REVIEW® of Ophthalmology

October 2014 • revophth.com

Can You Still Do It All?

The Challenge to the General Ophthalmologist P. 30

Choose BAK-free TRAVATAN Z® Solution for sustained IOP lowering

Sustained 30% IOP lowering

at 12, 14, and 20 hours post-dose in a 3-month study[1,2]*

TRAVATAN Z® Solution has no FDA-approved therapeutic equivalent[3]

Help patients start strong and stay on track with the Openings Patient Support Program

INDICATIONS AND USAGE

TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dosage is 1 drop in the affected eye(s) once daily in the evening. TRAVATAN Z® Solution should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP-lowering effect.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Pigmentation—Travoprost ophthalmic solution has been reported to increase the pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. The long-term effects of increased pigmentation are not known. While treatment with TRAVATAN Z® Solution can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes—TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Use With Contact Lenses—Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Adverse Reactions

The most common adverse reaction observed in controlled clinical studies with TRAVATAN Z® Solution was ocular hyperemia, which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus. In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

Use in Specific Populations

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

For additional information about TRAVATAN Z® Solution, please see the brief summary of Prescribing Information on the adjacent page.

***Study Design:** Double-masked, randomized, parallel-group, multicenter non-inferiority comparison of the efficacy and safety of travoprost 0.004% preserved with benzalkonium chloride (BAK) to TRAVATAN Z® Solution after 3 months of treatment in patients with open-angle glaucoma or ocular hypertension. Baseline IOPs were 27.0 mm Hg (n=322), 25.5 mm Hg (n=322), and 24.8 mm Hg (n=322) at 8 AM, 10 AM, and 4 PM for TRAVATAN Z® Solution. At the end of Month 3, the TRAVATAN Z® Solution group had mean IOPs (95% CI) of 18.7 mm Hg (-0.4, 0.5), 17.7 mm Hg (-0.4, 0.6), and 17.4 mm Hg (-0.2, 0.8) at 8 AM, 10 AM, and 4 PM, respectively. Statistical equivalent reductions in IOP (95% confidence interval about the treatment differences were entirely within ±1.5 mm Hg) were demonstrated between the treatments at all study visits during the 3 months of treatment.

References: 1. Data on file, 2013. **2.** Lewis RA, Katz GJ, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. *J Glaucoma.* 2007;16(1): 98-103. **3.** Drugs@FDA. FDA Approved Drug Products: TRAVATAN Z. www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed July 31, 2014.

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

Alcon®
a Novartis company

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.
TRAVATAN Z® (travoprost ophthalmic solution) should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 2 hours after the first administration with maximum effect reached after 12 hours.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Pigmentation
Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with TRAVATAN Z® (travoprost ophthalmic solution) 0.004% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
TRAVATAN Z® Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
TRAVATAN Z® Solution should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z® Solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Angle-closure, Inflammatory or Neovascular Glaucoma
TRAVATAN Z® Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The most common adverse reaction observed in controlled clinical studies with TRAVATAN® (travoprost ophthalmic solution) 0.004% and TRAVATAN Z® (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with TRAVATAN® or TRAVATAN Z® Solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C
Teratogenic effects: Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (250 times the maximal recommended human ocular dose (MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 mcg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 mcg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 mcg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of ≥ 0.12 mcg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies of TRAVATAN Z® (travoprost ophthalmic solution) 0.004% administration in pregnant women. Because animal reproductive studies are not always predictive of human response, TRAVATAN Z® Solution should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN Z® Solution is administered to a nursing woman.

Pediatric Use
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Geriatric Use
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

Hepatic and Renal Impairment
Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 mcg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [250 times the maximum recommended human ocular dose of 0.04 mcg/kg/day on a mcg/kg basis (MRHOD)]. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (75 times the MRHOD).

PATIENT COUNSELING INFORMATION
Potential for Pigmentation
Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of TRAVATAN Z® (travoprost ophthalmic solution) 0.004%.

Potential for Eyelash Changes
Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with TRAVATAN Z® Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice
Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of TRAVATAN Z® Solution.

Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z® Solution and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Rx Only
U.S. Patent Nos. 5,631,287; 5,889,052, 6,011,062; 6,235,781; 6,503,497; and 6,849,253

Alcon®

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9/14 TRV14066JAD

REVIEW NEWS
Volume XXI • No. 10 • October 2014

Review: Avastin & Lucentis Equally Safe in AMD Patients

Health policies that favor using ranibizumab (Lucentis) for treating eye disease in older people over safety concerns for a cheaper alternative should take account of a new *Cochrane Review* published on Sept. 14. The researchers looked at the results of studies which compared the safety of two drugs used for treating age-related macular degeneration, ranibizumab and bevacizumab (Avastin). Contrary to what was argued by some experts, the review has found that the cheaper drug, bevacizumab, does not appear to increase deaths or serious side-effects compared with ranibizumab in people with neovascular age-related macular degeneration.

Bevacizumab was developed to treat cancer, while ranibizumab is marketed specifically for age-related macular degeneration. The authors conclude that health policies that favor the much more costly ranibizumab instead of bevacizumab for macular degeneration, for reasons of safety, are not supported by current randomized controlled trial evidence. A larger *Cochrane Review*, which will assess additional sources of evidence, is now planned to help reduce the remaining uncertainties around the relative benefits and safety of these drugs.

Bevacizumab and ranibizumab are related biological drugs that work to prevent the abnormal growth and swelling of blood vessels that are characteristic signs of macular degeneration. Although the beneficial effects of the two drugs are believed to be similar, only ranibizumab has been licensed as a treatment for macular degeneration; bevacizumab is currently approved only as a cancer therapy. Despite this, an unlicensed preparation of bevacizumab is often used off-label as treatment for macular degeneration, because it is cheaper than ranibizumab. It has been suggested that the two drugs have different safety profiles, such that bevacizumab might cause more systemic harms, and the review investigated this concern.

Lorenzo Moja, from the University of Milan, stated, "This review represents an important step forward in the knowledge about differences in systemic harms between bevacizumab and ranibizumab and mitigates past disputes around evidence. The review authors were able to collect evidence from nine trials, including three unpublished studies, while most other reviews focus primarily on published data". He continues "This result was possible through the collaborative effort of researchers across several countries (France, Germany, Italy, UK and the United States), many of who were involved in the original trials. It shows a remarkable level of commitment of trialists and health-care systems to answer an important clinical question. I am unaware of other examples with such a large number of head-to-head, non-industry-sponsored RCTs."

Editor in Chief of *The Cochrane Library*, Dr. David Tovey, added, "This review addresses a question of immense importance to health systems in many countries. One of the many considerations in decision-

Endothelial Cell Dysfunction Implicated in Glaucoma

In a unique study of human ocular cells, a multi-institution research team led by a biomedical engineer at Northwestern University has found a new glaucoma culprit: a mechanical dysfunction of endothelial cells.

The researchers found that endothelial cells from eyes with glaucoma are stiffer than cells from healthy eyes. This stiffness limits the cells' ability to deform and allow aqueous humor to cross the endothelium and drain into Schlemm's canal. The findings were published in the online early edition of the *Proceedings of the National Academy of Science*.

"There is no cure for glaucoma, which affects more than two million Americans," said Mark Johnson, PhD, the senior author of the study. "Our work shows that cells of this endothelial layer act as mechanical gates. Therapeutic strategies that alter the stiffness of these cells potentially could lead to a cure for this debilitating disease."

Dr. Johnson is a professor of biomedical engineering and mechanical engineering at Northwestern's McCormick School of Engineering and Applied Science and a professor of ophthalmology at Northwestern University Feinberg School of Medicine.

"The work appears to be one of the first times that the methods of mechanobiology—the study of the mechanical characteristics of cells—have been used to show that dysfunctional cell mechanics lies at the heart of a disease process," Dr. Johnson said.

making at policy level is not just understanding how effective treatments are, but also weighing up evidence of their safety."

The review included nine randomized controlled trials, none of which was supported by manufacturers of either treatment, involving a total of 3,665 participants, comparing bevacizumab with ranibizumab. The drugs were given for up to two years. The review found the systemic safety of bevacizumab for macular degeneration appeared to be similar to that of ranibizumab, except for gastrointestinal disorders. Although no statistically significant differences between the treatments were found, the review does not exclude the possibility that either treatment is less harmful than the other. The researchers estimated that if 1,000 people were treated with ranibizumab for one to two years, 34 would die; if treated instead with bevacizumab, between 27 and 53 would die. If 1,000 people were treated with ranibizumab, 222 would experience one or more serious systemic adverse events. If 1,000 people were treated instead with bevacizumab, between 200 and 291 would experience such an event.

They rated the overall quality of the evidence as low to moderate because of the uncertainty of the findings, and due to other study limitations. Additionally, the review authors indicated that they could not fully assess the quality of three of the studies as they had not yet been published.

Probes May Speed DR Detection

A new study published in the September issue of *The FASEB Journal* identifies a novel strategy to diagnose diabetic retinopathy before irreversible structural damage has occurred. This advance involves quantifying

Ophthalmic Product Development Insights

Matthew Chapin, Aki Tobaru and Van Sandwick • Ora Inc., Andover, Mass.

Leveraging Ex-U.S. Deals

Throughout all of our columns, we've provided succinct overviews of critical components of new ventures in ophthalmology—including defining a target product profile; considerations around raising money; building an intellectual property (IP) estate; and when to explore conducting an ex-U.S. trial. In this installment, we will build off of these topics by discussing the value of regional strategic partnerships and licensing. These partnerships can provide significant benefits to ophthalmic entrepreneurs' programs via additional capital, resources, conduct of activities to help move a program forward and/or credibility. Through this brief column, we hope that you'll continue to glean a few insights that may help your ophthalmic program best navigate early stage business planning and development, to bridge the valley of death and reach value inflection, as well as increase the overall value of your program.

As with all components of your new venture, we suggest that you approach this step of the process with your end goal in mind. The scope of this article doesn't permit a debate on the merits of the various outcomes, as each entrepreneur may have different end goals in mind. Instead, this is an overview of how a strategic regional deal can help in the early stages. Engaging in strategic partnerships that exchange commercialization rights, IP and/or equity for capital and/or resources for R&D—whether you've successfully raised funds or are still crafting your business plan—should be considered as options for your new venture.

Research and development, for small-molecule and biological therapeutics, is an expensive and time-consuming process. Entrepreneurs will try to utilize their financing road map to raise money to cover the R&D costs associated with reaching key, early value inflection points while trying to preserve value for themselves, as well. Regardless of your financial situation, exchanging the development and commercialization rights in ex-U.S. territories in exchange for R&D capital can allow you to rapidly progress to certain value inflection points.

Obviously there are many elements of a deal that need to be reviewed carefully. Here are a couple of structural points to keep in mind that can specifically help the early stage entrepreneur:

Entrepreneurs may be worried about losing the value of their precious ventures and potential impact of a global deal later. But many times a regional deal can help build value and move an early project forward. A regional deal can be non-dilutive—in other words, the entrepreneur retains the ownership of the company—compared with others models like venture capital where the financial investor secures equity in the company. However, the potential impact of not having rights for a global deal later needs to be considered. Terms that address how a regional partner may consider discussion with a future global partner can also be included, to leave that door open.

As larger pharmaceutical companies focus more on later-stage projects, smaller companies that are entering the space or looking to expand their pipelines (whether in the United States or ex-U.S.) may be open to earlier-stage deals in certain circumstances. We have seen this fit well recently, when capabilities needed to help move an asset forward reside within a regional partner's realm of expertise, for example, in the areas of formulation, conduct of animal models, manufacturing and toxicology, etc. In these cases, a partnership helps move a project down field, and builds value for the United States and other territories in which there are retained rights. These activities can be provided as part of the deal in exchange for a license, or option, in that territory.

Terms for how data from those activities performed by your regional partner can be leveraged by you in other regions should be included in the deal. As an example, we are currently involved in a program with a novel antibiotic (an isothiazoquinolone), ACH-702 (Achillion Pharma). Regional rights were licensed to an ophthalmic company in South Korea, Taejoon Pharm, and they are responsible for development and commercialization in Asia, and leveraging internal capabilities for specific activities like formulation and cGMP (current good manufacturing practice) manufacturing of the product for ophthalmology. The rights were retained for rest of world with terms in place of how data from the Asian development can be leveraged.

Much like data, IP rights are an area of particular importance to focus on, as IP (such as patents) may be generated by the activities performed with or by the regional partner. How those rights are shared, how costs are covered, and whether use of such inventions carries a different financial structure, all need to be thought through and become part of the agreement. Costs for filing and ongoing maintenance of existing patents at the time of the deal can be negotiated in terms of how those are shared, particularly as it pertains to patents in the territory subject to the deal.

In addition to the capital and resources for R&D, partnering with an ex-U.S. firm may increase the credibility of your program. Some investors may be more willing to invest in your program if they see that a third party has already conducted due diligence and moved forward. For the early-stage entrepreneur raising money to turn his ideas into a fundable development program, credibility is almost invaluable.

As the cost of capital for entrepreneurial development programs is quite high, ex-U.S. partnerships that allow you to help you achieve your first goal—U.S. approval—in exchange for development rights in territories that you may not have pursued initially is an attractive deal structure. Every development program in those regions may be different, but "giving away" future revenue in ex-U.S. markets in exchange for a boost that will advance your development program today is typically a win.

While the potential cons of giving up a program's ex-U.S. rights should be given serious consideration in advance of a deal, adding credibility and momentum to the U.S. program—and the entrepreneur— advances your program towards value inflection and FDA approval.

The authors are with the Corporate Development Group at Ora Inc. Ora provides a comprehensive range of product development, clinical-regulatory and product consulting for developers, due diligence support for investors and buyers, clinical trial services, and asset and business partnering and commercialization support in ophthalmology. They welcome comments or questions related to this or other development topics. Please send correspondence to mchapin@oraclinical.com.

the early molecular changes caused by diabetes on the endothelium of retinal vessels. Using new probes, scientists were able to distinguish the early molecular development of diabetic retinopathy.

"My goal is to establish a versatile clinical tool that alerts of a disease process right when the first molecular changes take place. This will then provide ample opportunity to act, as opposed to merely acknowledge that there is structural damage that we cannot do anything about," said Ali Hafezi-Moghadam, MD, PhD, a researcher involved in the work from the Center for Excellence in Functional and Molecular Imaging at Brigham and Women's Hospital and Harvard Medical School in Boston. "Here, we have shown it in an important disease, the diabetic retinopathy, but there is no reason to stop there."

Dr. Hafezi-Moghadam and colleagues identified a target on the intraluminal surface of the retinal vessels that is expressed at higher levels in diabetes. They found significantly more vascular endothelial growth factor receptor 2 (VEGFR-2) in the diabetic micro-vessels compared to control. They then custom-generated molecular probes and characterized their binding properties. Light-based live imaging was then used to quantify binding interaction. An unexpected finding in this work was that not only was VEGFR-2 higher in the retinas of diabetic animals as well as humans, but the molecule was found in the retinal micro-vessels, not in the larger vessels. When the imaging probes were injected into the blood stream of living normal and diabetic animals, they circulated throughout the animal's vasculature. With the help of live imaging of the retinal vessels, it was possible to visualize the interaction of individual probes with their endothelial targets. The probes transiently interacted with the intraluminal surfaces. In comparison, control probes with a surface moiety that does not interact with the inner vascular lumen freely flowed through the retinal micro vessels. Since the probe interaction with the inner vessel wall can be deduced to individual molecular interactions, the information gained from this study provides quantitative knowledge of target molecules in the retinal micro vessels.

"This study should be a huge eye-opener for doctors hoping to prevent eye disease resulting from diabetes," said Gerald Weissmann, MD, editor in chief of The FASEB Journal. "This study shows that it is possible to do this, and the next step is to make this accessible at the clinical level. The sooner doctors can detect that their patients might have a vision problem, the more time they have to save someone's sight."

Native American Ancestry a Risk Factor for DR

New research led by the University of Southern California Eye Institute, part of Keck Medicine of USC, shows for the first time that Native American ancestry is a significant risk factor for vision-threatening diabetic retinopathy among Latinos with type II diabetes. Diabetic retinopathy is the leading cause of blindness in working-age adults in the United States, affecting more than 4 million Americans age 40 and older. The research was published online in *Investigative Ophthalmology & Visual Science*.

"This is the first study, to our knowledge, that examines the contribution of genetic ancestry in vision-threatening diabetic eye disease in Latinos," said USC Eye Institute Director Rohit Varma, MD, MPH, professor and chair of the Department of Ophthalmology at Keck and the study's principal investigator. "Previous research has shown that Latinos have a higher prevalence of diabetic retinopathy than non-Hispanic Whites and African-Americans. Our findings suggest that one contributor to this heavy burden may be due to their Native American ancestry."

Latinos are a diverse group of people typically with a varying mixture of Native American, European and African ancestry. Dr. Varma's research team examined data from 944 Latinos with type II diabetes from the Los Angeles Latino Eye Study (LALES), the largest population-based study of eye disease in that ethnic group. The participants in the study were 40 years of age or older and hailed from the city of La Puente in Los Angeles County, Calif. Ninety-five percent of them were of Mexican origin. Of the 944 people with type II diabetes, 135 had vision-threatening diabetic retinopathy while 809 did not.

Using genetic assays and detailed ophthalmologic examinations, the team found that individuals with more than 50 percent Native American ancestry had an 87 percent higher chance of also having vision-threatening diabetic retinopathy compared to those who had less than 50 percent Native American ancestry, even after controlling for known risk factors for the disease.

"Our next steps will be to try to narrow down which genomic locations among those with a Native American origin might be contributing to boosting the risk for developing severe diabetic retinopathy," said Xiaoyi Gao, PhD, the study's first author, who started his research at USC. Dr. Gao is now an associate professor of ophthalmology in the University of Illinois, Chicago College of Medicine. REVIEW

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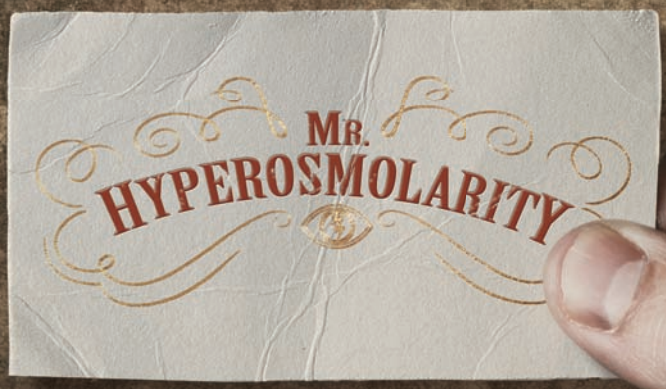

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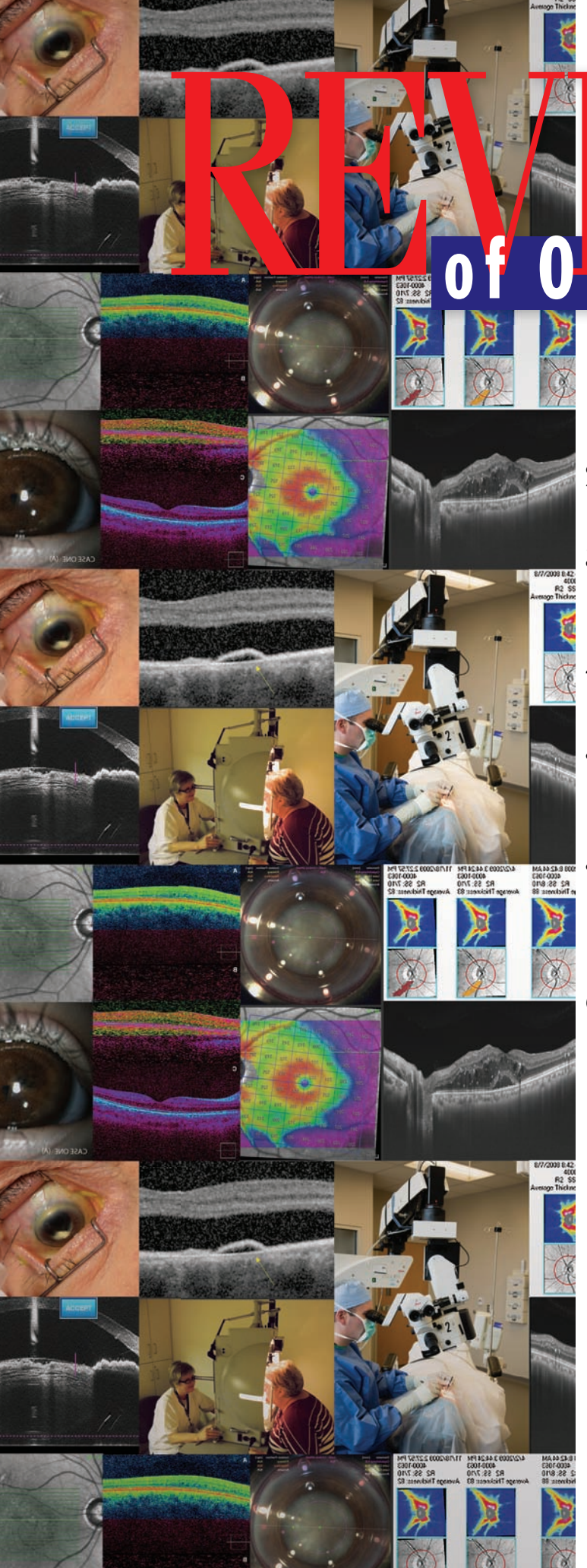

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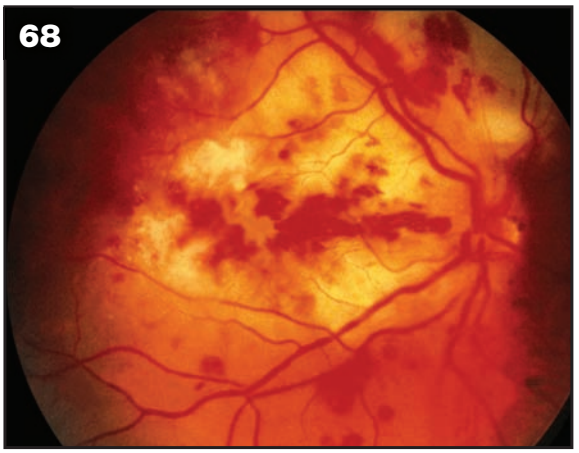

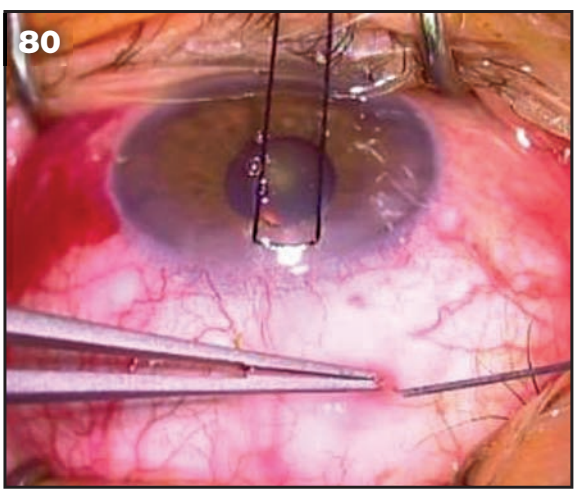

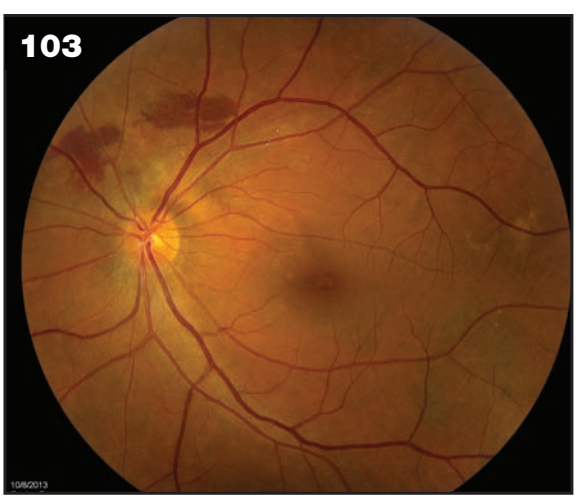

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Please see adjacent page for full prescribing information.

