow, and may have neuroprotective properties at the level of the retinal ganglion cell and through anti-endothelin-1 (a potent vasoconstrictor) activity.[61-64] Twice-daily unoprostone is less effective at lowering IOP than once-daily latanoprost but is additive to latanoprost, and improves its diurnal curve characteritics.[61,62] Bimatoprost 0.03% (Lumigan, Allergan) emerges as a prostamide-class that may or may not bind to the prostaglandin receptor, yet demonstrates similar side-effects.[65,66] Bimatoprost appears more effective in both its IOP-lowering effect and in its ability to lower IOP to achieve a target pressure in more patients than timolol.[66] Travoprost 0.004% (Travatan, Alcon Pharmaceuticals), a prostaglandin analog, is effective in once-daily dosing, does not require refrigeration, and appears to be more effective in black than non-black patients by a 1.8-mm Hg of IOP lowering effect.[67]

Latanoprost, bimatoprost, travoprost, and unoprostone — despite any differences in receptor affinity and site of action — all appear to increase iris and periocular skin hyperpigmentation and lash changes as well. The reason for the pigmentary changes induced by fatty acid-derivative agents remains unknown. The author hypothesizes that perhaps the UV-absorbing properties of the double bonds in the organic molecule act as photosensitizers, thereby inducing compensatory pigment changes in the iris and increased light-shielding properties of increased lash thickness.

Pressure-independent neuroprotective agents comprise a new and exciting area of research. Inhibition of nitric oxide synthetase in rats was shown to be protective of retinal ganglion cells, independent of the level of IOP.[58] Memantine, an N-methyl-D-aspartate (NMDA) or glutamate receptor antagonist, may serve as a pressure-independent neuroprotective agent.[68] Nipradilol is a neuroprotective agent with beta-blocking, alpha-blocking and nitroglycerine-like activities.[69] Studies in Japan have uncovered its ability to increase uveoscleral outflow in humans, and to protect retinal ganglion cells against NMDA-induced retinal damage and endothelin-1-induced retinal artery contraction in animals.[70,71] Gene therapy[72] and newer agents, such as brain-derived neurotrophic factor (BDNF),[73] calcium channel blockers,[74] angiotensin converting enzyme (ACE) inhibitors,[75] and cytoskeletal and angle-altering agents, such a cytochalasins,[76] latrunculins,[77] and ethacrynic acid[78,79] are in the early phases of study.

Selective Laser Trabeculoplasty

Since its introduction as a therapy for OAG in 1979,[80] argon laser trabeculoplasty (ALT) has emerged as an alternative to medical therapy as the initial form of therapy.[81] ALT produces coagulation damage to the