References: 1. Kempe CH. The use of antibacterial agents: summary of round table discussion. *Pediatrics*. 1955;15(2):221-230. **2.** Kowalski RP. Is antibiotic resistance a problem in the treatment of ophthalmic infections? *Expert Rev Ophthalmol*. 2013;8(2):119-126. **3.** Recchia FM, Busbee BG, Pearlman RB, Carvalho-Recchia CA, Ho AC. Changing trends in the microbiologic aspects of postcataract endophthalmitis. *Arch Ophthalmol*. 2005;123(3):341-346. **4.** Freidlin J, Acharya N, Lietman TM, Cevallos V, Whitcher JP, Margolis TP. Spectrum of eye disease caused by methicillin-resistant *Staphylococcus aureus*. *Am J Ophthalmol*. 2007;144(2):313-315. **5.** Hecht G. Ophthalmic preparations. In: Gennaro AR, ed. *Remington: the Science and Practice of Pharmacy*. 20th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000. **6.** Bacitracin Ophthalmic Ointment [package insert]. Minneapolis, MN: Perrigo Company; August 2013. **7.** Data on file. Perrigo Company.

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CONTRAINDICATIONS: This product should not be used in patients with a history of hypersensitivity to Bacitracin.

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ADVERSE REACTIONS: Bacitracin has such a low incidence of allergenicity that for all practical purposes side reactions are practically non-existent. However, if such reaction should occur, therapy should be discontinued.

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION: The ointment should be applied directly into the conjunctival sac 1 to 3 times daily. In blepharitis all scales and crusts should be carefully removed and the ointment then spread uniformly over the lid margins. Patients should be instructed to take appropriate measures to avoid gross contamination of the ointment when applying the ointment directly to the infected eye.

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Can You Do It All? No You Can't, Sure You Can

There was a great kerfuffle in publishing late this summer when it was revealed that Time Inc. had begun evaluating its editors, along with traditional criteria, on whether the editor produced content that benefited Time's advertisers' messages.

I mention this not to wade into the ethical swamp of the separation of church and state on editorial and advertising, or the more nettlesome "sponsored content," a hybrid of the two. (Our position on this appears at the bottom of every editorial page, anyway. If it's our editorial content, we say so.)

My interest at the moment is more in how editors of different generations react to this ethical challenge. I think a lot of it is based in the environment and mores of your early training. Younger people in this business who come of age in the online, digital, social-media world where the lines are more blurred have very different perspectives on this from mine, which is closer to the Gutenberg printing press generation.

I'm not suggesting that ethics change from generation to generation, but your view of "normal" absolutely does; hence the ubiquitous phrase, the new normal.

Since I've never been a doctor or even played one on TV, I have no personal grounding to assess the ultimate question raised by our cover story this month, whether you can still make it as a general ophthalmologist. But I bring up the editorial/advertising issue to illustrate my contention that how you answer that question probably depends on your generation, on the world in which you cut your teeth.

If you've been in practice for, let's say 20 years or more, the answer is no, a young person starting today could not possibly replicate what you did. But the good news is that if we had done this article 20 years ago, the same answer would apply. If we do it 20 years from now, same thing.

There are some very different practice models featured in our cover story this month (p. 30), though each of the physicians would self-describe as a generalist. Location, availability of specialty care and the level of training of the physicians described are a key part of how they practice today, and that will always be true.

But legislation, technology, insurance, reimbursement, changing demographics, new practice models, new classes of health-care providers and a litany of other influences will combine to make "doing it all," as the cover question proposes, mean different things to each new generation of ophthalmologists.

The truth is, you never could do it all. And the truth is, of course you can still do it all.

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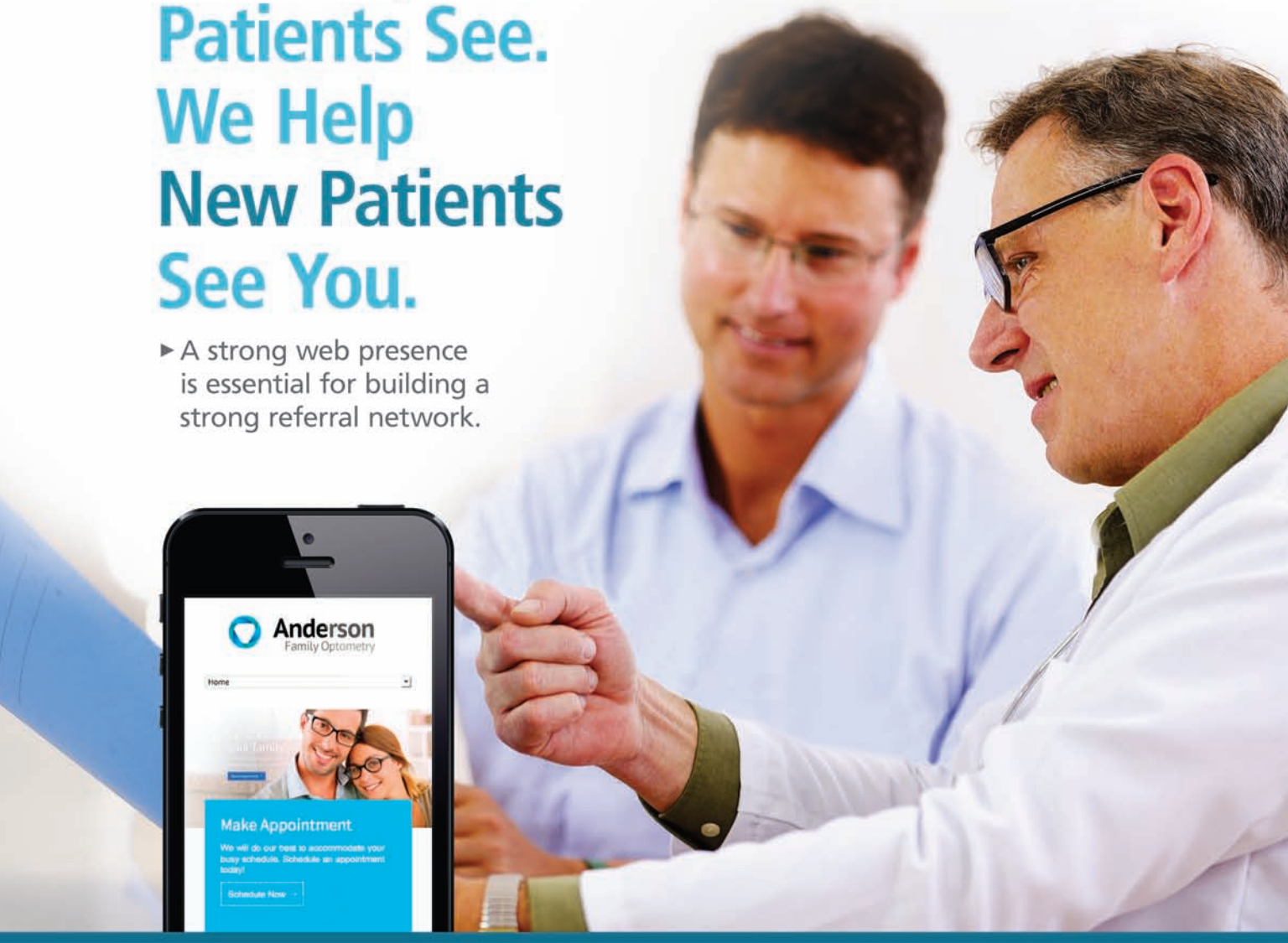

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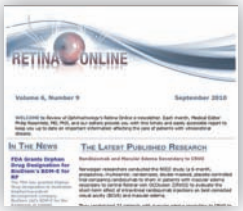

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Mobile Surgery Keeps on Trucking

A rundown of the companies that offer mobile surgical devices to ophthalmologists and how the arrangements work.

Walter Bethke, Managing Editor

Though fear of commitment is often discussed in negative terms, in some instances it can be a positive, such as when you're not really sure your practice can afford to buy a $400,000 femtosecond laser. If you'd like to offer a procedure such as femtosecond cataract or phacoemulsification to your patients but aren't sure that your patient volume can financially support the investment this would entail, one option is to look into mobile equipment. Here's a rundown of the purported benefits and possible drawbacks of using a mobile device provider, and a roundup of the offerings in ophthalmology.

A Sightpath Medical engineer unloads the LenSx laser at a surgery center. He will set it up in preparation for cases scheduled to begin the following morning.

Why Some Go Mobile

Mobile companies offer devices for many ophthalmic procedures, including phacoemulsification, selective laser trabeculoplasty, YAGs and now, femtosecond cataract surgery.

Warwick, R.I., ophthalmologist Paul Koch was interested in femtosecond cataract, but wasn't sure buying a laser was the right move for him. "We purchased an excimer laser for LASIK in 1995 when it was first approved," he says. "Over the years, we've had seven excimer lasers. They're very expensive, the maintenance fees are high, and they get upgraded frequently. Now the early generations of femtosecond lasers for cataract surgery have come out and we can picture them being upgraded every six to 12 months. By the time we purchase one and get used to it there'll be a new model coming out, but we'll be stuck with a half-million dollar white elephant on which we still have to pay our monthly fee and maintenance. So we decided early on we weren't going to be one of the early adopters of this technology." Dr. Koch decided to use the MoFe mobile LenSx femtosecond laser for cataract surgery, provided by Sightpath Medical. "We don't have the overhead and have an agreement that works for both us and them," he says.

Mobile cataract surgery equipment might also be a solution for low-volume cataract practices who still want to offer their patients the latest phacoemulsification technology. Ann Deters, chief executive officer of Vantage

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Outsourcing, says her company provides provides turnkey cataract services for hospitals and surgery centers doing fewer than 800 cases per year. "On a per-case cost analysis, our service option becomes a no brainer for low to medium volume facilities," she says. "For example, in facilities where different surgeons want two different brands of equipment, Vantage can provide both phaco machines for the same price as bringing in one."

Another mobile company, ForTec Medical, recently entered an agreement with AMO to provide a mobile Catalys femtosecond option to practices. Patrick Filipovitz, vice president of sales and marketing for ForTec, says that in addition to being "cash-flow positive" from the first case—since the practice didn't have to buy the laser—and being protected from equipment obsolescence, practices also appreciate the technician that stays with the laser during its use. "The technician that accompanies the laser and helps with the cases spares the practice the need to hire a new employee or provide additional training for a current one."

Mrs. Deters notes facility managers appreciate her company's ability to take away their "back-office" headaches. "Our staff takes care of ordering, financing and managing inventory; handling equipment maintenance and repairs; providing the required number of micro-instrument sets; and ensuring that the IOLs are there for a particular surgery day," she says. "For IOLs, this means making sure that the surgeons have the appropriate diopter lenses in the correct quantities."

The Sightpath engineer remains with the machine to assist the surgeon. Here, Danville, Ill., surgeon David Dillman (center) consults with the engineer (right) on surgery day.

Mobile Services

If a practice is interested in a mobile service, it has several companies to choose from. Here's a look at each one and how its service works:

• ***ForTec Medical.*** In addition to the recent addition of the AMO Catalys, ForTec also makes available the Ziemer LDV femtosecond LASIK laser, the Visx excimer, and various YAG, ophthalmic diode and photodynamic therapy lasers. ForTec, headquartered in Streetsboro, Ohio, serves most of the United States except for several areas in the north.

ForTec's Mr. Filipovitz, explains how the company's new femtosecond laser cataract service works. "The laser is set up in the doctor's surgical suite, either in the OR or in a different room nearby," he says. "The set up is typically done on the afternoon of the day before the cataract cases. The ForTec technician will set up and calibrate the laser, and will be there to run the equipment during the time the surgeon does the procedures, providing general technical assistance and acting as an active member of the physician's staff."

If surgeons are interested in ForTec's Catalys service, the company offers the chance to be certified on the laser without necessarily making any commitment. "We offer surgeons the opportunity to be certified through a didactic course given by an AMO clinical applications specialist," Mr. Filipovitz explains. "Then, the surgeon has to do at least 10 eyes with the Catalys under the supervision of the applications specialist. We will also provide some marketing support, consisting of brochures, an animation that explains the procedure and a tablet computer that will explain the procedure to patients. After the first 10 eyes and after the surgeon is certified, we'll ask for a one-year commitment with a minimum of 60 eyes to be treated in that timeframe." The company offers a 50-percent discount on the Catalys' liquid optics interface, a disposable instrument that enables the system to operate on a patient, for the 10 eyes operated on during this certification period.

If a practice enters into an agreement with ForTec Medical, for a single surgeon the company asks for a minimum of 10 eyes per visit. If it's a multi-surgeon site that can accommodate multiple surgeons in a day or over two consecutive days, ForTec will reduce that minimum to seven eyes per surgeon.

In terms of pricing, it's a per-eye price. "A typical per-eye price for a single surgeon doing a 10-eye minimum is $850 per eye," explains Mr. Filipovitz. "That covers the liquid optics interface and a small fee for the equipment rental."

For information, call 1 (800) 963-7101 or visit fortecmedical.com.

• ***Sightpath Medical.*** Sightpath, based in Minneapolis, serves every state except Hawaii, providing both mobile and fixed-site applications.

On the cataract side, Joel Gaslin, vice president of sales and marketing, says Sightpath can serve as a practice's "ophthalmology department." "We bring in a certified surgical tech, the microscope, phaco machine and all backup supplies," he says. "Sometimes, a practice might have the staff and the space and just want us to function as materials management. In that case, we provide all of the manufacturers' products and handle equipment upgrades and maintenance agreements."

On the refractive side, Sightpath is primarily mobile, though it also has some fixed sites. The company offers both Visx and WaveLight excimer lasers, and the IntraLase for LASIK. The company is also beginning to offer marketing services to help practices deliver their key messages to patients.

The latest addition to Sightpath's services is the MoFe mobile femtosecond for cataract surgery. With MoFe, a practice enters into an agreement with Sightpath and must have at least six femto cataract cases scheduled per visit. When a surgery day is scheduled, Sightpath's engineer will bring the laser to the practice the night before to calibrate it. "As we moved into MoFe, we found that for many of our clients this was their first exposure to this type of device and the possibility for a breakdown," Mr. Gaslin says. "So having that engineer there to get it going is important. Short of a major engine failure, our engineer can keep the device running."

The pricing of MoFe changes based on the practice's volume. "The more cases we do, the more efficient we get," says Mr. Gaslin. "So our pricing models are built to share that efficiency benefit with the practice as we do more cases. We've done 13,000 MoFe procedures now, and our average per-procedure price across those procedures is around $775. And, as you do more cases, it'll get down to where it's below $700." In terms of scheduling, Mr. Gaslin says that practices start at once a month and quickly want to go to every other week. "Practices agree to a schedule about a year in advance," he says. "But within that there is flexibility if they need more access or need to cancel—as long as they give notice at least five days ahead of time."

Vantage Outsourcing provides a surgical coordinator with its phaco equipment.

For information, call 1 (888) 975-5828 or visit laservision.com.

• ***Surgical Direct.*** Surgical Direct provides practices with phaco equipment and other cataract surgery materials, such as intraocular lenses and disposables. It also offers lasers for glaucoma procedures and YAG capsulotomies. The company's based in St. Louis, but can service the rest of the country. States it currently serves include Missouri, Illinois, Kansas, Louisiana and California.

Ted Barden, vice president of sales for Surgical Direct, says the technicians that accompany the equipment are a benefit to practices. "Some facilities may only do cataracts one time a month and then, 29 days later, all the staff in the OR has forgotten how to do cataracts," he says. "Our techs are in the room running the equipment and the microscopes. If someone's having trouble loading a lens, the tech can help him."

In terms of minimum cases, Mr. Barden says it varies based on the distance, the procedure they'll be doing and the volume. "There's no cookie-cutter minimum," he says. "We look at each facility individually and provide a solution for whatever will best fit their needs. Ninety percent of what we do involves signing an agreement with them, because sometimes, depending on their location, we may have to hire additional technicians and acquire additional equipment. Typically, it will be a two to three-year agreement, but there are situations where we've structured it differently.

"We also have an on-call service," Mr. Barden adds. "This is based on the fact that a lot of the surgical reps have their equipment in a facility. If their equipment goes down and they can't get a technician to fix it, but the surgeon has cases the next day, the facility will call us and we'll bring in the microscope and phaco machine."

For information, call (314) 997-4455 or visit surgicaldirectinc.com.

• ***Vantage Outsourcing.*** Vantage, based in Effingham, Ill., provides all major brands of phaco equipment, surgical microscopes from Leica and Zeiss; and YAG and SLT lasers. It also offers a fixed-site femtosecond laser cataract service through a partnership or lease arrangement. The company serves the continental United States.

Vantage's Mrs. Deters says the surgical equipment will be accompanied by a Vantage staff member, who delivers the equipment and organizes everything for each case, ensuring that the eye day runs smoothly. "At a minimum, we provide a surgical coordinator," she says. "Our coordinator is a highly trained tech offering equipment expertise and assistance with room turnover. We can also provide surgical scrub technicians."

Facilities enter into a contract with Vantage, the length of which varies but is a minimum of a year. The company then works out a visit schedule with the facility and physician practice. "Typically these times are blocked months in advanced, but we have some practices that may no-

tify us one week prior," Mrs. Deters says. "On a given day, Vantage may be providing services for 25 or more accounts, with each doing from five to 40 cases or more.

"Another scenario may involve a metropolitan physician who satellites to five different locations, all of which contract with Vantage," Mrs. Deters adds. The surgeons operate at these centers once, maybe twice a month. It's tough for these rural areas to recruit permanent surgeons, so we bring the surgeons to them and the local optometrists provide the postop follow-up. Patients love that they don't have to drive 30 miles for surgery."

For information, call 1 (877) 564-3937 or visit vantageoutsourcing.com.

Issues and Concerns

With femtosecond cataract surgery being the hot new technology, mobile providers are deciding the best way to implement it and avoid any potential problems.

Some think that the time required to calibrate the femtosecond after moving it makes it a planning problem for practices, and that a three or four hour setup time can cause logistical headaches.

ForTec Medical says any problems with the calibration time may be minimized in the future. "Right now, the install times are as much as three hours," says ForTec's Mr. Filipovitz. "With some optimization in training we can get it installed slightly faster than that. We have a protocol from AMO coming that should reduce that install time to below an hour. So, if a practice is worried about the inconvenience of having someone stay until 6 or 7 o'clock for us to set up the laser, yes that is a downside to mobile currently. But, in the future we're hoping that we can do it the morning of the cases and be less disruptive to the practice's schedule."

Another question surgeons raise with mobile companies in their discussions is how well surgical equipment can handle riding in a van. Mr. Filipovitz says they take these questions to heart. "There is a custom air-ride suspension in the new vans that we use to transport the Catalys," says Mr. Filipovitz. "There's also a device that slides underneath the laser to support it that was designed to withstand a shock 30 times more than the most aggressive pothole you could find in the United States. We've also been through three different shake tests, one with OptiMedica and two with the AMO staff, to make sure there would be no risk of the system underperforming due to some transport shock. We've had no issues caused by mobility since we started performing cataract cases with it 120 days ago." REVIEW

Planning for a Smooth End-of-Year Landing

Charles P. Kroll, Contributing Editor

Take steps now to avoid negative year-end shareholder compensation and tax surprises.

With the fourth quarter under way and the clock running, time is of the essence to chart your financial flight plan through the end of the year. Identify planning opportunities and potential pitfalls, and stay on course to meet your 2014 compensation, tax and other financial planning objectives.

A proactive approach eliminates the risk of making decisions under pressure in mid-to-late December, with few options available and too late to take remedial steps.

Nine months of actual year-to-date data provides a solid foundation to confidently project your financial condition through December 31. Once established, you have the tools at your fingertips to address the following questions, among others:

- Are we on track to make our targeted shareholder compensation pool for 2014? If not, why not?
- Do we need to add more doctor days between now and the end of the year to make our objectives?
- How much cash flow can be generated by aggressively working down the accounts receivable?
- Will we be in compliance with bank line of credit and loan covenants as of December 31st?
- How much income do we retain in the practice for practice valuation and future investment purposes?
- Will we have the cash and what options are available for year-end shareholder distributions?
- What are the tax-planning opportunities at the practice and individual shareholder level?

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Reference: 1. Data on file. LENSAR, Inc.

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Balance Sheet as of 12-31-14	
Cash in Bank	*Is this sufficient to fund year-end shareholder distributions?*
Net Accounts Receivable	*Can AR > 90 days be reduced to less than 10 percent by year-end?*
Line of Credit Outstanding	*Are there sufficient reserves for 2015 cash flow emergencies?*
Shareholders' Equity	*Will equity, or "book value," increase or decrease in 2014?*

2014 Income Statement	
Net Revenue	*Are net collection percentages by lines of business as budgeted?*
Cost of Goods Sold	*Are surgical supplies as a percentage of net revenue as anticipated?*
Operating Expenses	*Have steps been taken to control operating expense bleeders?*
Income from Operations	*Does this cover shareholder compensation and debt service?*

projection components:

1. Financial statements and ratios.
2. Practice valuation at 12-31-14.
3. Federal and state taxable income.
4. Shareholder compensation pool.

All of these features can be captured on one Excel worksheet, updated as circumstances dictate and summarized for shareholder and management decision-making through the end of the year.

• ***Projected financial statements and ratios through December 31, 2014.*** January through September actual year-to-date financial statements, married to your October through December budget—modified as necessary for year-to-date line-item "bleeders"—is the formula to project out your practice's financial statements through December 31st.

Trust your accounting team to sweat the details; there are only a handful of vital signs that should be on shareholders' radar screen, with related questions, as illustrated in the tables above.

You also have the ability to calculate estimated financial statement ratios to determining compliance with bank line of credit and loan covenants, as well as setting the table for negotiating any 2015 financing requirements with your banker.

• ***Projected Practice Valuation as of December 31, 2014.*** Estimate your practice valuation at year-end based on your buy-sell agreement or other valuation formula, and accelerate physician recruitment, retention and retirement planning by six months. There's no need to wait on final 2014 valuation numbers with the issuance of your accountants' report in 2015 to start the planning process now.

• ***Projected 2014 corporation and shareholder taxable income or loss.*** Simple modifications to your financial statements will produce preliminary numbers for calculating federal and state taxable income, and associated tax liabilities. Built into your projection worksheet, these steps can be automatically updated through the end of the year.

Collaborating with your tax adviser, make sound tax planning decisions, effectively "target" corporation and shareholder taxable income and associated tax liabilities, and avoid April 15th surprises.

• ***Targeted 2014 shareholder compensation pool and cash available for year-end distribution.*** As questioned above, is your projected Income from Operations sufficient to cover your targeted 2014 shareholder compensation pool, taking into consideration debt service payments and out-of-pocket capital investments? If not, what steps need to be taken now?

Unless there are compelling tax or business reasons, borrowing money to fund year-end distributions sabotages the financial integrity of your practice and places pressure on cash flow in 2015. Does projected cash flow support scheduled distributions without the need to tap into your line of credit?

There are only 20 business days between Thanksgiving and New Year's, with frenetic clinic schedules and heavy surgical case loads. Eleventh-hour reductions in shareholder compensation, or 2015 announcements of missed 2014 financial goals, seriously undermine the credibility of and confidence in your financial management team.

Proactively manage your practice's financial health by utilizing these predictive tools for a smooth landing on December 31st. REVIEW

Mr. Kroll has more than 20 years of health-care experience, including 11 years with Minnesota Eye Consultants, P.A., providing financial management and consulting CFO services to independent and hospital-affiliated specialty and primary-care medical clinics. Contact him at cpkroll@gmail.com or on Twitter at https://twitter.com/CharlesPKroll.

Can a Comprehensive Practice Still Survive?

Christopher Kent, Senior Editor

As pressures on all ophthalmologists continue to mount, generalists may be facing the greatest challenges.

As the world becomes more complex and knowledge in every field becomes more extensive and detailed, it's increasingly difficult to master everything in any one area. This is certainly true in the field of ophthalmology, which is undoubtedly one of the reasons for the recent trend towards specialization. However, this is only one of many factors contributing to the shift. Today, the multitude of pressures affecting ophthalmologists in general—and comprehensive ophthalmologists in particular—has become so oppressive that many doctors wonder whether comprehensive ophthalmology can survive.

Here, three ophthalmologists accustomed to offering multiple services share their experiences and thoughts regarding the future of comprehensive ophthalmology.

Outlook: Negative?

Douglas K. Grayson, MD, assistant professor of ophthalmology at New York Eye and Ear Infirmary of Mount Sinai and medical director of Omni Eye Services of New York and New Jersey, believes the outlook for small, comprehensive practices is not good. "Having a small, general ophthalmology practice is becoming more and more difficult," he says. "Consider the perspective of younger individuals coming out of residency. They have to manage the overhead and administrative costs of trying to set up a practice that's compliant with all of the electronic health record guidelines and HIPAA regulations, and they have to get onto insurance panels, which has become particularly oppressive. Even if you have the financial resources to do all of this, the amount of time and work necessary becomes so burdensome that you can't really practice and take care of patients. As a result, I believe the trend is going to be toward bigger, hospital-based practices, completely devouring the smaller practices and just hiring associates out of residencies and fellowships. Nobody's going to be out there empire-building. Patients will go to large centers where there are multiple ophthalmologists, and whoever is there that day is who they'll get to see.

"Twenty years ago," he continues, "it was fairly common for an ophthalmologist to say, 'OK, I'm a comprehensive ophthalmologist, I do glaucoma, lids, cataracts, LASIK and I'm running the whole practice myself.' Bigger groups were less common than the guy offering multiple services. But I think that's changing. The only way to afford the overhead necessary to manage all the

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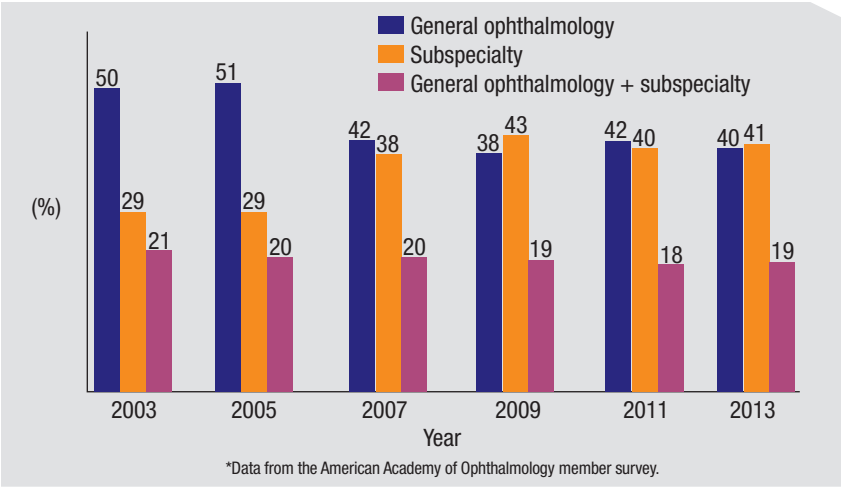

*Data from the American Academy of Ophthalmology member survey.

government compliance issues is to be part of a big practice, or a hospital-based practice where they have other sources of revenue to offset any losses they may experience."

Dr. Grayson notes that many general ophthalmologists are choosing to narrow their focus and join a larger practice as a result of the current conditions. "An ophthalmologist could stick to cataracts and maybe some basic glaucoma," he says. "This would avoid some of the stress that comes with trying to manage even more patient problems. However, today, even doing state-of-the-art cataract and glaucoma is becoming a real challenge.

"Our practice is currently in the process of acquiring a solo practitioner," he adds. "He was comprehensive and had a partner. When the partner left, he became a solo guy managing three offices. He was overwhelmed dealing with the records and trying to see all of the patients. He could have tried to bring new people in, but he's in his 50s and likes doing surgery, so instead we're acquiring his practice. We're putting our infrastructure in place, our EMR system, our techs and our scribes. Now all he has to do is show up, see his patients and go home. Before, he was doing a little PRP, glaucoma lasers and cataracts; now he's just going to do cataracts. And he's happy. Making the move lifted a tremendous burden from his shoulders."

Mark H. Blecher, MD, co-director of the cataract department at the Wills Eye Hospital in Philadelphia and medical director of the Kremer/TLC laser center in Cherry Hill, N.J., notes that he feels the pressures mounting in his practice. "I'm a comprehensive ophthalmologist in a multi-doctor private practice that's closely affiliated with Wills Eye Hospital, but not owned or managed by Wills in any way," he explains. "I think we're a very progressive and well-managed practice. Nevertheless, the challenge of increasing regulation and pressure from insurance companies is getting to be almost insufferable.

"At the same time, it's not clear what viable alternatives we have," he adds. "Are the larger health-care systems interested in ophthalmology? How are they going to provide eye care? Will they subcontract with private practices like mine, or bring things in-house? It's not clear yet, nor is it clear whether such an offer would be a good option for us. The ground is shifting very substantially at the moment, partly because of the Affordable Care Act and partly because of the ongoing changes in health care that started 30 years ago. I think a lot of us are feeling a lot more pressure and uncertainty than we did in the past."

On the Other Hand …

Despite the current pressures, many MDs still offer multiple services and are happy to do so. "A lot of the issues surrounding being a general ophthalmologist have to do with when you were trained, how you were trained and where you live—the demographics of your area," says David Gossage, DO, associate clinical professor of ophthalmology and director of the residency program at Michigan State University. (Dr. Gossage is in private practice in Hillsdale, Mich.) "If you live in a major urban center where you have a retina specialist next door, a glaucoma specialist across the street and a cornea specialist around the corner, you have to ask yourself whether you want to continue to offer those services to your patients. Maybe it would make sense to do only cataract surgery. But if you're in a rural setting where the closest retina guy is an hour away, the cornea guy is an hour and a half away and a glaucoma specialist is nonexistent, you're going to have to take care of many more things than you would in that urban setting."

Dr. Gossage notes that the training a doctor receives makes a difference in how comfortable he or she is offering multiple services. "If you were trained years ago when super-subspecialists were almost nonexistent, you were probably trained to perform many procedures," he says. "As a result, you may feel very comfortable taking care of multiple problems, problems that doctors who received less-broad training might be more inclined to refer. And of course it makes a difference how well you believe you were trained. I was trained back in the early 90s in pretty much everything from oculoplastics to glaucoma to retina, so I feel comfortable handling many dif-

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ferent aspects of comprehensive care.

"Right now I'm living in a rural setting where I do many different procedures and take care of patients with many different pathologies," he continues. "I know my limitations; if it's something like a surgical retina case, I'll send that patient off to a retina specialist. If it's a surgical cornea case, I'll send that patient off to a cornea specialist. But for the most part, I do the things I was trained to do. The rest of the services I offer are newer procedures I learned to do as they appeared. For example, when I was in residency, there was no such thing as LASIK, so I had to learn it after residency. Intravitreal injections were not common either, so when that became mainstream I had to learn about it. I continue to stay up-to-date on the studies and current therapies relating to that."

Dr. Gossage points out that there are some real advantages to being a comprehensive ophthalmologist. "One big advantage is that you're not putting all of your eggs in one basket," he says. "If your livelihood depends on refractive surgery or LASIK, what happens when all of a sudden a new procedure eliminates the need for your services? What if all you do is cataract surgery and someone invents a drop that gets rid of cataracts? And if you're very focused on one procedure, what happens if Medicare or other insurance carriers decide to cut the reimbursement for that procedure by 50 percent? It's really going to take a toll on you. In contrast, if you do a little bit of everything, and you do it well, I think you're much better off.

"I still do eyelids and blepharoplasty and ptosis repair," he continues. "I'll treat squamous and basal cell carcinomas of the face and lids. I still manage pretty much everything except surgical retina or pediatrics (the latter because my wife is a pediatric ophthalmologist, eliminating the need for me to address those cases). At one time I did a lot of LASIK, but right now I don't because the mobile laser that used to come and support our community is no longer with us. Again, as a comprehensive ophthalmologist, I'm able to take changes like those that have impacted LASIK in stride.

"One big advantage [of being a comprehensive ophthalmologist] is that you're not putting all of your eggs in one basket."
—David Gossage, DO

"It's like the stock market," he concludes. "You want to be diversified. Being a comprehensive ophthalmologist is like having a balanced portfolio. As long as you maintain good relationships with the super-subspecialists in your area, they can help you when a case goes beyond your skill level. Meanwhile, because you offer a variety of services, you can weather a storm when one arises."

The Cataract Surgery Factor

Naturally, cataract surgery is a mainstay offering of most general ophthalmologists. However, like many other areas in ophthalmology, this surgery has become increasingly complex, requiring more high-tech equipment and greater skills and precision than ever before. Today, it also requires managing patient expectations that have gone through the roof.

"Cataract surgery has become much more difficult, between trying to become familiar with femtosecond laser cataract surgery, the ever-changing tools for IOL-related measurements and learning to manage toric lenses," says Dr. Grayson. "Mastering the technology involved in trying to improve your cataract surgery outcomes requires a lot of time and focus and understanding. That makes it tougher for a cataract surgeon to also do glaucoma trabeculectomies, or ptosis or pterygium procedures, or even refractive surgical procedures such as LASIK—plus whatever new options arrive for presbyopic refractive correction."

Dr. Grayson says he currently does glaucoma and cataract surgery; other members of his practice group manage retina, LASIK and plastics services. Today, however, he's finding that even providing two services is increasingly challenging. "It's becoming oppressive for me to manage both glaucoma and cataract patients, given the time now that I have to spend with my cataract patients," he says. "Managing cataract patients used to be very straightforward. Now, patient expectations are much higher, and we have to discuss different lens options and femto vs. non-femto technique. At the end of the day it's the surgeon who has to talk to the patient about all of this, regardless of how much ancillary education your staff gives the patient. The patient wants to hear what the doctor thinks, and that takes time. Either you end up working until 8:00 at night, or you start seeing fewer patients, which means getting decreased reimbursements.

"Keeping up with the technology is also a problem," he continues. "For example, it took us a year to integrate femtosecond laser cataract surgery into our practice. Use of the laser is fairly straightforward, but the techniques for taking out the cataract are different, so there's a learning curve. When you first use the technology, you're going to have complications, and this is with patients who just paid extra for supposed state-of-the-art cataract surgery. It's not quite as difficult as the transition from extracap to phaco, but it's a challenge, and it will

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Reference: 1. RESTASIS® Prescribing Information.

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add to the burdens already faced by a comprehensive ophthalmologist.

"At first, the slowdown in our practice resulting from this transition was enormous; we were getting home at 10:00 at night from a normal surgery day that used to end at 5:00," he says. "Eventually we streamlined the process and our techs learned how to dock the patient on the femtosecond laser, but getting there took a long time. Now we're introducing the ORA instrument, allowing us to do intraoperative IOL power calculation. That's another whole slowdown that requires more time, focus and energy."

Dr. Grayson says that one upside of spending more time on cataract patients is that some elements of the surgery are now paid for by the patient out-of-pocket, circumventing the insurance system. "Because of that we can do fewer cases per day and still break even, or stay slightly ahead of where we were when we were doing a lot more cases," he says. "But at a certain point, when you've been in practice a long time, you get into your 50s and you start to get tired. You don't have the same energy level you had when you were 30. At age 30, staying until midnight wasn't such a big deal to me. Now, it is. As a result, I've decided to narrow my focus to just cataracts. I'm interviewing glaucoma associates now."

Dr. Gossage acknowledges that cataract patient expectations and the complexity of the surgical options today have increased dramatically, but doesn't see it as an insurmountable obstacle. "After LASIK became popular in the early 2000s, patients seemed to assume that all eye surgeries should produce equally fast and ideal outcomes," he notes. "This puts much greater demands on the cataract surgeon. And if you're committed to being a general ophthalmologist you have to offer toric lenses, limbal relaxing incisions and multifocal lenses, and have the related equipment—

The Malpractice Factor

Douglas K. Grayson, MD, assistant professor of ophthalmology at New York Eye and Ear Infirmary of Mount Sinai, acknowledges that in some geographic areas, limited medical resources might allow comprehensive ophthalmology to remain a viable option. Nevertheless, he worries about the risks entailed in offering multiple services that are increasingly complex with patient expectations rising. "The risk of malpractice comes into play," he says. "At some point you start doing things that are not in your comfort zone, or that you do very infrequently. If there are more competent people who could do that specialty procedure, you're exposing yourself to medico-legal risk. And since there's been absolutely no tort reform in the United States or in most individual states, what happens when you get sued has become more and more burdensome.

"Unfortunately, these days everybody gets sued," he continues. "It's not a question of if, it's a question of when, because it doesn't matter how good or bad you are. To the patient, and a plaintiff attorney working on contingency, it's like winning the lottery. The patient's got nothing to lose. On the other hand, the surgeon has a lot to lose in terms of time, because these cases take a lot of time to resolve. There are meetings, conferences and discussions, all of which will fall within the attorneys' schedules, between 8:00 a.m. and 6:00 p.m. on weekdays, which is exactly when you should be seeing patients. And you may end up having to close your office for a three-week trial."

Dr. Grayson points out that being sued can have other impacts as well. "Twenty or 25 years ago, if somebody sued you might settle for some amount, maybe $100,000 or $125,000, to make it go away," he says. "What's made that much more difficult is national databank reporting of settlements over $10,000. Insurance companies won't admit this, but if you settle once or twice, they may drop you. If they drop you, then you're forced into a high-risk policy where premiums can run over $150,000 a year, rather than a standard premium of $20,000 to $40,000 a year. And, if it happens again, even the high-risk guys may not take you. I know some ophthalmologists in Florida who actually go without malpractice insurance; they explain this to their patients upfront. Ironically, plaintiff attorneys are less likely to go after them because they know there's no easy way to get to their money.

"In contrast, your exposure is limited if you're in a big hospital-based practice where the organization may even have an in-house defense attorney," he adds. "The exposure of the solo practice doctor is much greater than if a patient sues after going to Columbia University or Wills Eye and seeing four doctors. The potential liability there gets spread around. Sadly, I don't think this situation is going to change, given our government's structure and the plaintiff attorney lobby. It's only going to get worse."

—CK

topographers and tools such as the IOLMaster or Lenstar. However, you probably don't have to purchase the most cutting-edge equipment, such as the ORA, which would be a huge practice expense.

"In any case, none of these changes to cataract surgery has undercut my ability to offer multiple services and maintain quality for our patients," he says. "And if I encounter a complex case that I feel would benefit from the most advanced equipment that's out there, I still have the option of referring the patient."

Other Issues

Comprehensive ophthalmologists are subject to a number of other pressures as well:

• ***It's hard to do everything well.*** "If an ophthalmologist is doing a little of everything, he's not necessarily doing it as well as he could because there's so much to do," says Dr. Grayson. "The first patient might be a cataract, the next patient a retina focal laser; he's got to stay relatively current in a lot of areas. As it is, just staying current in cataract and glaucoma requires a big time commitment. You want to offer the best, state-of-the-art treatments to your patients, and that means attending meetings, taking classes, going to lectures and then integrating the new ideas into your practice. And every new piece of equipment is a challenge. It's not acceptable to do a little of everything poorly; you have to do everything as well as you can, and that takes time and effort."

While Dr. Gossage agrees that procedures are getting more complex, he doesn't believe that's an argument against a general ophthalmologist learning and performing them. "I do think you have to make a commitment to stay up-to-date on new techniques and procedures, as well as the risks and benefits of any type of procedure you're performing," he says. "In the past, like many ophthalmologists, I would sometimes combine cataract surgery with trabeculectomy. When endoscopic cyclophotocoagulation became available, I learned that and sometimes did that along with cataract surgery; I felt it was a little bit safer for those patients long term. Now I'm learning micro-invasive glaucoma surgeries. I don't believe you have to be a glaucoma specialist to do those.

"On the other hand, if a patient needs a tube shunt or Molteno, I'd send that patient to a glaucoma specialist because I don't do enough of them," he continues. "I wouldn't try to treat a patient if it's in his best interests

to be sent to a subspecialist. But if I can control the patient's pathology and disease process while keeping him in the practice, so the patient is comfortable and doesn't have to travel so far, I think that's better for the patient. Every day I have patients say they can't thank me enough for being here. They really do appreciate not having to travel out of the area."

• ***Keeping up with the technology can be costly.*** Dr. Gossage acknowledges that staying truly comprehensive can be a financial burden. "Reimbursements are going down, but you have to keep up with the latest technology, and that's expensive," he admits. "If you're going to continue to do retinal treatment or glaucoma care, you have to be willing to invest in the latest technology, such as OCT, digital fluorescein angiography and software that can help you with things like glaucoma progression analysis. It's a necessary evil. But I've always felt it was worth it, as long as it's in the best interests of our patients. I've always been an early adopter. You have to take the plunge and get the tools you need."

• ***Insurance companies are trying to minimize usage.*** Dr. Blecher notes that insurance companies are adding to the burdens faced by comprehensive ophthalmologists. "Insurers are getting very exclusive and cracking down on their practitioner pools, insisting on precertifications and placing limitations on where you can do your work," he says. "It's different in each part of the country, but here in the Northeast insurers are trying to make it more difficult for patients to use their insurance by putting doctors through more hoops to get things approved. For example, a lot of insurance companies are requiring us to call and get a preauthorization for every Avastin or Lucentis injection we do. They can't tell people not to use their insurance, so they try to make it inconvenient or expensive for either the patient or the practitioner.

"This isn't a new phenomenon," he notes. "They've been doing variations on this for 30 years; it's just getting more acute now. A while back, HMOs used to require precertification for everything we did, but they eventually backed off. Today there's very little competition in the insurance industry, so the companies are feeling that they can be more stringent in their requirements. They're starting to get very feisty about wanting to control the use of their services."

"To offset decreasing reimbursements, you can try to see more patients, but then you're likely to miss things. You'll miss the subtle macular degeneration, you'll miss the subtle glaucoma."
—Douglas Grayson, MD

• ***When managing everything, it's easy to miss something.*** "The ophthalmologist trying to manage every problem is going to be overwhelmed," says Dr. Grayson. "Something's got to give. To offset decreasing reimbursements, you can try to see more patients, but then you're more likely to miss things. You'll miss the subtle macular degeneration, you'll miss the subtle glaucoma. I can't tell you how many patients I see who have significant glaucoma but were not diagnosed by their general ophthalmologist because the doctor didn't look carefully enough at the optic nerve. It's an every day occurrence.

"Unfortunately," he adds, "this problem is compounded by some general ophthalmologists not referring patients out in a timely fashion because they think they can do it themselves and they don't want to lose the patient. The latter problem doesn't arise in a multispecialty practice; all the issues get taken care of in a timely fashion. Ego and patient protectiveness don't become part of the equation."

• ***Electronic records add to the practitioner's burden.*** Dr. Grayson points out that the move to electronic medical records is another time and energy sink that makes it more difficult to stay current with multiple subspecialties. "When we transitioned from paper to electronic records it took us a year and a half to get comfortable dealing with the EHR system," he notes. "We went live in October of 2012, and it's just now, two years later, that we're starting to not have any paper records to manage from patients' previous visits. It's a big transition and a big expense.

"Yes, you do get some money back from the government if you meet the meaningful use criteria, but it's not easy to meet those criteria," he continues. "Then there are the HIPAA compliance issues. We have a person come in two days a week to make sure our systems are HIPAA-compliant. Then there are all the licensing agreements and all the expenses associated with using the software. Furthermore, we've found that you can't just see a patient on your own with an EHR system—you need a scribe. There's no way you can turn away from the patient and start typing on the keyboard without depersonalizing the patient-doctor interaction tremendously. And of course, scribes cost money, increasing your overhead.

"The bottom line is that switching to electronic records is another burden, another thing you have to learn to use

and maintain," he says. "If you're offering multiple services as a comprehensive ophthalmologist, this is yet another set of things you have to deal with."

Dr. Gossage describes his feelings about electronic health records as a love-hate relationship. "Electronic health records are expensive, and the IT support you need to help you with them is extremely expensive," he says. "We currently use both the Compulink system and Forum, so we have to have two monitors in every room—one for each program. When our system works, it can make things more efficient. But when the system crashes, or when the system is upgraded periodically and key things change, it's a big problem.

"In some ways, EHR is helpful for a comprehensive ophthalmologist," he continues. "It makes some things much easier, such as tracking a glaucoma patient's IOP over time. Now instead of manually charting it, you can just click a button and the chart is there. And the Forum system makes it easy to bring up past and current OCT scans for comparison, without having to use the OCT machine to manipulate the data. But it does slow you down and adds a lot of expense. For a general ophthalmologist I think it's a mixed blessing."

• ***The aging population may make comprehensive ophthalmology even more burdensome.*** "People are living longer and having more trouble with their eyes," notes Dr. Grayson. "If you're comprehensive, and you're treating macular degeneration in addition to cataracts and glaucoma, that means you're going to be giving a lot of injections. If the nearest retina specialist is three hours away, then there's no other choice, but I think that's a rarity in this country. Managing macular degeneration on top of cataracts and glaucoma is a huge amount of work. The result is that you can't possibly do it all as well as somebody who just does a single specialty. And you can't be as current, as state-of-the-art."