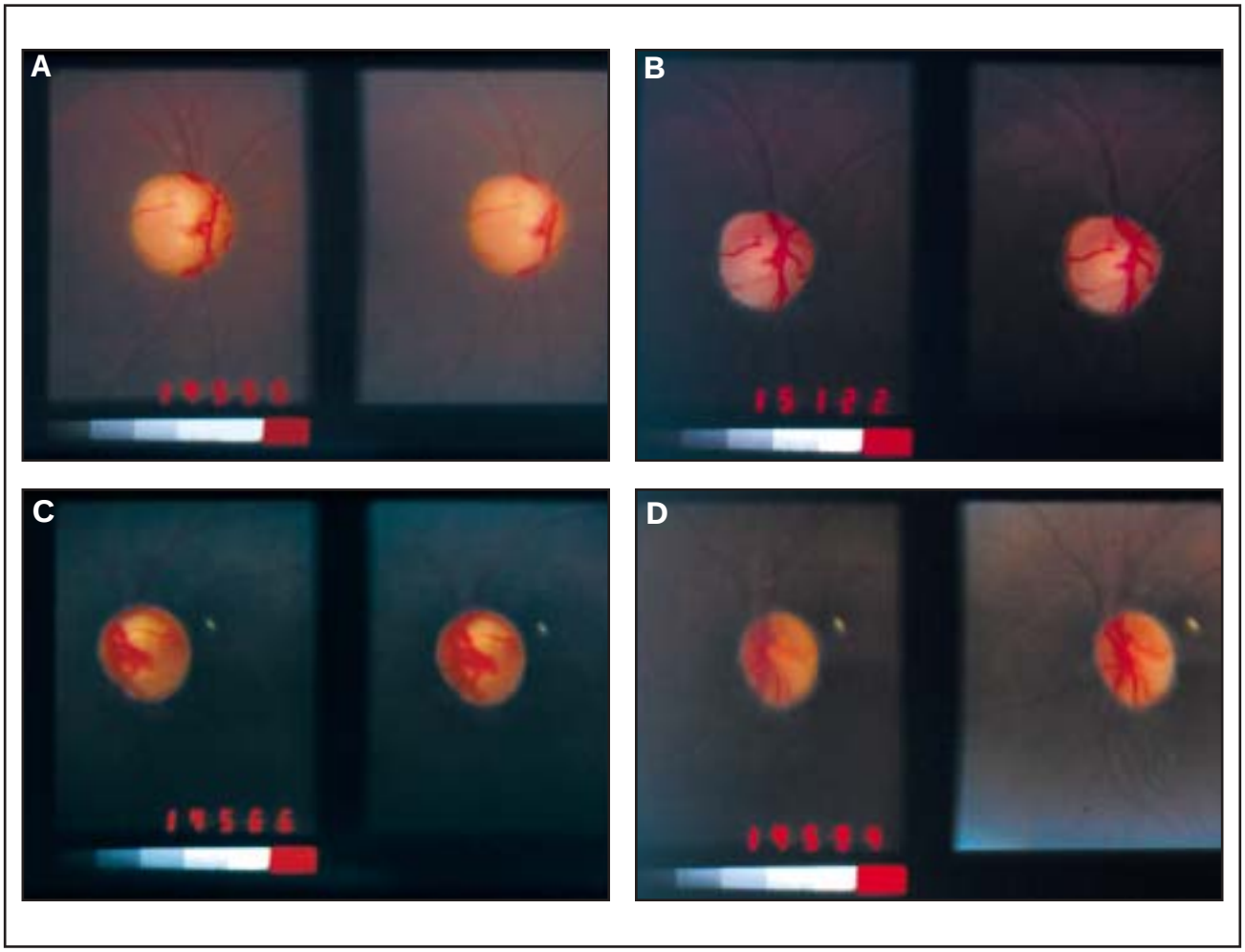

Fig. 1 Reversal of optic nerve head cupping after bilateral trabeculectomy. (A) Preoperative optic nerve photo OD; (B) Postoperative optic nerve photo OD; (C) Preoperative optic nerve photo OS; (D) Postoperative optic nerve photo OS. The preoperative IOPs of 48 mm Hg OD and 51 mm Hg OS were reduced to 4 mm Hg OD and 7 mm Hg OS after bilateral trabeculectomies with mitomycin-C. The preoperative and postoperative photo interval was 2 months.

trabecular meshwork that results in scarring and consequent alterations in trabecular outflow, yet potentially limits retreatment.[81-83] The Q-switched 532-nm Nd:YAG laser selectively targets trabecular meshwork cells, without coagulation of the trabecular meshwork, and has thus been termed selective laser trabeculoplasty (SLT).[84,85] SLT shares an equivalent IOP-lowering effect to ALT, yet appears better than ALT in patients who have had previous ALT and is easier to perform.[85,86] SLT exerts its effect through a biological response of increased phagocytic activity of some trabeculocytes, alterations in turnover or synthesis of glycosaminoglycans, increased trabeculocyte division, and an induced inflammatory response.[87] In short, ALT produces a combined "biologic and mechanical effect," while SLT can be repeated due to its selective "biologic effect."

New Approaches to Angle Surgery

New approaches to glaucoma surgery involve attempts to bypass or remove the juxtacanalicular tissue, the site of highest resistance to outflow in glaucomatous eyes.[88] In non-penetrating deep sclerectomy (NPDS) with or without collagen implantation, a large lake of intrascleral aqueous is created, and a small bleb is usually seen.[89,90] In the variation known as viscocanalostomy, no bleb is produced.[91,92] The juxtacanalicular tissue and the inner wall of Schlemm's canal are bypassed by exposing Descemet's membrane, allowing aqueous to reach the surgically

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opened Schlemm's canal by Descemet's membrane.[91,92] Since aqueous is directed back into Schlemm's canal, a bleb does not form. Unfortunately, Descemet's membrane is not permeable enough to relieve the increased IOP of glaucoma.[93] Recent histopathological analysis suggests that such mechanisms may not be as clear-cut as once thought, since viscocanalostomy has been shown to create a complete removal of the entire inner wall of Schlemm's canal.[94] The procedure is more successful than YAG laser goniopunture of the trabecular meshwork,[95,96] since the insertion and origin of the inner wall are completely avulsed, preventing the two cut ends of the torn wall from closing in a scar.[94] With goniocurettage, the inner wall of Schlemm's canal is removed by curettage, although damage to collector channels during meshwork removal could limit the effectiveness of this procedure.[97-99] Still, by not excising large portions of the trabecular meshwork externally, hypotony, hyphema, the need for a peripheral iridotomy and bleb-related complications are reduced.[91,100] In some cases, no antimetabolites are used. Perhaps the next phase of angle surgery will involve the use of intracannalicular stents.

Although there are reports of excellent success with some of these newer techniques, the IOP attained may not be as low as that obtained with trabeculectomy.[92] Perforation into the anterior chamber results in the need for a peripheral iridotomy,[101] and iris incarceration may occur.[102] Furthermore, the large intrascleral lake of aqueous[88,89] (typically 5 x 5 mm) would be expected to produce a significant scarring of the conjunctiva and greatly thinned sclera that may preclude future filtration surgery in this area.