Dr. Gossage sees the aging population more as an issue of being increasingly at the mercy of government regulations and changes. "As general ophthalmologists, we mostly take care of elderly patients because they have the diseases—macular degeneration, cataract and glaucoma," he says. "And as the number of elderly people in the population increases, so does the proportion of our patients on Medicare. When I first started in practice I was seeing about 65 percent Medicare, maybe 25 or 30 percent commercial insurance patients and 5 percent self-pay. Nowadays my practice is 90 percent Medicare, 5 or 6 percent commercial insurance and 2 or 3 percent self-pay. That's a big shift toward Medicare patients.

"The problem is that we're subjected to a lot of pressure because we're really government employees," he continues. "The government is our biggest payer. So whatever Medicare does is obviously going to affect our practice reimbursement levels and the way we can practice. For that reason I think the shifting demographics are having a huge impact on our comprehensive practice. Specialists who don't have a high Medicare volume may not be impacted as much."

• ***Referrals may be getting more problematic.*** Dr. Grayson says another problem faced by comprehensive ophthalmologists is referral sources. "People are usually referred to ophthalmologists by two sources: their regular medical doctor or their optometrist," he points out. "If the referring medical doctor is part of a large practice or hospital, he's likely to refer to a specialist who's part of that group. Optometrists, in my experience, also prefer to refer to specialists. They're sophisticated enough today to know what the patient's problem is and what needs to be done. Their view is, why should I send this patient to a guy who does a little cataract, a little retina and a little plastics, when I've got access to a cataract specialist, a retina specialist and a plastics specialist? Again, it tends to cut the generalist out of the loop."

• ***Patient gratitude may be a decreasing reward.*** "Medicine is still rewarding, but all of the restrictions and requirements we're dealing with today take away from the philosophy that was much more dominant 20 years ago," observes Dr. Grayson. "Back then the idea was, 'We're helping people and making a few bucks along the way, and that's the way it should be.'

"Today it's about survival," he says. "And it's not as easy to work with patients as it used to be. Patient expectation levels are much higher, and often unrealistic. With Internet access, everyone is their own medical advisor, which can become problematic. You get some thank-you's, but a lot fewer than you did 20 years ago."

Can Generalists Survive?

Dr. Blecher notes that more and more ophthalmologists—like doctors in general—are starting to think about selling their practices to health-care systems. "Until recently, health-care systems were not very concerned about bringing ophthalmologists onboard," he says. "That may change going forward. Years ago these kinds of organizations bought up a lot of physician practices, both internists and general practitioners, as a way to control patient flow. Eventually they realized this wasn't producing the expected result, so they sold a lot of them back off and lost money. But now they're circling around to doing it again. This time around, physicians—especially in the primary-care field—don't want to be in practice any more. It's become

(continued on page 106)

Can Continuing Medical Education Be Saved?

By Frank Celia, Contributing Editor

Reformers and industry vie to reshape how physicians achieve professional development.

Does any occupation but medicine rely so heavily on the fresh acquisition of knowledge? The calculus that engineers use to design a suspension bridge hasn't changed much since Newton and Leibniz invented it. And the wheels lawyers grind to transform the law move at a notoriously cautious pace. We hear a lot about revolutionary change from the technology sector but, contrary to its marketing campaigns, the lives and wellbeing of millions seldom hang in the balance. Great as the new smartphone surely is, it won't restore lost sight.

Only health-care employees face this challenge: the possibility that what was exemplary job performance just a few years ago could today draw charges of gross negligence. Since the 1950s, practitioners have relied on continuing medical education to stay informed about evolving health-care standards, and almost every state mandates some minimum of CME credits for re-licensure. In short, everyone agrees on CME's vital contributions to the profession.

Unfortunately, among interested parties, that is largely where agreement ends. Over the past decade, the CME world has undergone a sort of slow-moving, self-appraising upheav-

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***- Dr. Ming Wang,** MD, PhD, Director Wang Vision Institute, Nashville TN*

al, mainly centered upon what role the pharmaceutical industry should play in the funding and content of educational courses. Between 1990 and 2006, spending on prescription drugs in this country grew fivefold.[1] As their market expanded, pharmaceutical companies began taking greater interest in physician instruction. Between 1998 and 2007, direct commercial contributions to CME activities quadrupled, from $301 million to $1.2 billion.[2] Critics said those funds amounted to veiled advertising, and matters culminated in a 2007 Senate hearing during which the CME industry took a public beating. Although the debate sparked reforms that put barriers on bias and commercial influence, and by 2013 industry's CME contributions had receded to $666 million, the backlash continues. Many critics are still calling for additional, stricter reforms, and some for the complete elimination of industry funding. The most recent hot-button issue has been whether CME will be exempted from the Affordable Care Act's so-called "Sunshine Act" provisions. *(See Here Comes the Sun, right).*

On a different level, CME is undergoing other, less volatile changes as well. Education providers are moving away from traditional, lecture-hall-centered formats in favor of more interactive, competency-based strategies that include online teaching tools, point-of-care CME and patient outcomes measurement aimed at tracking practitioner performance improvement. If some of these efforts are successful, they could radically change the way physicians acquire professional development in the years ahead.

Here Comes the Sun

The latest in a long series of skirmishes over CME's future flared up this summer when on July 3, on the eve of the holiday weekend, the Centers for Medicare & Medicaid Services proposed a rule change by which CME activities would no longer be exempted from the Affordable Care Act's Open Payments Program, also known as the Sunshine Act.

The move caused an uproar among CME providers, who for over a year had been operating under the belief that they and their commercial sponsors would be exempt from the new program, which calls for cash and value transfers to physicians to be tracked, recorded and made available to the public via an online database.

"So what this means is that pharmaceutical and device companies will have to literally draft an account of every dollar they spend to support an accredited CME event," says Andrew Rosenberg, senior advisor to the CME Coalition, a trade organization. Not only would this reporting present a logistical nightmare for event organizers, but it also would likely discourage physicians from participating in educational activities by creating a "false stigma" surrounding the public disclosure, Mr. Rosenberg says.

However, CMS, along with some legal scholars, have pointed out that the July 3 proposal does not affect the ACA's statutory exclusion of "indirect" third-party payments to physicians, which had been part of the exclusion's requirements from the outset. Hence, the argument goes, as long as the commercial sponsor does not know the identity of the physicians to whom the third-party payment or value transfer has been made, the CME event would remain exempt from the reporting requirements.

Not so, say CME providers. Relying on the less specific "indirect" payment exemption means event sponsors would have to remain unaware of participants' identifies both before and for 18 months after the event occurs—an unreasonable standard. "Industry could learn the identities of speakers/faculty and potentially participants after the funds have been transferred through brochures, programs and other publications, or through their physician-employees' participation in CE activities (either as speakers/faculty or attendees)," according to a letter submitted to the CMS by more than 100 medical societies, including the AMA. "Our organizations are concerned that this would have a significant, chilling impact on CE, which runs contrary to the public interest."

On the other side of the debate, many disdain the open payment program as toothless, regardless of CME's potential inclusion. "The vast majority of drug company CMEs are produced through third-party medical education and communication companies who are hired to create pharma-friendly content with cooperative physicians," according to statement issued by PharmedOut, an organization dedicated to exposing pharmaceutical marketing practices. "Drug companies are not currently required to disclose indirect payments, so most physician payments for involvement in industry-funded CME will continue to fly under the radar." The organization also points out that the Sunshine Act does not apply to non-physician practitioners, whose participation in CME has skyrocketed over the last decade and who account for 25 percent of all prescriptions written in the United States.

The CMS accepted public comments on the proposed policy change until Sept. 2, and is expected to make a final decision sometime before the end of the year. *—F.C.*

The Wild West

Ophthalmology has long had a proscholarship mien. In 1916, it was the first specialty to establish a board, the American Board of Ophthalmology, which in turn was one of the founding members of the American Board of Medical Specialists (ABMS) in 1933. A decade ago ophthalmology led the way among specialties in creating a core curriculum (the Practicing Ophthalmologists Curriculum), which has served as a model for other medical societies seeking to devise educational criteria. It can even be said that many of the changes described in this article owe a great deal to the efforts of one particular ophthalmologist, Bruce E. Spivey, MD, MEd, MS.

When he became president of the Council of Medical Specialty Societ-

ies in 2000, one of Dr. Spivey's first acts was to appoint a task force to investigate ways to reform and reposition CME. The task force, named The Conjoint Committee on CME, issued its first report in 2002, and has released several others since then. The committee's works have served as foundational documents for many of the reform efforts that have occurred over the past decade. One of its main themes is the call for greater reliance on adult learning techniques, such as "directed self-learning" and "non-traditional" educational approaches.

"The effectiveness of traditional CME has been questioned for some time," Dr. Spivey has written about his decision to appoint the task force. "The literature documents a lack of behavioral change as a result of the traditional lecture format, and a variety of alternatives to traditional CME have been proposed.

"The idea was not to not to dismiss all aspects of present CME," Dr. Spivey continued, "but to systematically review the literature and the variety of proposals for change that have been expressed."

At the core of Dr. Spivey's motivation was the idea that that CME system as it existed left considerable room for improvement. In one paper he wrote: "Throughout most of our CME experience, the predominant modality of delivery is journals and the large lecture hall—dimly lit, sporadic in focus, often with topics primarily of interest to the speaker (teacher) and too often, an opportunity for la siesta. And even if a lecture is captivating, a number of studies have demonstrated that isolated, single-exposure, lecture based CME does not result in physician behavior change."[3]

Around this time, scrutiny also began to fall on the burgeoning influx in commercial money to the CME system. In 2003, the Department of Health and Human Services issued guidelines prohibiting those with commercial interests to have control over certified CME content. The following year, the Accreditation Council on CME, the organization that credentials CME providers, updated and strengthened its "standards for commercial support" of CME activities. The new standards set criteria for independence, resolution of conflicts of interest, and development of unbiased content. In 2007 the ACCME strengthened those standards and broadened the definition of "commercial interest," requiring all CME providers to cut off all relationships with industry marketing/promotional employees. In 2009, it implemented rapid response measures to identify compliance infractions and place accredited providers on probation.

The ACCME has made no secret of ousting organizations that fail to comply with these standards. According to one of its press releases, "In 2008 and 2009, the ACCME reviewed 30 accredited providers that appeared to be affected by the change in the definition of a commercial interest, and found that 17 would be considered commercial interests. Of those, 14 successfully restructured and retained their accreditation; three did not restructure and withdrew from accreditation."

One industry-sponsored white paper refers to the period before 2005 as the "pre-reform era," and puts forth the notion that any studies based on data from that time period should be considered outdated.[4] The authors add: "Some CME professionals looked back on the period between 1984 and 2004 and labeled it the 'wild west.' While this may be an overstatement, there were a number of unhealthy practices in need of reform, including but not limited to dialogues between CME funding organizations and accredited providers regarding faculty selection and content."

The pre-reform era's laissez-faire approach to ethics finds confirmation

elsewhere. In her blog, "CME in the Raw," Brandee Plott describes starting out as pharmaceutical rep in the 1990s and working her way up to a medical education professional. "When I hear stories about the bad actors who gave medical education a bad public reputation, I believe all of it and more because I've seen it with my own eyes," she wrote in a post last year, recounting a cardiologist who offered to prescribe her company's drug more frequently if she would agree to send him to an "advisory board" meeting at a five-star hotel in the tropics. Describing her time at a medical communications company in the early 2000s, she wrote: "Back then pharma companies were not called commercial supporters. They were just called clients. I organized a CME satellite symposium at the biggest infectious disease meeting of the year. The pharma company's marketing department sent the faculty slide sets for their presentations, and during the final slide review, it was the pharma company's product manager calling the shots."

Such behavior no longer occurs, she says. "People in the industry on the provider side, pharma side and organizations like the ACCME, IOM [Institute of Medicine] and others cared enough about CME to come together and make some major changes. Now, medical education is evidence-based and commercial support is closely regulated."

Masked Marketing?

While reforms have had a positive impact, many critics believe they have failed to address some fundamental issues, and commercial funding therefore remains problematic. As the general public's favorable opinion of large pharmaceutical firms continues to decline, calls for additional regulation have found a sympathetic audience. A report published by Pew Charitable Trusts last year recommended the elimination of all industry-funded CME wherever possible. "In situations where industry funding is nonetheless being considered, academic medical centers should implement additional safeguards beyond compliance with the [ACCME]'s Standards for Commercial Support," the report concluded. "Examples of such safeguards might include: creating a 'blinded' pool of industry funds; requiring that any activity be funded by more than one company; calling for physicians to use some of their own money (such as paying for their own meals); and locating the continuing medical education activity within an academic setting or other appropriate venue conducive to education [instead of vacation resorts, etc.]."

Concerned about the knotty ethical questions still extant, in recent years some academic institutions and health-care systems have taken the step of declining industry supported CME programs altogether, the report notes. These include Memorial Sloan-Kettering Cancer Center; Stanford University Medical Center; University of Michigan Medical School; Kaiser Permanente; and Brody School of Medicine of East Carolina University.

Even the American Medical Association, hardly a hotbed of radical politics, saw fit in 2011 to speak out against industry-funded CME. Its Council on Ethical and Judicial Affairs concluded that CME activities should be developed without industry support "when possible," and adopted ethical guidelines discouraging both industry funding and CME lecturers who have relationships with industry.

Another broadside aimed at industry funding erupted late last year from a pair of Journal of American Medical Association articles. In one, a retrospective study of 2010 grant registries of 14 pharmaceutical and device companies, investigators found that, of 6,493 recipients of more than $657 million in industry-sponsored grant awards, privately owned communication firms received 26 percent of the grant money—more than academic medical centers or disease-targeted organizations.[5]

In the companion article, Lisa M. Schwartz, MD, MS and Steven Woloshin, MD, MS, of the Center for Medicine and Media, Dartmouth Institute for Health Policy and Clinical Practice, delivered a cri de coeur against private CME providers that accept money from industry: "All companies will feel unconscious (and perhaps explicit) pressure to present their clients' products in the best light. Bias can easily occur in the selection and training of speakers, in their presentations, on the websites, and even in the test questions."[6]

Elaborating on the editorial, Dr. Schwartz explained the question was not so much whether industry directly influences content, but rather whether CME providers paid millions by industry could reliably produce objective content about that industry. "If the financial entity as a whole is beholden to a particularly high-paying customer, to what degree does that influence produce content to satisfy that customer? The [companion] article documented how much money is coming from pharmaceutical companies into CME. It's substantial. Industry wouldn't necessarily be happy with content that portrayed their products in a negative way. That's the concern."

Puncta Caecum

Though it is possible to find practitioners with strongly held opinions on both sides of the CME funding issue, most fail to see it as more than a minor concern. Physicians tend either to believe that industry has little influence on CME course material, or that if it does, the profession is smart enough to separate facts from marketing, according to Adriane Fugh-Berman, MD, an assistant professor

of pharmacology and physiology at Georgetown University, and director of PharmedOut, an industry watchdog organization.

What many practitioners fail to realize, Dr. Fugh-Berman explains, is that marketing for a new drug can begin as long as seven to eight years before it gains Food and Drug Administration approval. Companies may put out CME materials about a disease's prevalence (invariably described as underdiagnosed and underappreciated) or a rival therapy's inadequacies long before the drug even exists. "Can doctors pick up on overt advertising of a drug? Sure. But you're never going to see overt advertising in a CME," she says.

For example, CME may suddenly be inundated with programs about a newly discovered system, such as the endocannabinoid system. "Well, of course that was meant to prepare the market, for—surprise—an endocannabinoid drug."

But even if we ignore the overt financial and marketing forces that taint industry funded CME, other hazards can undermine the impartial practice of medicine, says Dr. Fugh-Berman. These are non-financial and subconscious inducements.

In a paper published last year by the *Journal of Law, Medicine and Ethics*, Dr. Fugh-Berman and a co-author explored sales techniques aimed at exploiting subconscious bias.[7] Most physicians view with repugnance the idea that they would accept gifts or compensation in exchange for making therapeutic choices. "Physicians who would never, for example, engage in a quid pro quo exchange of money for prescriptions, may believe that such a conscious and genuine commitment to ethical behavior renders them immune to commercial influence. This righteous but wrong assumption derives from not knowing that many psychological processes occur below conscious awareness," according to the paper.

"For example, studies consistently show that promotion increases the prescription of targeted drugs, yet research also finds that physicians believe their own prescribing behavior is unaffected by industry influence, although they concede that other physicians are susceptible to such influence," the authors write. Social psychology has found that humans have a "bias blind spot" rendering them more likely to identify bias in others than in themselves, according to the paper.

In addition, CME represents a main avenue for the influence of nonfinancial inducements, which the paper defines as "the use of deference, the opportunity to be revered as an expert, and the publication productivity facilitated by industry-funded ghostwriters that furthers the health care professional's career."

Or to put it another way, CME offers the opportunity to become a key opinion leader, a role usually reserved for high-status, respected, academic physicians. Industry not only sends these influential physicians to CME events to sway and guide the opinions of their peers but also dangles the possibly of becoming a KOL to entice rank-and-file practitioners, according to the study. "The industry's use of opinion leaders is clearly a use of authority, but it also is a use of scarcity—the concept that opportunities are more valuable when they are limited: not every physician is eligible for the plum job of KOL."[7]

Dr. Fugh-Berman sees no place for industry funding in any aspect of continuing education, even if that prohibition results in fewer CME events. "We have enough non-industry funded CME just on our [PharmedOut's] website for physicians to get all of their credits if they want. There's a lot of CME out there that is not industry funded," she says, concluding that, "participation in industry funded CME can only worsen your prescribing habits."

Mistaken Conflation

Defenders of industry-sponsored CME concede that many real and potential conflicts of interests exist in the relationships between commercial enterprises and medical practitioners. However, they contend those conflicts have been misidentified as occurring in the world of accredited CME. There is widespread confusion about the distinction between promotional programs—which often combine educational messages with marketing ones and are sometimes even labeled "education"—and certified CME presented by accredited providers that adhere to ACCME standards, they say.

"Most reports comingle discussion of conflicts under the broad category of 'education,' which often includes certified CME activities under the same umbrella as promotional programs that are directly funded by industry," according to an industry white paper. "The confusion appears to occur when authors and editorialists consider all forms of so-called 'education' as certified CME. The CME enterprise often is impugned based on the fact that authors do not acknowledge the separate rules that govern accredited CME providers."[4]

Indeed, the JAMA article cited above that studied grant registries made just such an error, according to Murray Kopelow, MD, president of the ACCME. It erroneously lumped medical communication companies together with medical educational companies. "By conflating medical communication companies with medical education companies, the article presents a misleading, inaccurate, and imbalanced picture of accredited continuing medical education and the stringent requirements in place to safeguard its independence," he said in an interview published on a website that covers event planning and medical meetings.[8]

MOC: Learning or Earning?

As the bureaucratic and compliance responsibilities of physicians continue to multiply, many are beginning to wonder whether board certification, a time-consuming and not inexpensive process, is worth the effort. A growing number of specialists see maintenance of certification (MOC) as redundant in light of CME and maintenance of licensure (MOL) requirements, and some have gone so far as to suggest the process exists primarily to generate revenue for the credentialing boards.

An organization called Change Board Recertification, established in 2010 and run by California physician Ron Benbassat, MD, says that support for its mission continues to expand. "The data are thoroughly convincing," its website states. "MOC has evolved into a discriminatory money-making juggernaut without any reasonable proof of efficacy and is slowly being tied to the right to practice medicine."

Aware the board certification process was losing esteem among specialists, the American Board of Medical Specialties in February introduced new standards designed to address time and cost pressures associated with MOC. Inspired by changes occurring in the CME world, the new standards include a greater reliance on adult education precepts, and performance-improvement and quality-improvement activities.

Critics were not mollified. In April, the Association of American Physicians and Surgeons sued the ABMS in federal court, alleging anti-trust violations and restraint of trade, and also of depriving patients' access to physicians. In March, an online petition began which called for certification testing to be limited to no more than once every 10 years. As of this summer, it had gathered 17,000 signatures.

Prior to 2000, when the 24 boards that make up the ABMS began changing their policies, board certification had been a lifetime appointment. The American Board of Ophthalmology scrapped lifetime board certification in 2006. About 95 percent of ophthalmologists are board certified, slightly higher than the national average, which is 85 percent. Board certification remains voluntary, but as MOC participation becomes increasingly linked to hospital privileges, reimbursement and network participation, it is now often viewed as a de facto mandatory requirement.

"I think the concept of MOC is a good one," says Bruce E. Spivey, MD, MEd, MS, an immediate past president of the International Council of Ophthalmology who has been deeply involved in professional development issues throughout his 50-year career. "Nobody likes taking tests. It's a hassle. But if you are going to measure knowledge, we don't have many other ways than an oral or written examination." The system as it exists now may require fixing, he says, "but I think over time it will become an accepted part of medical life."—*F.C.*

According to many who work within it, the business really has changed for the better. "We have completely retooled. We are a completely different company than we were 10 years ago," says Thomas Sullivan, president and founder of Rockpointe Corp., a medical education company based in Columbia, Md. "Our science is a lot stronger. We spend a lot of time doing needs assessment to see if the topic is really important to practitioners. We perform outcome studies after every program to determine if we have made a significant difference in the way our participants practice."

There is no hint of marketing in anything his company does, Mr. Sullivan says. "At this point everything in this business is pretty much completely separated from marketing. There is no one in marketing involved, even at the smallest company. Our only goal is to educate physicians. It's no longer about positioning a drug in the marketplace. Those days are long gone."

Additional reform efforts, especially those imposed by the federal government such as the Sunshine Act, will only result in chasing more industry

dollars out of the CME business at a time when health care needs medical education programs more than ever, according to Mr. Sullivan. "We've seen commercial funding decline year after year for about the last seven years now. It's created a sort of perfect storm for doctors, because they are getting less travel money from their employers, and even the government is sending fewer people to conferences. More doctors are taking CME classes online, which is not necessarily a bad thing, but it does cut down on the kind of interaction you get at a live conference where physicians can exchange ideas with experts."

Of particular concern is the deepening estrangement of primary-care doctors from specialists, says Mr. Sullivan. In decades past, primary-care physicians and specialists would mingle with each other at hospital settings. But now hospitals are increasingly hiring their own full-time physicians, who interact less often with their specialist colleagues in private practice. "When they took primary-care physicians out of doing rounds and put in 'hospitalists,' what happened was the primary-care physician now has less access to experts. They don't talk to specialists because they don't run into them in the hospital hallway anymore." More frequent participation in live CME events would help to integrate a health-care system ever more subject to what many call the "silo-ization" of human resources and knowledge, he says.

Virtual OR

When 41-year-old orthopedic surgeon Selene G. Parekh, MD, MBA, began wearing Google Glass in the OR, it was originally meant as a strategy for live broadcasting educational videos to India, where he had been performing charity clinics for several years. But he soon realized the instructional potential of the device—which is essentially a head-mounted, voice-activated smart phone—was a two-way street.

"In my mind, one of the most significant features Google Glass offers is it can bring any surgeon from around the world into any OR around the world to affect patients' health," he explains. If a surgeon encounters an anomaly during a procedure, he or she could, via voice command, contact another surgeon who is an expert in the field and is also wearing a Google Glass. "You can bring that expert into the OR with you at the exact moment when you need help," he says. "To me that is an amazing power."

The next generation of learners, the ones who have recently graduated medical school or are in it now, will have a greater interest in learning in this point-of-care fashion, according to Lawrence Sherman, FACEHP, CCMEP, senior vice president of educational strategy at Prova Education. "These people are ready for a fast-paced, ever-changing, lifelong learning environment," he says. "So we are going to have to keep up with their needs, to provide CME at the point of care, on the mobile device, in the operating room, at places where the clinical question comes up."

Groundbreaking change, however, will not occur overnight. Although point-of-care and quality-improvement CME credits have been available since 2005, as a practical matter, putting these sorts of CME programs into practice, especially on a global scale that crosses national borders, still presents many daunting challenges, says Mr. Sherman: "Not all best practices cross borders. Not all procedures are the same. Not all formularies are the same. So at the end of the day the education that is developed in the U.S. may not even be relevant in the practice environment in which learners in other countries are operating."

Unintended Consequences

It seems axiomatic in a field as complex, unpredictable and multifarious as medicine that the manufacturers of the products designed to serve that field should have some sort of official channel of communication to the end-users of those products, no matter how regulated or fiercely guarded that channel may ultimately need to be. Even the Pew report cited above concedes that exceptions to its suggested prohibition of commercial funding be made for device manufacturers to instruct physicians on how to operate new instruments. And the federal government appears to endorse the importance of commercial funding via the FDA's Risk Evaluation and Mitigation Strategies (REMS) program, which compels pharmaceutical companies to educate practitioners about problematic drugs.

Moreover, the absence of commercially funded CME could force industry to turn to non-accredited educational events, such as dinner lectures at restaurants and satellite symposia at professional society meetings, venues devoid of any oversight whatsoever. A too-harsh stance toward CME regulation could result in "unintended consequences," according to one journal editorial: "If changes in the CME landscape drive physicians away from accredited events toward these non-accredited activities, the overall state of medical education will not have improved."[9]

On the other hand, despite industry's commendable efforts at self-regulation, the issues of topic choice and true content objectivity remain matters that appear to merit additional scrutiny.

Few believe CME's long transformation has run its course. When asked if a decade's worth of reform had had an impact, Dr. Spivey put it succinctly: "It's a work in progress." REVIEW

Mr. Celia is a freelance health-care writer based in the Philadelphia area.

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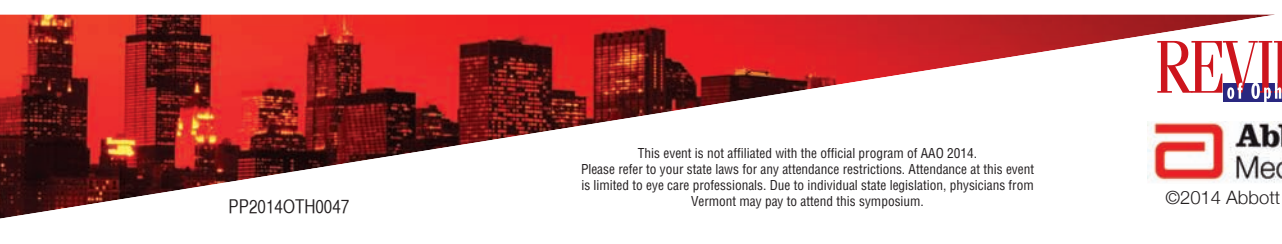

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How to Bring on a Retinal Specialist

Walter Bethke, Managing Editor

Hiring a retinal specialist can be a good move—for the right practice.

As the population ages, and retinal conditions in the older patient demographic continue to proliferate, some comprehensive ophthalmology practices may begin to wonder if they should be the "one-stop shop" for their patients and bring on a retinal specialist to take care of these problems. Though the intention behind this is admirable, experts say it pays to take a cold, calculating look at your practice's actual numbers before bringing on someone new. Here, physicians and ophthalmology business consultants share the dos and don'ts involved if you're considering entering the retinal arena.

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Bigger Is Better

Surgeons and experts say that the volume of patients your practice sees will dictate whether you can bring on a retinal specialist.

"The first question is, 'Do you have associate doctors?' " says Kevin Corcoran, co-owner of Corcoran Consulting Group in San Bernardino, California. "If you are solo, the number of patients needing attention from a retinal specialist is likely very small, so the proposition is very weak." Multiple doctors, however, have an easier time bringing on a retinal specialist because they have the patient volume to justify it. In general, Mr. Corcoran says it takes about 20 ophthalmologists to support a full-time retina specialist.

If you don't have a large enough volume to support a full-time retinologist, though, you may be able to come to an agreement with someone to attend to your patients on a part-time basis. "More multispecialty practices are adding retina, as their primary and secondary care provider bases grow to the scale where they can support such individuals," says practice management consultant John Pinto, whose San Diego consulting firm specializes in ophthalmology. "They'll often do this by bringing in part-time medical or surgical retinologists from an-

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other pure retina practice. They fill more and more of that person's schedule—one day per week, two days per week—until they reach the crossover point where it's more cost-effective to bring a person in-house." A bit of luck may be needed, however, because it can be challenging to find someone willing to come in part time, since his own retinal practice would probably keep him busy enough. "The decision to bring in a retinal specialist quite often depends on who replies to your classified advertisements and who you're able to recruit," says Mr. Pinto.

Bringing Someone In

Keith Casebolt, chief executive officer of Medical Eye Center in Medford, Ore., says he and his staff did an analysis of their patient composition and referral patterns and decided to hire a retinal specialist last year. Here's a look at his practice's experience, accompanied by comments from experts on various aspects of this process.

• ***The practice's makeup.*** "We now have six MDs and two optometrists," Mr. Casebolt explains. "The ophthalmologists are all subspecialty-trained: two glaucoma; two cornea; one oculoplastics and one retina. Of the cornea specialists, one does anterior segment procedures while the other just does LASIK."

• ***A referral analysis.*** Mr. Casebolt says retina filled a niche for the practice. "The thinking was that, of the specialties we didn't have, retina would be the easiest one to add, given that a retina surgeon wouldn't be in competition and splitting volume with the other ophthalmologists. In our analysis, we looked at how much we were referring out and what kind of diagnoses were in our database. We applied some assumptions to those diagnoses such as how many times per year those patients might need to be seen by a typical retinologist and then we kind of backed into a number of visits and expected revenue to create a *pro forma* on how we thought it would work." Mr. Casebolt says his practice's retinal specialist was full-time from the start, rather than part-time. "It's tough to find people who are looking for part-time work," he says. "And we were confident that we had enough volume to keep someone busy."

• ***The capital outlay.*** One thing that stops some practices from adding a retina specialist is the fact that he needs a number of expensive pieces of equipment. Phil Rosenfeld, MD, medical retina residency director at the Bascom Palmer Eye Institute at the University of Miami, lists equipment that will probably cost around $200,000 to $250,000 all told. "The most important thing is to make sure the office is equipped adequately with OCT imaging, photographic and autofluorescence imaging and angiographic imaging," he says. The practice would also need lasers to perform retinal laser procedures, when necessary.

Since anti-VEGF injections are such a mainstay of retinal treatment, the practice will also have to manage those drugs. "We have to keep an inventory of anti-VEGF drugs," says Mr. Casebolt, "The handling of these drugs is a significant element of the process. We ended up purchasing a piece of software that tracks those injections all the way from ordering and receiving them, to using them and determining whether or not they got billed correctly and we were paid properly. The software, called the Physician Office Drug Inventory System [General Medical Services, Kenilworth, N.J.], has saved us thousands of dollars, even though we thought we had done a pretty good job prior to that with the basic system that we had. With it, we're catching about one mistake per month: For instance, if you have it coded as Avastin but it's really Lucentis. That's a big, big error and, if you make it, you're writing off a lot of money. We also found instances where we got the units wrong and a variety of other small mistakes."

• ***Compensation.*** Though there are many different permutations of how a new physician employee can be compensated, they're usually variations on a base salary plus a bonus when the doctor surpasses a certain level of collections. For instance, some practices pay $225,000 plus 30 percent of any collections that go above twice that salary amount. "Our typical formula for an employee position is a base salary, then we multiply that base by 2.5," says Mr. Casebolt. "We give them a percentage of everything above that that they collect."

Mr. Corcoran recommends obtaining advice from legal counsel and a tax advisor about the terms of the engagement. He says it can be designed as: 1) employment; 2) independent contractor; or 3) landlord/tenant. "Some practices seek to save money on employer taxes by electing independent contractor agreements rather than an employment arrangement," he says. "Because the IRS might not agree with this election, you should test it using the Internal Revenue Service 20 Questions [http://art.mt.gov/artists/IRS_20pt_Checklist_%20Independent_Contractor.pdf)]. The principle that separates employee from independent contractor is based on control. According to the IRS, an employer exercises control when it provides equipment for work, determines work schedules, provides staff and collects money. If a practice hosts a visiting retina specialist, the degree of control is an important question that has a bearing on the terms of the engagement and the method of compensation. An arrangement that relies on paying the retina specialist a percentage of collections is likely based on an employment agreement rather than an independent contractor agreement." He says this is another reason practices without enough patient volume must think long and hard before trying to

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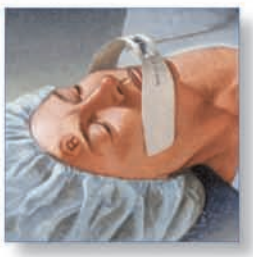

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Keith Casebolt

Medford, Ore., administrator Keith Casebolt says his practice has a dedicated waiting area for retina patients.

work with a retinal specialist on an intermittent basis. (The third option, landlord/tenant, is almost never appealing because the practice will only be able to charge about $100 to $150 per month in rent.)

• ***Staffing requirements.*** The practice has to be prepared to provide the extra manpower necessary to treat retinal patients. "Your billing staff, front-desk staff and technician staff will have to adjust to the retinal doctor's volume," says Mr. Pinto. "Typically, in retina you need 1.2 tech payroll hours per visit. So, for example, if the retinal specialist will be seeing 250 patients per month, multiply 250 by 1.2 hours/patient, then divide that by the 173 hours that constitute one full-time equivalent, and you'll see that you'd need 1.7 tech full-time equivalents, or almost two full-time techs to support the retinal specialist. You also might need extra front desk and billing help. All in all, it usually takes 2.5 hours of lay staff time for each patient visit in a clinic. When you multiply that by the usual $22/hour wage, it means you can expect about $50 or $60 of incremental staff cost per patient visit."

• ***Revenue for the practice.*** Experts say that, as long as you have the patient volume to support him, in addition to servicing your patients who would have had to go elsewhere for their care, the retinal specialist will be providing a revenue stream that didn't exist previously. Mr. Casebolt, whose retinal specialist also performs surgery, says the retinal cases have ramped up more slowly than they predicted, but that there are signs of growth. "Our retinal revenue is up to $1.2 million per year, excluding the cost of the anti-VEGF injections such as Lucentis, which, at $2,000 per injection, would distort the revenue amount if they were included." The revenue does, however, include the fees they receive for performing the injections. "I think our *pro forma* was a little more optimistic regarding the number of patients we thought we'd be referring internally," Mr. Casebolt adds. "I'll balance that by saying we live in a region where, compared to the size of the population, it was already very well-served by the number of retinologists in the community. So, we didn't receive any outside retinal referrals, even though we assumed we'd get a few. Having said that, over time we're starting to get more referrals from outlying areas two or three hours away. All the counties around us are sparsely populated and have begun referring people to us for cornea, cataract, glaucoma and oculoplastics, and are now starting to refer retinal cases to us, too. Now we're one-stop shopping for them for patients with eye problems that they can't deal with."

Mr. Pinto says the economics of bringing in a medical retinal specialist vs. a surgical retinal specialist depends less on whether he's surgical or non-surgical and more on how relatively clinically assertive or aggressive he is. "There are retinologists, both medical and surgical, who hit a plateau at $1 million or $1.2 million per year in revenue, and just don't seem to climb above that," he says. "Then there are other retinologists who readily climb to a figure approaching $2 million or more and are ready for more beyond that. So, as a practice considers bringing in a physician, I'd put less weight on whether he's medical or surgical and more weight on his career history and whether he's used to a larger or higher volume practice and is ready to do the work."

• ***Bumps in the road.*** If you do end up hiring a retinal specialist, as with any change to your practice, there will be some growing pains, experts say.

"Retinal exams tend to take longer, so patients are typically in your building longer, and therefore your waiting room is more full," says Mr. Casebolt. "So, you have to think about the space and if you have an adequate number of exam lanes, waiting room space and rooms to put your new equipment in. The longer exams mean patients are in your building longer, so they may get fatigued or grumpy. For the general ophthalmologist's patient who has a comprehensive exam, the total visit duration from the time he comes in the front door to when he walks out is between 70 and 90 minutes. But, for a new retina patient—not just someone coming in for an injection—he's going to be here for two and a half hours. So, there are just more issues with more cars in your lot, more people in your waiting rooms and bathrooms getting heavier usage. We try to manage retina patient expectations by letting them know ahead of time that these will be long visits." Mr. Casebolt says the practice, which is laid out like a wheel with a pre-workup area in the hub and four "pods" that radiate out to individual doctors' areas, can get crowded. "Sometimes the pod where our retinologist works is full or close to it," he says. "But we've never exceeded our capacity."

Mr. Corcoran indicates that the supply of intravitreal medications such

as Lucentis, Eylea, Avastin and other agents pose significant practice-management challenges. Carefully managing inventory is important. Obtaining payment for drugs is critical. "Losing just one vial of Lucentis represents a $2,000 error," he says. "Your Medicare reimbursement includes a small handling fee of about 6 percent, which isn't enough that you can make too many mistakes," he opines.

In addition to logistical and financial concerns, there may also be the issue of personality clashes. "When you are hiring any type of sub-specialist, you'll find they're often more challenging to manage and temperamental than a generalist," says Mr. Pinto. "Neurosurgeons or invasive cardiologists are more temperamental than pediatricians, for example. Note that not every sub-specialist is like this—this isn't universally present—but if it is present it can be challenging for a manager. This personality might manifest itself as an undue fussiness about equipment or the staff that are required. It might manifest as 'empire building'—wanting their own separate techs or wing of the building, or it can express itself as a higher level of neediness or a sense of entitlement. To help avoid this, it's important to do your homework, do your vetting and make sure the chemistry is going to work out."

Mr. Casebolt says he's been lucky in this regard with his retina person, but is aware that it could happen in some practices. "I think a lot of it can be avoided by setting expectations and sticking to them," he says. "It's not just retina, though. You could find a lot of surgeons who have high expectations and are very driven people. Like any situation where there is someone with a strong personality, the only way it will work is if you have very frank discussions about the working situation before he's hired. Be as crystal clear as you possibly can, and get most of it in writing because managers might forget what they told people before they came onboard. It's good to have a long e-mail or a contract to go back to."

Do It Yourself

Though it's great if a multispecialty or large group ophthalmology practice can recruit a retinal specialist, experts say there are also populations of underserved patients, with no retinal specialist nearby, for whom it might make sense for a comprehensive ophthalmologist to provide medical retina services. The key, physicians say, is that the general ophthalmologist can't just dabble in retina; he or she has to approach the task seriously and be armed with the proper training.

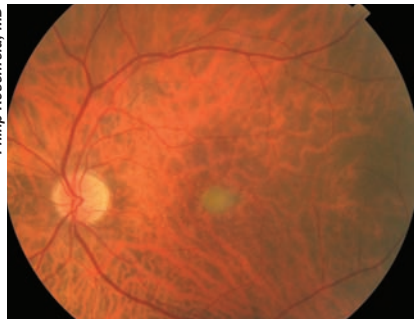
The objections raised by the retina

community usually center on the fact that providing medical retina is not just about administering anti-VEGF injections, but instead it's also about diagnosis, understanding clinical trials and, importantly, knowing when and when not to inject. Retinal specialists also worry that comprehensive ophthalmologists may skimp on instrumentation, such as an OCT machine, which could affect their diagnoses.

Katherine Johnson, MD, a comprehensive ophthalmologist practicing in Fairbanks, Alaska, understands these concerns. She says, however, that her excellent residency training and her commitment to technology and continuing retina education make her well-qualified to manage many of her patients' retinal conditions.

"I'm comprehensive in every sense of the word," Dr. Johnson says. "I'm 400 miles from any other specialist, so my practice is half medical retina, a reasonable amount of cataract volume, glaucoma and a decent amount of neuro-ophthalmology. I do 25 anti-VEGF injections per week, which is a good amount by Alaskan standards. The injections are scattered in with everything else, such as retinal lasers. I'm procedure-heavy, because the people who come to my clinic tend to have advanced disease or really odd things. I don't see the diabetic well-eye exams, but instead the ones with massive amounts of proliferation who haven't seen an eye doctor in 10 years. I see the advanced glaucoma. And, of course, the wet AMD; anyone with dry AMD is seen by my optometrist."

Dr. Johnson says she owes her proficiency with these cases to her training. "I trained at Bascom Palmer, which has a phenomenally retina-heavy training program," she says. "There, you do focal lasers as a first-year resident; you get all the PRP and laser demarcations that you could want. You also do an enormous amount of macular degeneration at the VA. I was lucky in that Avastin came out during my second year as a resident. So, my first year was laser heavy and then my second year enabled me to do Avastin injections. I had hundreds of injections under my belt before I left residency."



Philip Rosenfeld, MD

Vitelliform lesions can fool a generalist into thinking they're wet AMD, say experts.

Dr. Johnson says there's even an advantage to the generalist managing anti-VEGF injections. "I do a number of injections combined with cataract surgery," she says. "This means the injection is done in a sterile environment. I also inject vancomycin in my cataract surgery eyes, mainly because endophthalmitis is a concern when you're hundreds of miles away from the nearest vitrector. So, when I do an injection of anti-VEGF at the time of cataract surgery, it's as low-risk as you can possibly get. It also makes it easy for the patient, because it's painless, and she can enjoy the benefits of having it done in the sterile OR."

Dr. Johnson says one of the keys to her success managing retina patients has been having an advanced digital imaging system that lets her send confounding cases to someone else for consultation, and to know when to refer a patient out. "I have referred some things, such as an acute retinal necrosis patient, with whom I wasn't willing to do her tap-and-inject. I thought she was beyond the medical-legal scope for the non-fellowship-trained person if the case were to go bad. I sent that patient down to Anchorage. Other times, perhaps once per month, I'll send patient images to get advice and ideas. But for most cases, such as diabetes, retinal tears, AMD and vessel occlusions, I'm perfectly competent managing them." In over 7,000 injections, Dr. Johnson's had one instance of "questionable" endophthalmitis in which the patient had an inflammatory reaction that was culture-negative. Dr. Johnson did a tap-and-inject, and the patient's vision returned to baseline.

Bascom Palmer's Dr. Rosenfeld says that though it's possible for a comprehensive ophthalmologist with the right training to manage retina, there are still conditions to watch out for. "I see quite a few patients come in with an AMD diagnosis who don't have AMD," he says. "There are a few conditions that look like AMD, such as chronic central serous chorioretinopathy. And there are lesions that look like neovascularization that aren't, such as vitelliform lesions. Managing retinal pigment epithelium detachments is always a challenge for the non-retinal specialist, as well."

Dr. Johnson acknowledges that, in some locations, it might not be politically feasible for a generalist to manage retina. "In a lot of places, if you're doing medical retina and cataract surgery, the retinal specialists might not send you their cataracts if you don't send them your retina patients," she notes. "I think these politics are more important in some of the larger towns where you're not as remote and you have to maintain a patient referral base. There, it's a legitimate issue."

Ultimately, Mr. Corcoran advises that adding a retina specialist is a big step and it needs to be handled carefully. "As a practice gets larger, it makes sense to consider offering retinal sub-specialty care as part of an ophthalmic center of excellence," he says. "However, dabbling in medical retina as a dilettante is problematic, potentially dangerous, and unlikely to be financially rewarding. Do it seriously or just refer the cases out. Bottom line: Do what you do really well, or don't do it at all." REVIEW

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Treating Persistent Pupillary Membranes

Aparna A. Shah, MD, Mauricio Perez, MD, Michael E. Snyder, MD, Frederico Marques, MD, PhD, Daniela Marques,MD,PhD

Three cases illustrate how to treat this condition, which can afflict infants to young adults.

Persistent pupillary membranes represent incomplete regression of the tunica vasculosa lentis, which normally involutes by the sixth month of gestation. When this process is incomplete, strands of connective tissue may attach to the iris collarette.[1]

Usually, minimal connective tissue remnants do not affect vision, although, if symptomatic, mydriatic agents may occasionally mitigate a partially obstructed aperture.[2] Larger membranes may disrupt the visual axis, resulting in either visual symptoms or amblyogenic opacities[3] requiring surgical excision or laser lysis.[2,4]

In each of the following three cases of clinically significant persistent pupillary membranes. the membrane was crucial to the clinical management.

Background

During the first year of life, most PPMs undergo atrophy and require no treatment. Membranes persisting after one year are less likely to regress spontaneously, increasing the risk of deprivational amblyopia. A 1.5-mm pupillary opening is necessary for adequate retinal stimulation and visual cortex development.[3,5]

Thick, fibrotic membranes may also require surgical excision.[4,5] Surgery is generally performed in the first weeks or months of life, with good visual prognosis[4] and consists of excision of the pupillary membrane using Vannas or vitreous scissors. Older patients with thin, sparse membranes may be candidates for Nd:YAG laser membrane lysis.[4]

Visual impairment caused by pupillary membranes can increase as the membrane progresses, and surgical excision returns visual function to baseline, demonstrating that pupillary membranes may not always be amblyogenic in earlier years,

Table 1. Pre- and postoperative CDVA

	Preoperative		Postoperative	
Case	**OD**	**OS**	**OD**	**OS**
1	*F & F*	*C, S*	20/300	*F & F*
2	20/50	20/50	20/25	20/20
3	20/125, 20/70 -2 *w/PH*		20/50, 20/40 *w/PH*	

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No shaking required to resuspend drug[1,4,5]

LOW PRESERVATIVE AND TWO KNOWN MOISTURIZERS[1,2,4,6]

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Indications and Usage

- LOTEMAX® GEL is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery

Important Risk Information about LOTEMAX® GEL

- LOTEMAX® GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures
- Intraocular pressure (IOP) increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored
- Cataracts—Use of corticosteroids may result in posterior subcapsular cataract formation
- Delayed healing—Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification
- Bacterial infections—Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infections
- Viral infections—Use of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex)
- Fungal infections—Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use
- Contact lens wear—Patients should not wear contact lenses when using LOTEMAX® GEL
- The most common ocular adverse drug reactions were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%)

Please see brief summary of full prescribing information on adjacent page.