Cataract and Glaucoma Surgery

The traditional trabeculectomy has benefited from the introduction of phacoemulsification, compared with extracapsular cataract extraction, especially the clear-cornea approach with foldable intraocular lens insertion. The success of combined phacoemulsification and trabeculectomy appears to approach that of trabeculectomy alone.[103] Yet, the one-site technique requires more medication to maintain IOP control than the two-site approach.[104] In eyes with previous filtering blebs, clear-cornea phacoemulsification does not adversely affect IOP control.[105,106] Nevertheless, for the failing bleb, tissue plasminogen activator, which has fibrinolytic activity, can be administered intracamerally as an adjunct therapy for reviving newly failing blebs after other anterior segment surgery; it can be administered in the immediate post-operative period.[107,108] Also, the foldable intraocular lens itself carries the advantage of a marked decrease in Nd:YAG laser posterior capsulotomy rates, compared with the relatively older, rigid intraocular lens designs.[109] Topical anesthesia for the cataract extraction and subconjunctival supplementation for the trabeculectomy represents a newer approach to combined surgical intervention, aimed to prevent the reduced ocular blood flow seen with retrobulbar block with epinephrine use and digital compression.[110] Other developments in anesthesia care and wound healing modulation continue to develop. For now, 5-fluorouracil and mitomycin-C remain the main antifibrotic agents used during trabeculectomy surgery.

Glaucoma Implant Devices

Glaucoma drainage devices or setons serve as an important therapeutic option in the management of refractory glaucomas. These inorganic shunts maintain aqueous drainage by way of a tube, placed into the anterior chamber, which directs the aqueous to a reservoir or plate that provides the surface area for filtration and is secured to the episcleral surface of the eye. Shunts that incorporate a valve between the tube and the reservoir, such as the Ahmed implant (New World Medical, Inc., Rancho Cucamonga, California), allow for immediate and controlled aqueous passage and intraocular control. Non-valved implant devices, such as the Baerveldt implant (Iovision, Inc., Irvine, California), usually provide a greater surface area for filtration, and thus a lower long-term IOP, but require ligation or occlusion in order to prevent hypotony in the initial few weeks post-operatively. After a few weeks, a normal healing response occurs in the form of a fibrous capsule sheath that provides the flow limitation and thus protects the non-valved implant from inducing hypotony.[111,112]

Seton placement is indicated for previous trabeculectomy failure, or it can be used as a primary procedure in patients at high risk for trabeculectomy failure, such as those with neovascular glaucoma, uveitis, extensive scarring or conjunctival loss, impending need for a corneal graft or need for other ocular surgery (such as scleral buckling procedures).[111-117] Glaucoma implants benefit from low risk of hemorrhage, infection, hypotony and leakage, comparable to or better than risk of these complications with trabeculectomy, laser cyclodestruction, and other modalities.[100,113,118-121] In general, the final IOP achieved with glaucoma implants is not as low as that achieved with trabeculectomy, unless topical ocular-hypotensive agents are used.[113] The simultaneous placement of two implants (one valved and one non-valved) has the advantages of immediate postoperative IOP lowering from the valved implant and greater long-term IOP reduction provided by the increased surface area of the non-valved implant.[122] While the fibrous sheath that forms around the plate of an implant may result in a severe restriction of aqueous flow, manifested clinically as a hypertensive phase,[123,124] it may be possible to reduce the severity of the hypertensive phase of one implant by shunting some aqueous early in the procedure into a

second filtration site, which is analogous to the use of aqueous-suppressing medications.[122] In fact, the simultaneous implantation of two glaucoma implants[124] appears to result in 30% lower IOP, after 4 months of follow-up, (author's unpublished observations) when compared to delayed, sequential[125] implantation of two implants.

Conclusion

As our understanding of the pathophysiological mechanisms of POAG continues to expand and improve, our definition of the disease continues to evolve. This has allowed for detection methods, treatment endpoints, and therapeutic options to be modified accordingly. Perhaps classification of OAG by IOP criteria is not as accurate or as all complete as we once believed. We have crossed significant barriers in our understanding of glaucoma, and likely more obstacles will be overcome in the near future. Diagnostic technologies approach the disease from new angles. Medical management continues to expand with the introduction of new ocular hypotensive agents and pressure-independent therapies. Surgical intervention has evolved new approaches to combined glaucoma and cataract surgery, angle surgery and glaucoma implants. These new advances in the diagnosis and the medical and surgical management of OAG are designed to achieve earlier recognition of disease onset, more sensitive markers of disease progression, as well as safer, more effective and better-targeted therapeutic interventions. Indeed, the future of glaucoma diagnosis and therapy holds great promise and excitement. ❑

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