References: 1. LOTEMAX GEL Prescribing Information, September 2012. **2.** Fong R, Leitritz M, Siou-Mermet R, Erb T. Loteprednol etabonate gel 0.5% for postoperative pain and inflammation after cataract surgery: results of a multicenter trial. *Clin Ophthalmol.* 2012;6:1113-1124. **3.** Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. *J Pharm Bioallied Sci.* 2011;3(1):89-100. **4.** Data on file, Bausch & Lomb Incorporated. **5.** Coffey MJ, Davio SR. Viscoelastic and sedimentation characterization of loteprednol etabonate ophthalmic gel, 0.5%. Poster presented at: Association for Research in Vision and Ophthalmology (ARVO); May 6-10, 2012; Fort Lauderdale, FL. Poster #6283/D1143. **6.** Lotemax Prescribing Information, April 2006. **7.** Rajpal RK, Roel I, Siou-Mermet R, Erb T. Efficacy and safety of loteprednol etabonate 0.5% gel in the treatment of ocular inflammation and pain after cataract surgery. *J Cataract Refract Surg.* 2013;39:158-167.

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Brief Summary: Based on full prescribing information.

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INDICATIONS AND USAGE

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops.

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

LOTEMAX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when LOTEMAX is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

FOR MORE DETAILED INFORMATION, PLEASE READ THE PRESCRIBING INFORMATION.

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA
US Patent No. 5,800,807

as shown by the multiline visual improvement showed on our second case.

Pupillary membranes are not all dense, fibrotic or evident. In case number three, it appeared as though the vitreous had prolapsed into the anterior chamber, which was compatible with an inferior lens subluxation. Careful slit lamp examination showed that the strands originated at the pupil margin and the zonular apparatus, although stretched, had no structural gaps, revealing the presence of a misleading pupillary membrane. This clinical finding modified the surgical plan and avoided an unnecessary anterior vitrectomy. Accurate recognition and understanding of PPM's clinical implications can guide the clinical management of complex anterior segment cases.

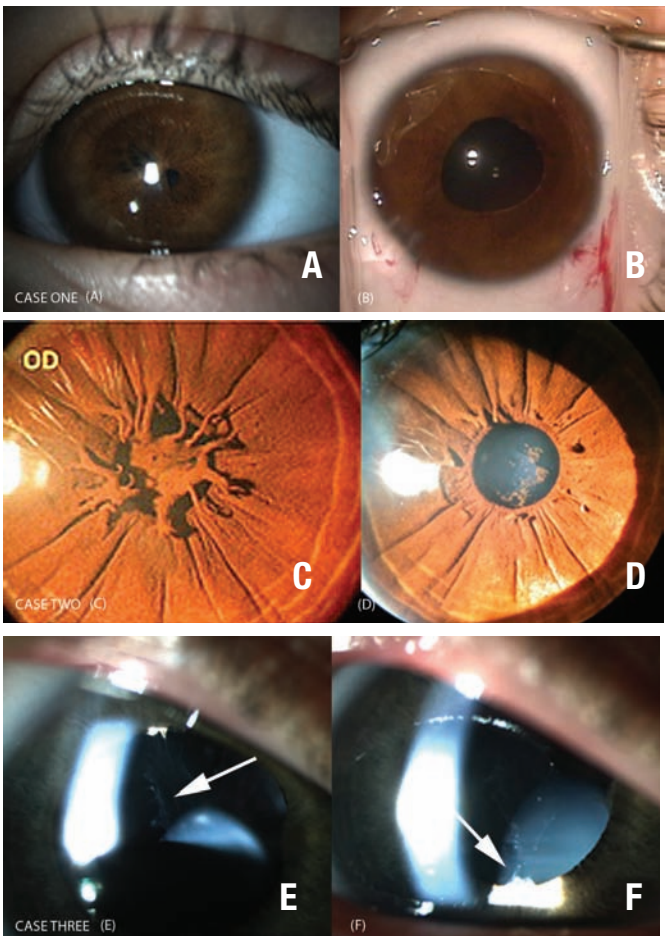

Figure 1. From top to bottom, preoperative pupillary membranes on the left for cases 1, 2 and 3 respectively, with postoperative results at right.

Case One

A 2-year-old boy presented with an abnormal pupillary aperture in his left eye, associated with a 20 prism diopter esotropia. Biomicroscopy demonstrated a thick pupillary membrane obscuring the majority of the aperture and precluding a view of the fundus *(See Figure 1A)*. Surgery was recommended to reduce the risk of ambylopia. The membrane was surgically excised from the collarette without incident *(See Figure 1B)*. Postoperatively, progress was made in the amblyopia therapy.

Case Two

A 23-year-old male presented with progressively decreasing vision and a corrected distance visual acuity (CDVA) of 20/50 in both eyes. Biomicroscopy revealed a network of thick and pigmented strands over both pupils, attaching at the collarette, with apparent apposition to the clear crystalline lens *(See Figure 1C)*. The potential acuity meter tested 20/30 for both eyes.

After surgical excision, vision improved to 20/20 on the left eye and 20/25 on the right eye, despite the presence of a few intralenticular blisters *(See Figure 1D)*.

Case Three

A 28-year-old male was referred for surgical management of inferiorly subluxed microspherophakic lenses in both eyes with a CDVA of 20/70 with pinhole. Slit lamp examination of the right eye revealed a subluxed and mobile microspherophakic lens, moderate posterior subcapsular crystalline lens changes and a wispy greyish white rete over the stretched superior zonules protruding to the anterior chamber through the pupil *(See Figure 1E, F)*. The "prolapsed" anterior chamber wisps appeared nearly identical to condensed anterior hyaloid gel, yet with scrutinizing inspection, attachments to the collarette and absence of zonular gaps confirmed a thin pupillary membrane as the entity.

The membrane was peeled at the time of capsulorhexis and phacoemulsification with a sutured capsular tension ring and in the bag IOL insertion was successfully performed.

This congenital anomaly may be frequently encountered in practice, but with succesful treatment, outcomes can be very favorable. REVIEW

Dr. Shah is a resident at William Beaumont Hospital. Dr. Perez is a fellow at University of Toronto - Toronto Western Hospital. Dr. Snyder is on the Board of Directors at Cincinnati Eye Institute and volunteer faculty at the University of Cincinnati. Both Drs. Marquez practice in São Paolo, Brazil.

Herpes Zoster Virus: Vaccinate & Treat Early

Michelle Stephenson, Contributing Editor

If not treated within 72 hours, the virus can have life-altering and life-threatening consequences.

While herpes zoster is frequently a mild disease, the cases that ophthalmologists treat are usually much more serious. To prevent the more serious morbidity, early treatment is key. "Most cases of herpes zoster ophthalmicus present within a few days of skin lesions appearing," says Jay Pepose, MD, PhD, medical director of the Pepose Vision Institute and president of the Lifelong Vision Institute, St. Louis.

Treatment typically consists of antiviral therapy and needs to be initiated immediately. According to Elisabeth J. Cohen, MD, professor of ophthalmology at the NYU Langone Medical Center, the recommended treatment is Valtrex 1,000 mg three times a day for a week or Famvir 500 mg three times a day for a week. "The key thing is that treatment should begin within 72 hours of the onset of the rash. That's how it was studied, and that's how it is approved and recommended. You need to use the correct dose, which is higher than the dose used for herpes simplex infections," she says.

Even with prompt antiviral treatment, some patients develop painful neuralgias, which can be difficult to treat. These neuralgias are not so much from the acute viral infection, but from the inflammation that the virus elicits along with damage to sensory nerves, Dr. Pepose explains. According to him, treatment in these cases can include gabapentin and tricyclic antidepressants. "Additionally, people have tried lidocaine patches and capsaicin to treat the pain," he explains.

Herpes Zoster Ophthalmicus

According to Thomas Liesegang, MD, who is in practice at the Mayo Clinic in Florida, ophthalmologists see the worst cases of zoster. "We see more complicated cases on the surface of the eye, on the surface of the skin and on the surface of the conjunctiva, but it also can manifest itself intraocularly. There can be inflammation within the retina and the optic nerve. It can cause blindness and affect the motility or movement of the eye, and it can lead to paralysis and proptosis. It can also get into the brain, which increases the incidence of stroke. The virus can get into the vessels within the brain and can cause an inflammatory reaction," he says.

Dr. Cohen knows this all too well. She contracted herpes zoster ophthalmicus, which caused her to lose vision and have to give up cornea

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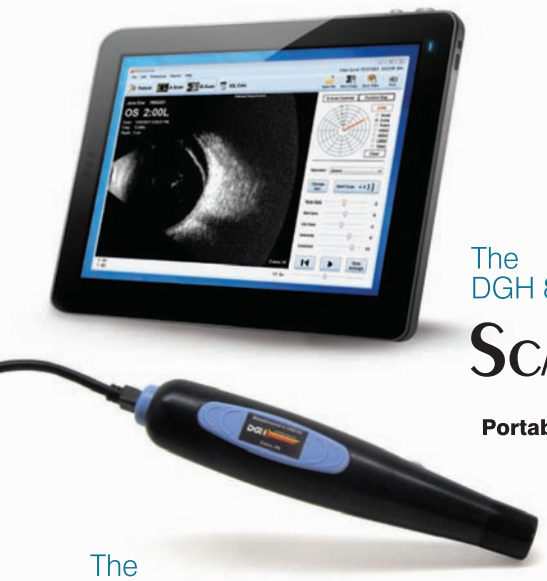

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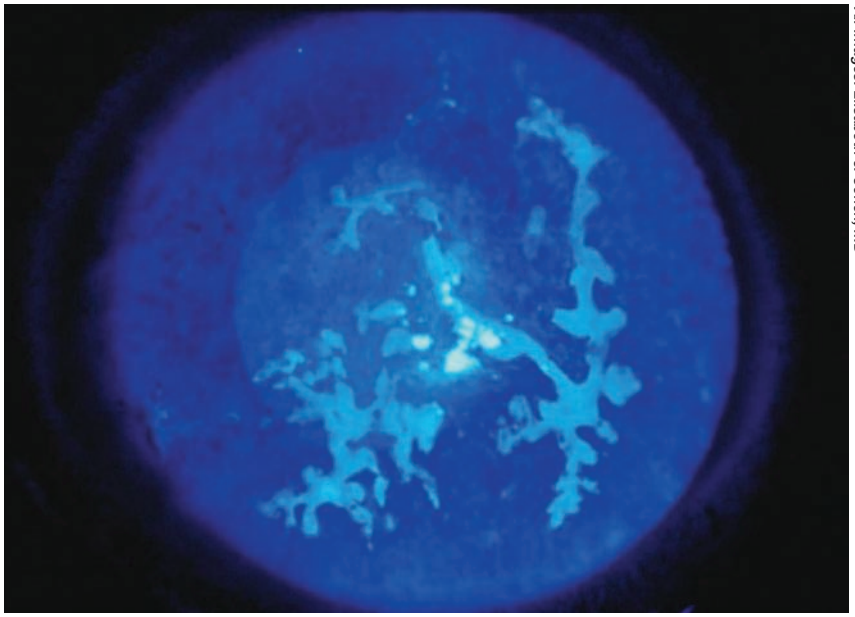


All images: Elisabeth J. Cohen, MD

Figure 1. Late dendriform keratitis, which is polymerase chain reaction-positive for herpes zoster virus.

surgery. "I have a friend in whom it spread to her spinal cord, and she has involvement of her legs," she says. "Of the people who get herpes zoster in cranial nerve 5, division 1, half will have it in their eye, and about 30 percent will end up with chronic eye disease."

She is currently working on a randomized clinical trial looking at a year of suppressive antiviral treatment compared with placebo in people with herpes zoster ophthalmicus to try to reduce complications of eye disease and recurrent eye inflammation, as well as a post-herpetic neuralgia. "This approach was highly effective in herpes simplex eye disease, says Dr. Cohen. "We now know that many of the complications of herpes zoster are related to chronic active infection after an episode of shingles. It makes a lot of sense to evaluate chronic suppressive treatment in addition to the acute recommended treatment for a week. We are applying to the [National Eye Institute] for a trial to study it in people who either have zoster in their eye of recent onset or chronic disease with a recent episode. We are looking at people who are younger than 60 years compared to 60 years or older at the onset of zoster, because the disease is a little different in the younger and older groups."

Herpes Zoster Vaccine

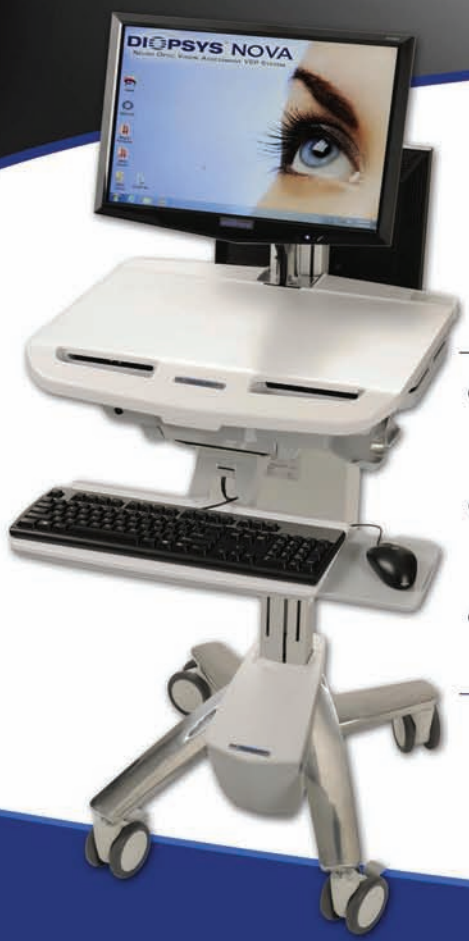
Because herpes zoster can have such severe complications, prevention is better than treatment. Dr. Cohen notes that the herpes zoster vaccine (Zostavax) is currently recommended by the Centers for Disease Control & Prevention for people who are 60 and older, where it has an efficacy of 50 percent in preventing shingles, and 66 percent in reducing the severity of post-herpetic neuralgia.[1] "Additionally, it is [Food and Drug Administration]-approved for people aged 50 to 59 years, where it is almost 70 percent effective at reducing the incidence of shingles. Unfortunately, the CDC has not extended its recommendations to people in their 50s, I think erroneously, because they are concerned about the cost of immunizing a lot of these people, and they don't think it's as cost-effective because people in their 50s are not as prone to post-herpetic neuralgia. In addition, they are concerned about the duration of the efficacy of the vaccine," she says.

According to Dr. Pepose, the availability of Zostavax has not yet markedly decreased the incidence of herpes zoster. "We have been surprised that many non-immunosuppressed people who are eligible candidates for the vaccine really haven't been vaccinated," he says.

A recent study found that prevention modalities, such as the vaccine and long-term oral antiviral therapy to reduce ocular herpes zoster infection recurrence, are underused.[2] The study was conducted to assess the spectrum of disease and treatment among patients with herpes zoster ophthalmicus and herpes simplex virus infection. The study included 64 patients (40 with herpes zoster ophthalmicus and 24 with ocular herpes simplex infection). Patients with herpes zoster were older (mean age: 51 ±15 years) than those with herpes simplex (mean age: 33 ±16 years).

In this study, 73 percent of patients with herpes zoster ophthalmicus were younger than 60 years, and of these patients, 90 percent were immunocompetent. The most common decade of onset was during patients' 50s. The study included 12 patients who were eligible to receive the herpes zoster vaccine, but none of these patients had received the vaccine. Twenty-four patients had ocular herpes simplex virus infection, and of these, seven patients had corneal stromal disease and 10 had infectious epithelial keratitis. None of the patients in this study were treated with long-term oral antiviral prophylaxis.

"People think it is a disease of old folks, but the average onset of dis-



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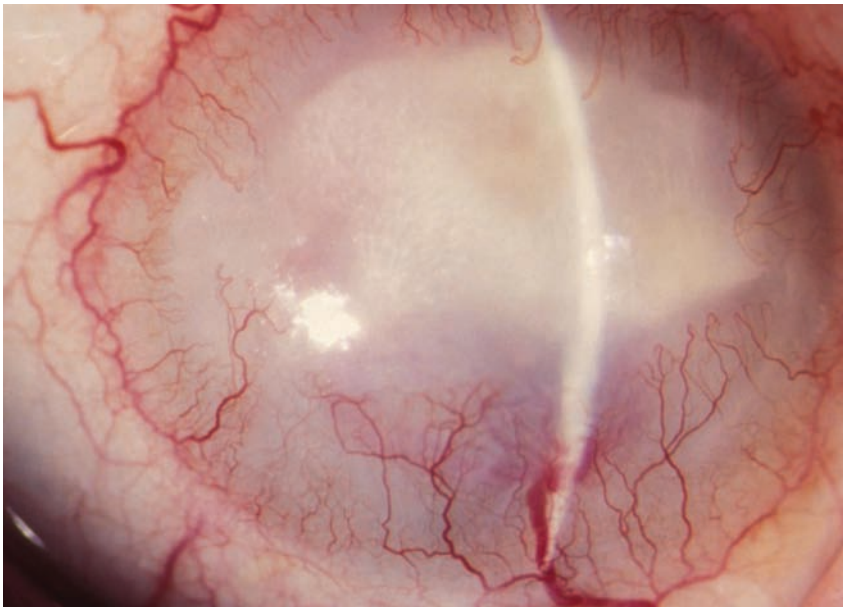

Figure 2. Corneal opacification and neovascularization from very severe herpes zoster ophthalmicus.

ease in the United States is 52 years. At least half of all cases occur in people younger than age 60, and more than 90 percent of people who get shingles have healthy immune systems and are not sick. This disease has life-altering and life-threatening consequences, including strokes," says Dr. Cohen.

In one retrospective study assessing the link between herpes zoster ophthalmicus and subsequent stroke, patients with herpes zoster ophthalmicus had a 4.5 times higher risk of stroke than the control group.[3]

There is concern that people who get the vaccine in their 50s wouldn't be protected as they get older and may need a booster. Additionally, because the CDC doesn't recommend it, many insurance companies don't cover it for people in their 50s. "It's an expensive vaccine, which certainly discourages its use. However, although post-herpetic neuralgia is less common in people in their 50s, it is still a terrible acute disease that causes severe pain for an average of at least a month, and some young people like myself get severe complications," says Dr. Cohen. "I don't think that we can accurately know how serious this disease is in people in their 50s due to the limitations of our national electronic records. I strongly recommend the vaccine for people aged 50+ without impaired cellular immunity." Most insurance plans cover it for people who are 60 or older, but there are significant copays, which can discourage people from getting it.

Dr. Cohen notes that, while a booster would raise the cost of preventing the disease—if in the future it becomes recommended—we should look at the cost of the disease and not the cost of the vaccine. According to her, at least $1 billion a year is spent on this disease. "We in the United States may underestimate the burden of this disease because it's very difficult to gather the data," she says.

Dr. Liesegang agrees: "The cost of treating zoster is great, he says. "The virus can cause post-herpetic neuralgia and depression. There are many other complications of herpes zoster, which may be more of a financial and medical burden to care for. The question is whether we are shifting the incidence from chicken pox to zoster and whether this is good or bad. Other countries have looked at these data and have decided that the potential increase in zoster in the elderly is one of the reasons why they don't routinely recommend the chicken pox vaccine."

Questions remain about the effect of the chicken pox vaccine on children as they age, as well as on the elderly population who have not had the chicken pox vaccine and who are no longer exposed to chicken pox later in life. "The theory is that, the older you get, your cellular immunity dwindles and so you are more likely to reactivate the zoster that you got as a kid when you had chicken pox," Dr. Pepose says. "Young people now get vaccinated for chicken pox with Varivax, which uses an attenuated strain of varicella. We don't know what effect this varicella vaccine will have many years from now with respect to reactivation as zoster when these children are 50 or 60 or older."

In addition to children not being exposed to chicken pox in the community, older adults are also no longer being exposed to wild-type chicken pox virus. "Previously, when you were 50 to 60 years old, you were occasionally exposed to chicken pox when visiting someone's child," Dr. Pepose says. "Now, young people don't get chicken pox very frequently because they are vaccinated, so older people don't get that periodic boost in their immune systems by coming in contact with chicken pox. The herpes zoster vaccine may be more important now than it was prior to the varicella vaccine being offered to children."

Dr. Liesegang points out that there was a concept, which is still held today, that if a grandmother is in the household of a child with chicken pox, the exposure to chicken pox

boosts the grandmother's immune system and protects her against zoster. "If you do away with chicken pox by giving a vaccine, the whole elderly population will no longer be exposed to chicken pox," he says. 'Whether their zoster immune response will decline even faster is a question that we have had for 20 years."

He adds that the incidence of herpes zoster in developed countries has been increasing, but the increase started before the introduction of the varicella vaccine, and there has not been a dramatic increase since universal chicken pox vaccination.

Dr. Liesegang recommends the zoster vaccine, but notes that there are some cost considerations. "It is not covered under Medicare part B, which is where vaccinations are usually covered," he says. "The vaccine has only gotten to about 10 percent to 15 percent of the population for whom it is recommended. Additionally, the vaccine is not easy to store. It has to be stored frozen and thawed. It cannot be re-frozen, so you must have several patients lined up, and it is not convenient for physicians to store in the office."

He explains that family physicians tend to see the milder cases of zoster, and they are the ones who are recommending or giving the vaccinations. "They tend to think of zoster as a milder disease and are not as ready to recommend the vaccine as people who see the bad complications of zoster, such as infectious disease experts and ophthalmologists. Patients don't consider zoster a bad disease until they get it," he says. REVIEW

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2. Edell AR, Cohen EJ. Herpes simplex and herpes zoster eye disease: presentation and management at a city hospital for the underserved in the United States. Eye Contact Lens 2013;39(4):311-314.
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Treating Endogenous Endophthalmitis

This uncommon but potentially devastating eye infection needs to be diagnosed and managed promptly.

By Nidhi Relhan, MD, Thomas A. Albini, MD, and Harry W. Flynn Jr., MD, Miami

Endogenous endophthalmitis is an uncommon, but potentially devastating intraocular infection in which pathogens reach the eye via the blood stream. Endogenous endophthalmitis is less common than exogenous endophthalmitis, accounting for 2 to 8 percent of all end ophthalmitis cases in various studies.[1,2] Pediatric endogenous end ophthalmitis is even rarer, constituting 0.1 to 4 percent of all endogenous endophthalmitis cases.[2,3]

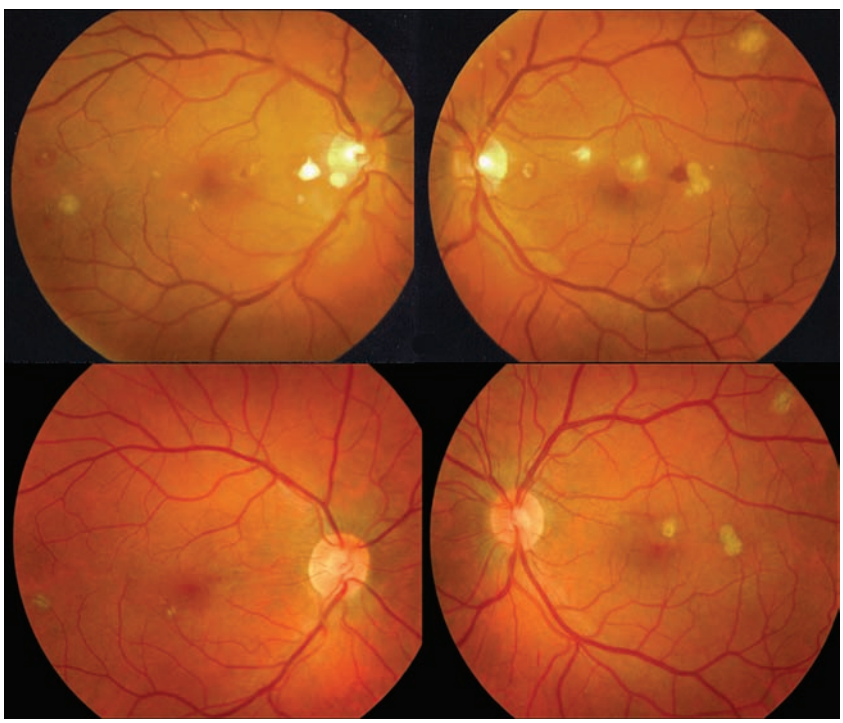

Figure 1. Color fundus photograph of both eyes in an IV drug abuser before sequential bilateral vitrectomy (top row) and after vitrectomy (bottom row). Prior to vitrectomy there was mild vitritis and a few vitreous opacities bilaterally. Areas of hemorrhagic retinochoroiditis are present. Following vitrectomy and five serial amphotericin-B injections to both eyes given twice weekly, residual retinochoroidal scars can be seen with resolution of retinal hemorrhage and vitreous opacity. This patient also received one month of oral ketoconozole.

Predisposing conditions are important in determining a patient's risk for endogenous endophthalmitis. In patients with acute or chronic panuveitis of unclear origin, invasive diagnostic procedures, most commonly pars plana vitrectomy, may be necessary to make the diagnosis. Identified risk factors for endogenous endophthalmitis include: chronic diseases (e.g., diabetes mellitus, renal failure, malignancies and acquired immunodeficiency syndrome); immunosupressive treatment; recent invasive surgery; intravenous drug abuse; indwelling catheter; endocarditis; hepatobiliary tract infections; organ transplantation; pregnancy or delivery; genitourinary surgeries; or dental procedures.[4] Eliciting a history of intravenous drug abuse is especially important and often difficult given

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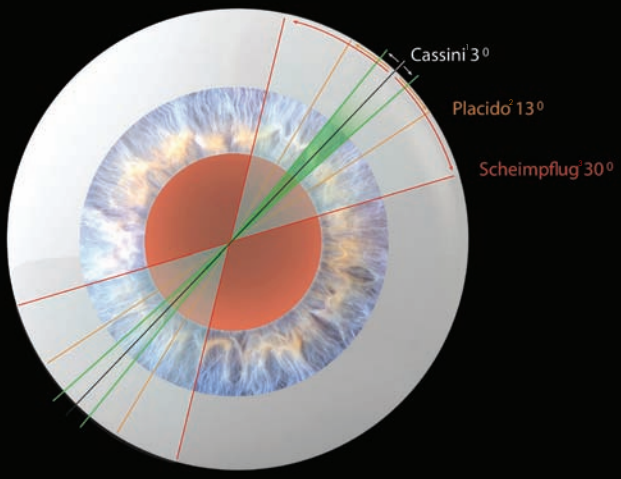

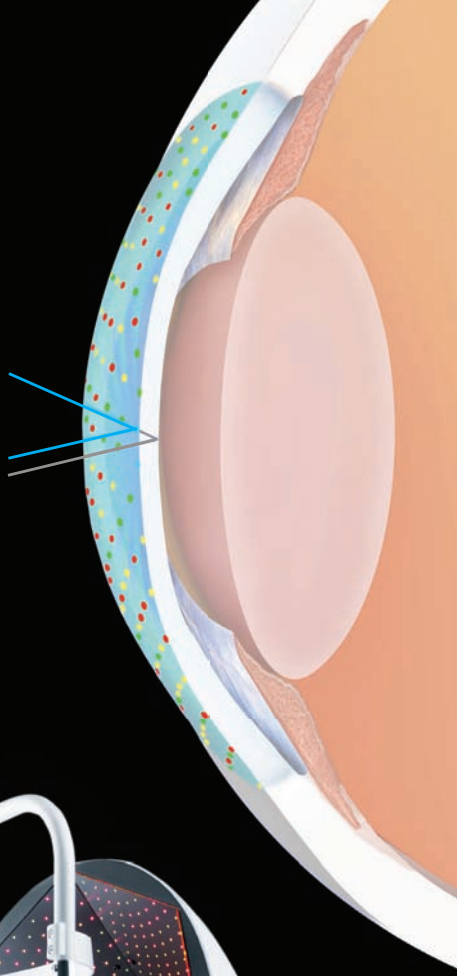

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[1] A. John Kanellopoulos, MD. Clinical Professor Of Ophthalmology New York University Medical School
[2] Karabatsas et al. EJO 2005, [3] McAlinden et al. IOVS 2011

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patients' reluctance to discuss this issue. Positive history of underlying medical conditions such as diabetes, cardiac disease and malignancy was reported in 90 percent of patients in a report by Annabelle A. Okada and colleagues in 1994.[5] A major review of endogenous endophthalmitis patients reported underlying medical conditions predisposing to ocular infection in 56 to 68 percent of cases.[6] Zenith H. Wu and colleagues reported identification of preexisting predisposing condition in 90.9 percent of patients and the most common systemic condition found was diabetes mellitus (50 percent).[7]

Endogenous endopthalmitis is most often caused by bacteria or fungi. Causative organisms vary geographically. A study from Bascom Palmer Eye Institute reported fungi as a more common cause than bacteria (62 percent fungi vs. 38 percent bacterial),[8] while a Hong Kong study reported bacteria as the more common cause for endogenous end ophthalmitis (72.7 percent bacterial vs. 27.3 percent fungal).[7] Literature from East Asia reported gram negative organisms being the more common cause (70 percent) and *Klebsiella* being the most common causative organism (60 percent).[9] Data from North America and Europe showed an increasing percentage of gram negative organisms from 32 percent in 1986 to 52 percent in 2003.[6] Yeasts are a more common cause and associated with better visual outcomes as compared to molds in fungal endogenous endophthalmitis.[10,11] *Candida* is the most common organism responsible for fungal endogenous endophthalmitis.[8,11,12] In immunosupressed patients, such as AIDS patients, atypical organisms such as *Cryptococcus*, *Mycobacterium avium*, *Nocardia* and *Pneumocystis jiroveci* need to be considered.

The involved eye may have pain, redness, floaters or decreased vision.

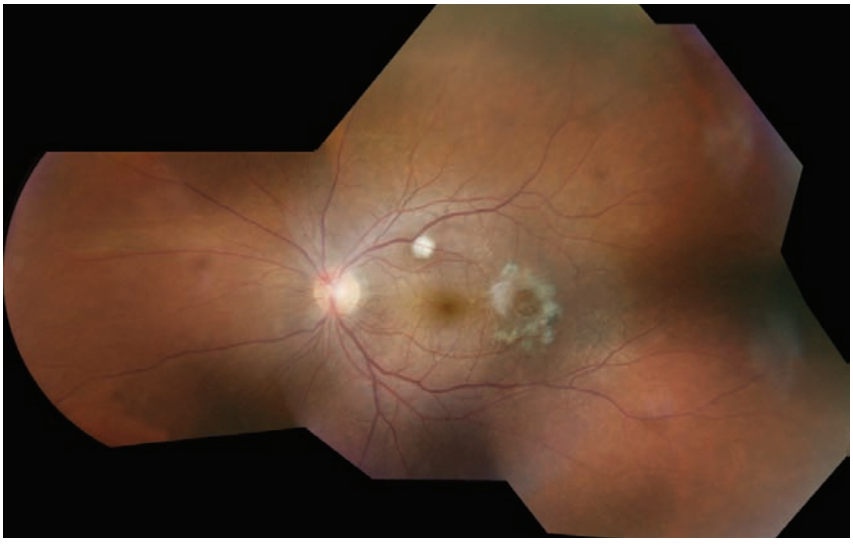


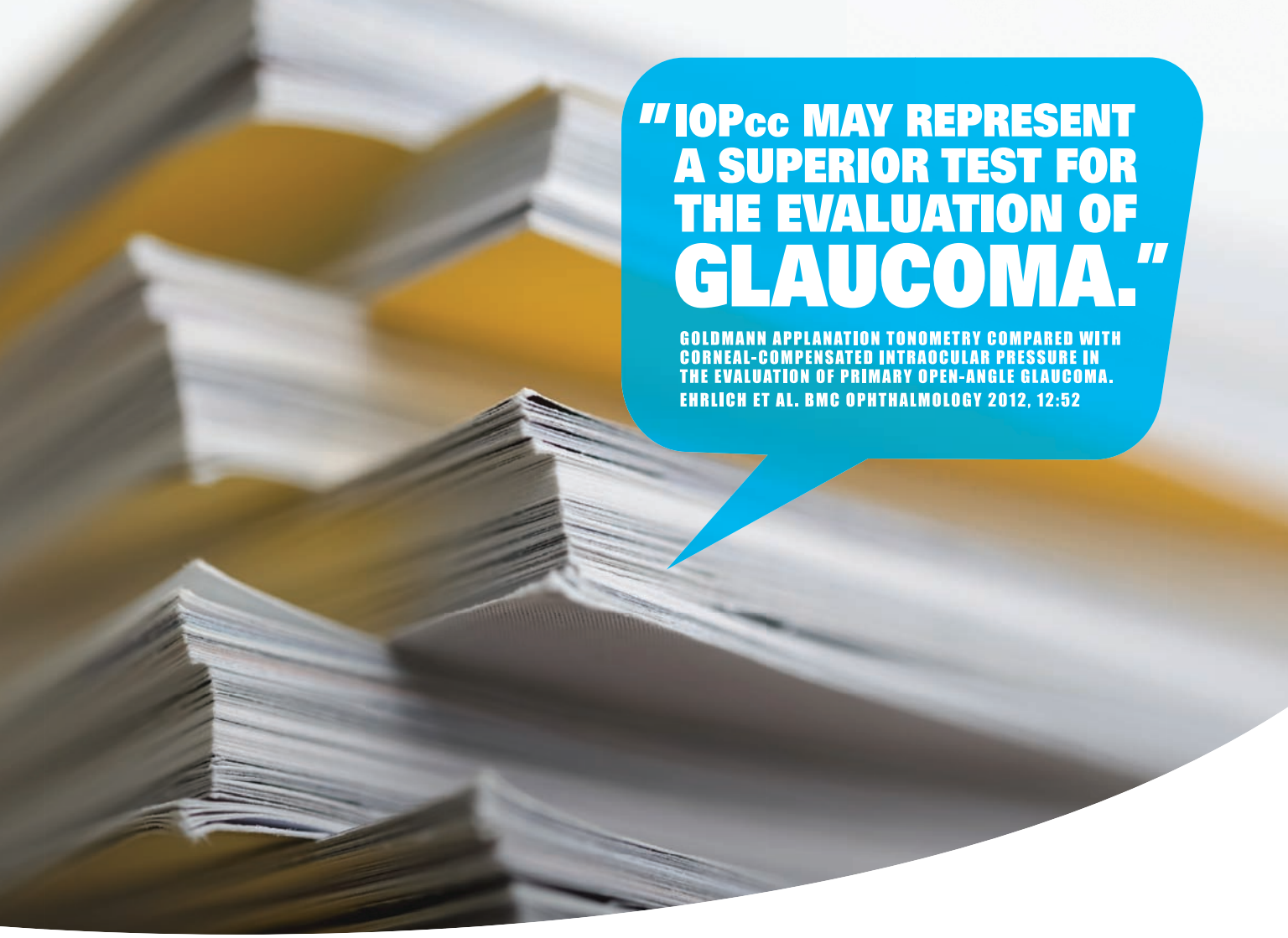
Figure 2. Color fundus photograph of the left eye of a patient with *Candida* endogenous endophthalmitis post-vitrectomy and treatment with five intravitreal injections of amphotericin-B given twice weekly showing white retinochoroidal lesions in the macula as well as an eccentric macular hole as sequelae of fungal endophthalmitis. Visual acuity was 20/30. This patient also received one month of oral ketoconozole.

Diagnosis is delayed in the pediatric population by inability to report symptoms early. Bilateral presentation is reported in 14 to 25 percent of cases and more commonly with fungi and bacteria like *Meningococcus*, *Escherichia coli* and *Klebsiella*.[6] Endogenous endophthalmitis may be unilateral to begin with and subsequently develop in the fellow eye. Bacterial or fungal infections may exhibit iris microabscess, hypopyon, varying grades of vitreous haze, discrete retinal nodules, perivascular retinal hemorrhage, arteriolar emboli or necrotic retina. Severe cases may progress to panophthalmitis. Presence of chocolate brown exudate in the anterior chamber suggests *Bacillus* as the responsible organism, while *Listeria* is characterized by brown hypopyon and *Serratia* by a red hypopyon.

Fungal endogenous endophthalmitis with *Candida* may have fluffy balls in the vitreous, chorioretinitis, hypopyon, perivasculitis, optic neuritis or chorioretinal lesions (creamy, deep and well-circumscribed). Infection with molds like *Aspergillus* is more fulminant, typically confined to the subretinal space and may have chorioretinal lesions (confluent with indistinct margins), intraretinal hemorrhages, vascular occlusion or full thickness retinal necrosis. Positive vitreous aspirate cultures are more difficult to obtain from molds than yeasts, perhaps because molds do not involve the vitreous as commonly as yeasts.[13]

Endogenous endophthalmitis may mimic conjunctivitis, non-infectious anterior uveitis, iritis, acute glaucoma, cellulitis, cataract and, especially, retinoblastoma in children. Misdiagnosis at initial presentation has been reported in 16 to 63 percent of cases, thus delaying the diagnosis and proper management.[6,12]

The diagnosis of endogenous endophthalmitis is typically made following microbiologic evidence of infection from an intraocular sample (aqueous or vitreous). Positive cultures from blood, cerebrospinal fluid or any extraocular site can be highly suggestive. Blood culture positivity



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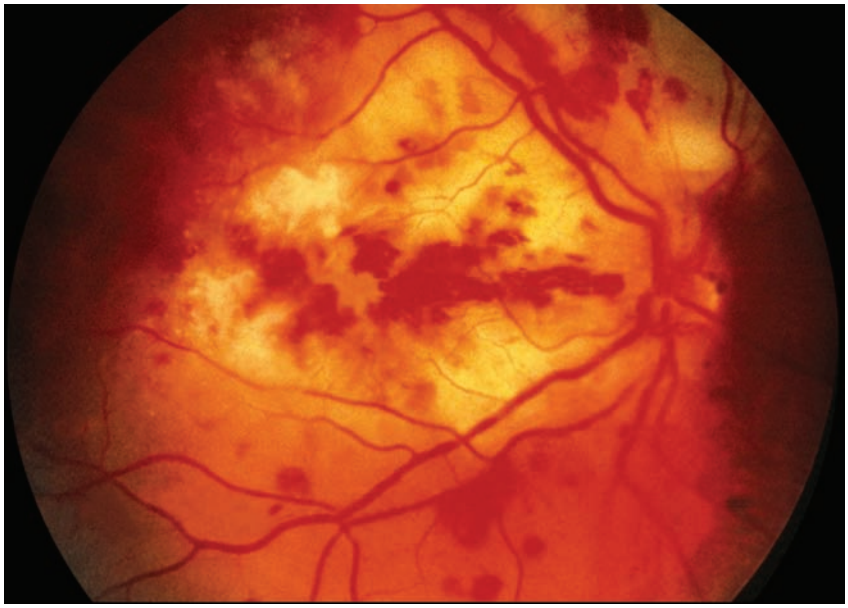

Figure 3. Color fundus photograph of the right eye of a patient with endogenous endophthalmitis caused by *Aspergillus*. Patient had a history of intravenous drug abuse and was managed with intravitreal and systemic amphotericin B, but had a poor visual outcome.

rate varies widely, from 33 percent to 94 percent of cases.[6,8] In the absence of localizing symptoms the diagnostic yield from blood in endogenous *Aspergillus* endophthalmitis is reported to be very low.[14] Cultures should be set up with both aerobic and anaerobic medium (chocolate agar, sheep blood agar and Sabouraud agar) and incubated for up to two weeks. Gram stain is commonly used to assess for bacteria. Fungal growth can be confirmed by Geimsa or Calcorfluor white stains. Polymerase chain reaction study of the tissue sample is a quick method to identify responsible organisms but has a drawback that it could not be used to assess antibiotic or antifungal sensitivity.

Ultrasound B scan of the eye is important in determining the extent and type of vitreous exudates, scleral thickness, choroidal abcess and presence of retinal detachment. Computerized tomography scans of the orbit help to identify orbital involvement. Other investigations such as chest X-ray, ultrasound abdomen, CT abdomen, echocardiography and Gallium-67 scans may help in identifying a systemic focus of infection.

Treatment

• ***Bacterial endogenous endophthalmitis.*** Soon-Phaik Chee and colleagues reported that systemic antibiotics can achieve therapeutic levels in the eye due to the disrupted blood ocular barrier.[1] Nevertheless, systemic agents are most often supplemented with intravitreal antimicrobials and vitrectomy, especially in the setting of prominent vitreous involvement. Vancomycin (1 mg/0.1 mL) and ceftazidime (2.25 mg/0.1 mL) remain the intravitreal antibiotics of choice. According to a review study, eyes undergoing pars plana vitrectomy are three times more likely to retain useful vision than those who did not undergo vitrectomy.[6] Also these eyes are three times less likely to require evisceration or enucleation. Broad-spectrum systemic antibiotics like vancomycin, ciprofloxacin, aminoglycosides or third-generation cephalosporins made up the mainstay of treatment previously but are now used adjunctively to local therapy. Recommended antibiotics are wide-spectrum antibiotics which cover most of gram positive and negative organisms. Systemic antibiotics are typically continued for at least three to four weeks or as the extraocular infection of the patient dictates.

• ***Fungal endogenous endophthalmitis.*** Treatment depends on the extent of ocular involvement. Systemic therapy alone is sufficient when the infection is isolated to the retina and choroid. Vitrectomy and intravitreal antifungal injections along with systemic therapy are recommended in cases where vitreous is involved.[15]

Intravenous amphotericin-B has classically been the drug of choice but needs careful monitoring in view of its systemic toxicity. Oral voriconozole or fluconazole in conjunction with local therapy are increasingly used. Intravitreal injection of either voriconazole (100 µg/0.1 ml) or amphotericin-B (5 to 10 µg/0.1 ml) ensures immediate, adequate levels of antifungal agent in the posterior segment. Voriconazole may have better coverage for *Aspergillus* species and some *Candida* species (like *C.glabrata* and *C.krusei*) where fluconazole or amphotericin-B are ineffective. Newer antifungal agents like posaconazole, echinocandins, micafungin, caspofungin and anidulafungin have poor ocular penetration and are not recommended for use in endophthalmitis.[16] Vitrectomy helps in decreasing the load of infection and better accessibility of antifungal agents to intraocular structures. The need for repeat intravitreal injections should be based on clinical improvement, status of the eye (vitrectomized vs non-vitrectomized) and pharmacokinetics of the antifungal medicine.

Local or systemic corticosteroids are generally avoided in fungal end

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ophthalmitis,[10] although their use remains controversial.[14,15]

Outcome

Endogenous endophthalmitis cases usually have a poor visual outcome. Visual acuity of counting fingers or more is reported in 22.2 to 41 percent cases.[17,18] Loss of vision due to blindness, evisceration or enucleation is reported in 55 to 69 percent of cases.[6] Visual outcomes after treatment are worse for endogenous *Aspergillus* endophthalmitis as compared to *Candida* cases, and it could be due to earlier detection of *Candida* infection, leading to more timely initiation of treatment.[15]

Patients who have extraocular foci of bacterial infection have a reported mortality rate of 5 percent[6] to 32 percent.[19] Factors such as infection with virulent organisms, poor host defense, misdiagnosis leading to delayed treatment, inadequate treatment, use of inappropriate antibiotics, panophthalmitis are considered to be associated with poor prognosis. Fungal infection has high mortality, with a 7-percent reported rate of mortality in systemic *Candida* infection.[20]

Endogenous endophthalmitis is a potentially devastating eye infection and needs to be diagnosed and managed promptly. Use of combined ocular and systemic antibiotics is common. Systemic co-infection is common and is associated with a high rate of mortality. REVIEW

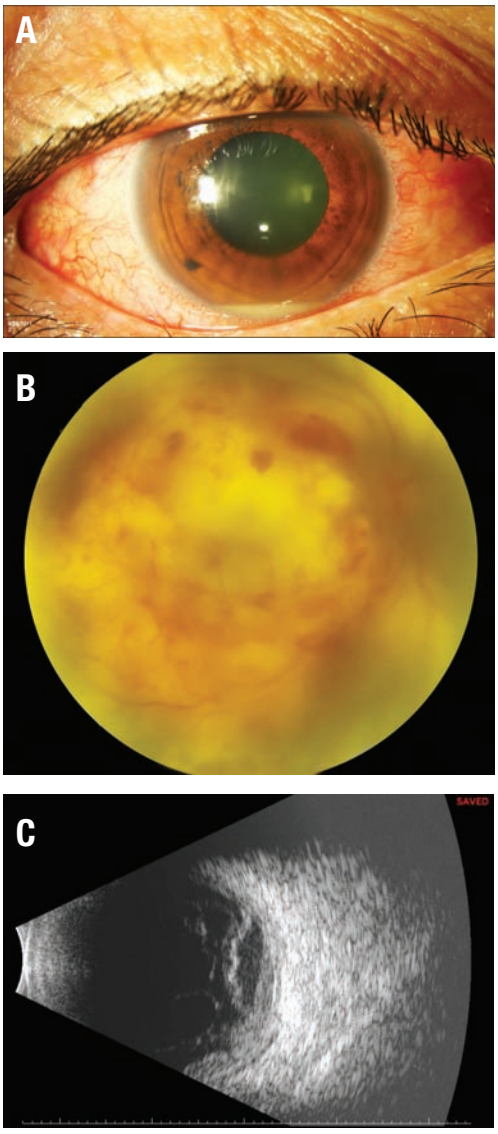

Figure 4. Nocardia endogenous endophthalmitis. The initial vitreous biopsy was negative and only subretinal biopsy yielded positive cultures. Top image (4a) shows hypopyon present at presentation. Middle image (4b) shows fundus findings, including a large submacular abscess. B-scan ultrasonography (4c) shows neurosensory detachment and a submacular mass.

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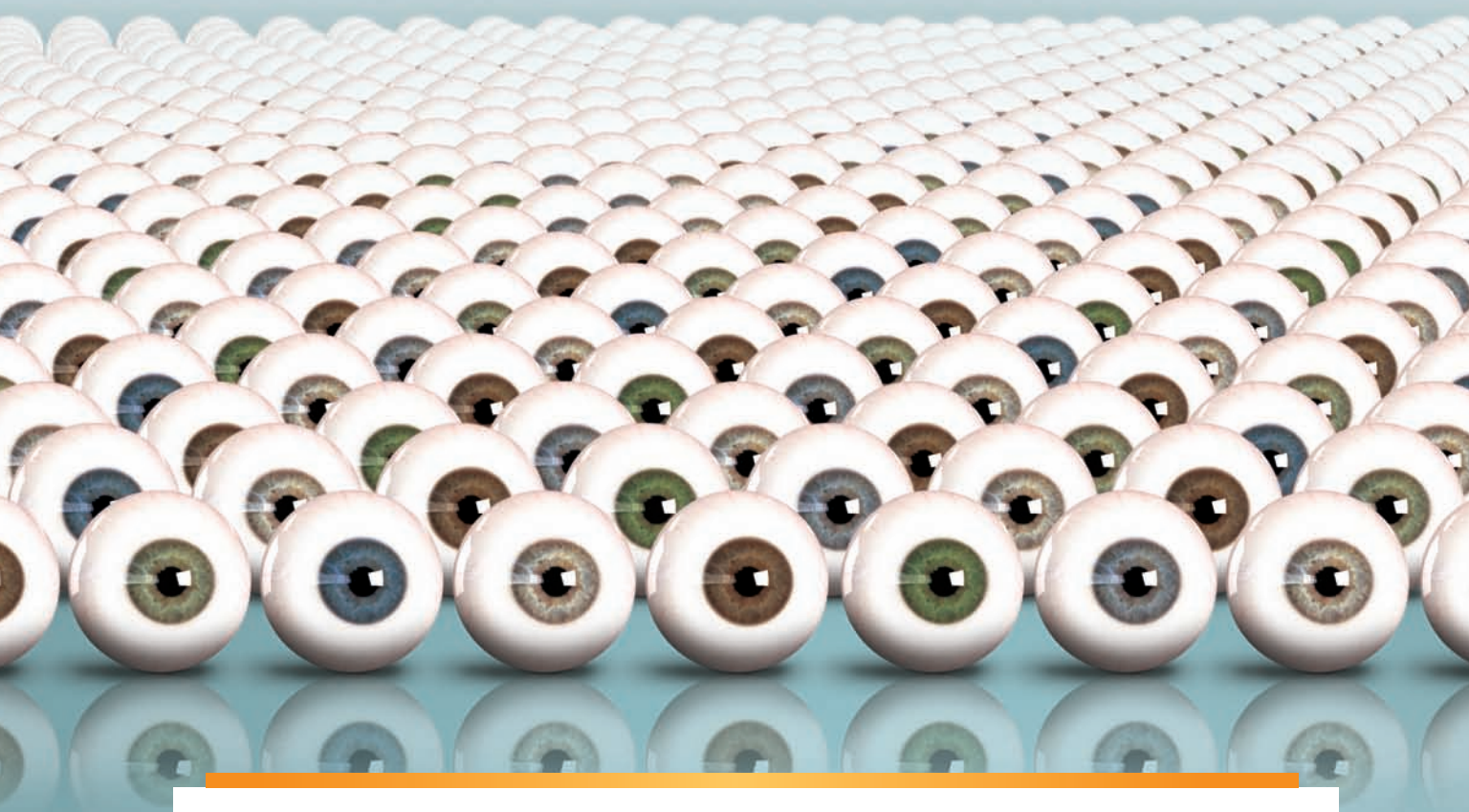

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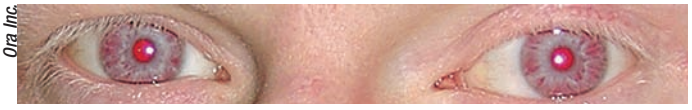
The Colors of Ocular Health

The genetics and aesthetics of eye color, and how its components affect ocular therapy.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and James McLaughlin, PhD, Andover, Mass.

Eye color is one of the defining features of the human animal. It is the subject of song and verse and at the same time features prominently on your driver's license and passport. It can even be used as a biometric identifier, akin to fingerprinting or voice recognition. Despite this prominence, iris pigmentation rarely enters into any significant clinical consideration even though the color of a patient's iris can impact his ocular health, and it can be a factor in drug efficacy and in the susceptibility to adverse drug effects. This month we delve into ocular pigmentation biology, pharmacology and genetics and ask the question: How does the color of patients' eyes affect the way we treat their ocular disorders?



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Despite its striking appearance, the most profound effects of the OCA1 type of oculocutaneous albinism are the spectrum of visual defects: poor acuity; foveal hypoplasia; nystagmus and strabismus.

Ocular Pigments

There are two major pigmented structures in the eye, the iris and the retinal pigment epithelium. While RPE cells are central to overall retinal function, here we will focus on the pigments found in the iris. The iris is composed of two layers: a stromal, anterior layer and a posterior pigmented epithelial layer.[1,2] The two layers both contain pigmented cells but are embryologically distinct. The stromal layer cells are derived from the neural crest, while posterior epithelial cells are ectodermal in origin. The melanocytes of both layers contain melanosomes, specialized organs that synthesize and store various melanins. There is no compelling evidence suggesting any of these pigmented structures are ever secreted from the melanocytes in the eye, although this is common in other tissues. What we refer to as eye color derives from a combination of factors, including the types of melanins synthesized, the pigments of the anterior iris and the light scattering properties of the anterior stroma.

The two major pigments synthesized in all melanocytes are the eumelanin (black/brown) and pheomelanin (red/yellow).[3,4] Melanocytes throughout the body can synthesize either or both of these pigments, and the ratio of the two is a significant factor in determining the color of the tissue. The posterior epithelial layer of the iris, as well as the RPE, produce eumelanin only, while the stromal melanocytes typically contain both pigments. Individuals with defects in melanin synthesis, whether partial or complete, display some level of albinism, either ocular or oculocutaneous. More critical for eye color than the ratio of the two pigments is the density of melanosomes in the stromal melanocytes. A continuum of iris color, from blue to gray, and then to green and brown, can be correlated with a corresponding graded increase in melanosome density. More subtle differences in grays, hazels and greens result from individual differences in pigment ratios.

The mechanics of pigment production rely on a family of related enzymes, the tyrosinases.[5] Two major family members, tyrosinase and tyrosinase-related protein 1, catalyze

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oxidations including the key conversion of tyrosine to dihydroxyphenylalanine. Several additional oxidation steps follow to ultimately generate both eumelanin and pheomelanin. The difference between the two pigments is that pheomelanin also includes cysteine as one of its building-block components, and so the availability of this precursor can also impact iris color. Expression levels of TYR and TYRP are critical to pigment synthesis, and genetic defects in their expression result in two types of oculocutaneous albinism, OCA1 and OCA3.

Genetics of Eye Color

The presentations of some forms of pigment disorders are striking, and so they may seem more common conditions than they really are; in the United States about 1:16,000, or 20,000 individuals, have some form of albinism.[6] The specific genotypes dictate the spectrum of disease and impact on visual function. Genes implicated in the four major types of oculocutaneous albinism, OCA1 to -4, have been identified, and an understanding of their function has provided important clues to the role of pigmented cells in the eye.[7]

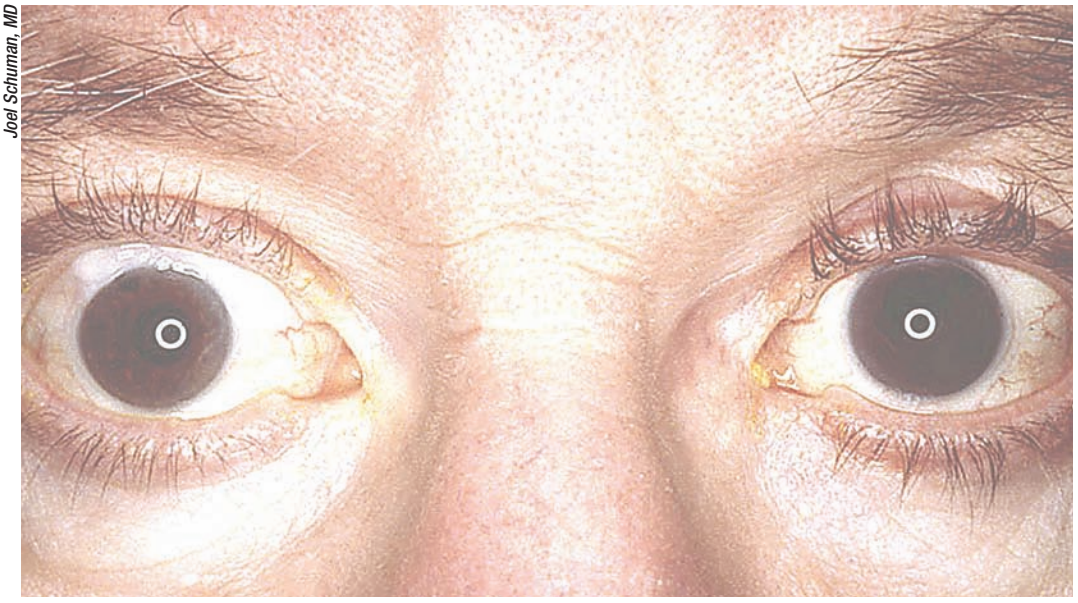
The most common form of the disease, OCA1, is caused by mutations in the TYR gene, and it results in either a partial or complete loss of melanin biosynthesis.[6,7] These patients have pinkish skin, blue-grey irides and a prominent photophobia. They typically have poor acuity, foveal hypoplasia, nystagmus and strabismus. Melanocytes are known to play extensive roles in development, and this may underlie both foveal defects and less common instances of chiasmic misrouting of nerve fiber tracts. Recent work has focused on correlating foveal organization and BCVA to try and understand the role iris pigmentation plays in ocular development.

Less profound types of albinism, including OCA2 and OCA4, are caused by defects in melanosome function that result in low amounts of eumelanin.[6,7] This shift in the ratios of pigments has subtle effects, both in terms of the affected individual's appearance, and in the extent of visual function impairment. Some pigments are visible at birth, and any color in skin and eyes increases with age. Ocular issues such as nystagmus and photophobia are present but less severe than in OCA1. The mutations associated with the OCA4 gene are most common in patients with a Japanese heritage. Mutations in the TYRP gene are classified as OCA3, and are most common in those of African ancestry. Affected individuals display reduced pigmentation and lighter-colored eyes, and have the mildest forms of nystagmus and strabismus.

Melanosome Control

One of the features of the melanosome that distinguishes it from other intracellular structures is an enzyme complex that includes TYR, TYRP and the melanocyte-stimulating hormone receptor.[2,4] This complex responds to MSH and other signaling molecules by increasing functional expression of TYR, leading to an increase in melanin synthesis. Melanins have several roles, but key among these is protection from the harmful effects of UV radiation, and both UVA and UVB wavelengths are readily absorbed by both pigments. In addition, exposure to excess UV light can trigger an inflammatory response (in the skin and in the eye) activating inflammatory responses including cyclooxygenase-dependent prostaglandin E2 biosynthesis. A consequence of increased expression of pleiotropic signaling

Joel Schuman, MD



Iris hyperchromia and increased lash length and density occur in some patients being treated with prostaglandins. At the time of this photo, the patient had been using Xalatan in the left eye for a year.

molecules such as PGE2 is a feedback stimulation of TYR expression.[8,9] This normal physiological response to sunlight is hijacked in the PG-induced iris hyperpigmentation seen in some cosmetic use of PGs. Small amounts of these formulations reach the ocular surface, where they can readily penetrate to the stromal melanocytes, activate increased TYR expression, and stimulate increases in melanosomes that result in a darkening of the iris that is only slowly reversible.

Patients using PGE2-containing formulations to enhance growth of eyelashes may also experience changes in the color and shape of the upper eyelids. This is due to the stimulation of skin pigment expression, and a reduction in the volume of fat deposits, an effect also stimulated by PGE2.[10] The resulting sunken ocular sulcus, particularly on the upper lids, is an effect that most patients will not be happy with. While some might make the aesthetic choice between longer lashes or sunken sockets, for those using PG agonists to treat ocular hypertension, it may be possible to mitigate this effect by switching to a different product.[10]

Disease Risk/Drug Interactions

Our discussion of eye color goes beyond genetics and aesthetics. There have been many studies published with the goal of correlating eye color with the risk of various ocular disorders, from melanomas to age-related macular degeneration.[11-13] There is no shortage of such risk assessments, and they do provide some information on the relationship between eye color and relative risks. For example, several studies have shown positive correlation between iris pigment and the risk of geographic atrophy or glaucoma. Similarly, the increased risk of ocular melanoma in those with lighter eye color is similar to other melanomas for which those with lighter skin are at greater risk of developing the disease. Despite these findings, focusing on epidemiological trends may overlook the greater potential impact of ocular pigmentation on drug pharmacokinetics.

Patients using PGE2-containing formulations to enhance growth of eyelashes may also experience changes in the color and shape of the upper eyelids.

Underlying the progression from baby blue eyes to black lies the potential for a confounding impact on any therapeutic agent, from artificial tears to the newest biologicals. A patient with deep brown irides has two to four times more ocular melanin than one with light blue eyes,[5] and the ability of melanins to bind and alter the pharmacokinetics of a drug may be the single biggest impact eye color has on therapy. This potential for altering the pharmacokinetics of drugs is particularly important because so many ophthalmic medications are delivered topically, where local drug binding can exert a greater relative effect. Many classes of drugs used in the eye, including alpha- and beta-adrenergics, antibiotics[14] and corticosteroids[15] have been shown to bind to melanin-containing tissues with high affinity.

This binding activity is seen across multiple classes of drugs, yet is predominantly drug-specific: For example, triamcinolone binds with high affinity, while dexamethasone does not. The importance of melanin binding is demonstrated by its inclusion as one of the required tests in the toxicological profiling of topically applied drugs.

Eye color is a trait we share with other higher vertebrates, yet it seems a very human attribute. While we can classify a person according to a predominant coloration, the patterns and intricacy of the iris help to remind us of our individuality. They can also serve as a reminder of each of our patient's unique (and not always predictable) response to their therapeutic regimes. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Dr. McLaughlin is a medical writer at Ora Inc.

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Mitomycin-C: The Injection Alternative

Applying the anti-scarring agent in this manner appears to be safe and may have advantages over using sponges.

Michele C. Lim, Sacramento, Calif.

Conjunctival scarring is one of the difficulties long associated with glaucoma surgeries such as trabeculectomy. This part of the healing response can undo the benefits of the glaucoma surgery by closing down the channels created to allow aqueous to escape and thus reduce intraocular pressure. For that reason, minimizing scarring has become an important part of these surgeries. One of the most effective ways to control scarring has turned out to be through the application of mitomycin-C.

The most commonly used method of applying mitomycin-C during glaucoma surgery is to soak a Weck-Cel sponge in a solution of the drug and then apply the sponge to the ocular tissues for a few minutes. However, many surgeons, including those in our practice, use a different approach; we inject the mitomycin-C directly into the conjunctival tissue. Our surgical results have been just as good since switching to this method, and it appears to have some potentially significant advantages over the sponge method. Here, I'll discuss the benefits and limitations of each technique.

Injecting Mitomycin-C

Although a number of surgeons have injected mitomycin-C for many years, it has not yet achieved wide acceptance. This undoubtedly reflects the fact that it hasn't been well-studied or discussed in the literature (many surgeons aren't even aware that it is an option). Of course, surgeons understand that mitomycin-C has potential downsides, so it's not surprising that even those who are aware of this approach would be cautious when considering a new method of delivery.

To help clarify the reasons for considering this approach, I'd like to begin by describing how we use this technique in our practice. First of all, in order to inject mitomycin-C in trabeculectomy surgery safely, it is important to pay attention to your dosages. The dose we use is more dilute than that used when applying mitomycin-C with the sponge method. With a sponge, surgeons generally use 0.1 mg/ml to 0.4 mg/ml of mitomycin-C, but when injecting it, a lower concentration of 0.05 to 0.1 mg/ml is used because of the direct injection into Tenon's layer.

Our preparation of the mitomycin-C includes mixing the drug with a sterile water diluent to achieve a starting concentration of 0.2 mg/ml. This is then diluted further with 2% lidocaine —the same lidocaine we would use in a retrobulbar block. Some surgeons believe it may be dangerous to use anything other than non-preserved lidocaine in this situation, since the mixture is injected into Tenon's layer. However, we've found that the regular 2% lidocaine works well without any complications.

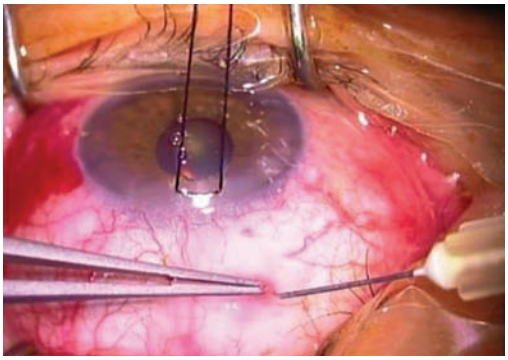
Once the solution is prepared, it is drawn up into a 1-cc syringe with a 30-ga. needle. We start the surgery by placing a traction suture in the cornea; then we inject approximately 0.1 ml total volume into the Tenon's layer, about 8 to 9 mm posterior to the limbus and a little off to the side to avoid the superior rectus muscle. The injection of fluid raises a little blister at the injection site. We irrigate the conjunctiva with balanced saline solution and then take a muscle hook and gently spread the injected bolus of mitomycin-C around the superior conjunctiva and Tenon's layer. The

This article has no commercial sponsorship.

fluid remains contained within the tissue as we spread it. Then we make our first incision and proceed with the surgery the way we normally would. (You can watch a video of our technique on YouTube at: youtube.com/watch?v=LxmHd136FOs.)

It's worth noting that some surgeons choose to inject the mitomycin-C prior to entering the operating room, when the patients are in the preoperative holding area. Toronto surgeon Ike Ahmed, MD, has posted videos on Eyenet demonstrating this approach. In our practice, however, we do it all in one step in the operating room at the beginning of surgery.

Another debate concerns whether it is necessary to irrigate the eye following the injection. Many surgeons don't believe it is. My feeling is that even with an injection, it is quite possible that some mitomycin-C seeps out from the tissue. I therefore irrigate to ensure that any remaining unbound medication doesn't remain on the ocular tissues. However, omitting this step has not appeared to result in a higher complication rate for my colleagues.



After placing a traction suture in the cornea, about 0.1 ml of mitomycin-C is injected into the Tenon's layer. The injection raises a small bolus of fluid at the injection site which can be gently spread around the superior conjunctiva using a muscle hook.

The Pros and Cons of Injecting

There are a number of advantages to injecting the mitomycin-C rather than applying it with a sponge:

• ***It takes less time.*** On average, surgeons leave the mitomycin-C sponge sitting on the eye for three minutes or so. (Some leave it longer.) Although three minutes doesn't sound like much, when you're trying to be efficient, sitting in the OR for three minutes with nothing else to do is like watching a pot of water boil—it feels like an eternity. You don't spend that time waiting if you inject the mitomycin-C.

• ***You're not dealing with sponges.*** Reports of losing mitomycin-C sponge fragments have appeared in the literature.[1] Sometimes a piece of a sponge breaks off and the surgeon doesn't realize it is still inside the eye, which can result in infection and necrosis. If you inject the mitomycin, this is not an issue.

• ***You know exactly how much mitomycin-C was delivered to the eye.*** You're injecting a known dose and volume, so you can calculate the exact amount of drug that is delivered to the eye. This can be a big advantage, especially for research purposes. When you soak a sponge in fluid and leave it on the eye, you really don't know how much drug you're delivering.

• ***The mitomycin-C can be spread as diffusely as you wish.*** When you apply mitomycin-C, the hope is that you will end up with a final bleb morphology that is very low-profile and diffuse—not focal, thin, avascular and cystic. The latter type of bleb is prone to leakage and infection. Peng T. Khaw, MD, PhD, at Moorfields Eye Hospital, promotes a fornix-based conjunctival incision that allows for the diffuse application of mitomycin-C sponges.[2] He believes that this methodology results in a lower profile, diffuse bleb. Likewise, with the injection technique, there's no border or restriction as to how diffusely you can spread the mitomycin-C.

• ***Outcomes may improve.*** Perhaps the most compelling reason to consider switching to injecting mitomycin-C is that early data suggests it may have a positive effect on surgical outcomes. So far, no one has conducted a prospective, randomized study comparing sponge application of mitomycin-C to injection, but our group was able to conduct a retrospective study of both techniques. We presented some of the results of that study at the 2013 meeting of the American Glaucoma Society and are currently preparing to submit the data for publication.

In our study we looked at patients who had received a trabeculectomy with mitomycin-C at the University of California, Davis. Fifty-seven eyes were treated with sponges; 126 received mitomycin-C delivered by injection. We assessed IOP reduction, IOP success rates, medication use and complication rates at one month and at one to three years after the initial surgery. The data indicated that the two groups were statistically similar in most respects, including visual outcomes. However, several findings were noteworthy:

— Despite our finding of no significant difference in the amount of pressure reduction between the groups, at 36 months the injection group was taking significantly fewer glaucoma medications than the sponge group.

— When we looked at procedures performed within a month after trabeculectomy surgery we found that the number of postop 5FU injections was significantly lower in the mitomycin-C injection group than in the sponge group.

— When we looked at complications occurring more than a month after surgery, we found a significantly

higher rate of tense, vascularized or encapsulated blebs (signs of excessive scarring) in the mitomycin-C sponge group (7 percent vs. 0 percent in the injection group).

• ***It doesn't appear to harm the tissue.*** We didn't find any postoperative differences between the groups in terms of complications such as choroidal effusion, hypotony, bleb leak or overfiltration. This is noteworthy, since one may worry that injecting the mitomycin-C will result in overtreatment, thus injuring or destroying conjunctival and Tenon's tissues. However, if that were the case, these complications would be more frequent in the injection group.

These results are encouraging, but of course these data are retrospective and should be interpreted with caution. Nevertheless, the differences we found indicate that this alternative technique might turn out to offer advantages over the sponge technique. At the very least, it is worthy of further study and a randomized, controlled, clinical trial is indicated.

In terms of downsides, there is always some danger of perforating the eye during the injection if the patient were to suddenly move, although we've never had anything like that occur.

A Promising Alternative

One thing about this technique that surgeons seem to appreciate is that it is very easy to do; it is not like learning a more complex procedure such as canaloplasty. Injecting mitomycin-C is a technique that anyone can do, since it is identical to giving subconjunctival injections of antibiotics or corticosteroids at the end of a surgical case.

One key question that our study did not answer is whether the injection technique actually produces better bleb morphology. A prospective, randomized study of this technique versus sponge application of mitomycin-C, employing a bleb grading scheme such as the Indiana Bleb Grading Scale,[3] would help to answer this question. REVIEW

Dr. Lim is a professor of ophthalmology and vice chair and medical director of the University of California, Davis Health System Eye Center in Sacramento. She has no financial ties to any products mentioned.

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How to Approach LASIK Enhancements

Surgeons say you have to weigh the pros and cons of another LASIK vs. correcting the error on the corneal surface.

Walter Bethke, Managing Editor

Though the rate of enhancement after LASIK is lower now than it was in the early years of the procedure, there is still the occasional patient in whom the procedure misses the mark. When a patient complains about poor vision after LASIK, however, surgeons say it pays to take the time to make sure the enhancement is warranted, and to choose the proper procedure when an enhancement is necessary. Here, expert surgeons discuss the pros and cons of the different methods they use to address these refractive do-overs.

Who Needs It?

Surprisingly, surgeons say they're seeing more patients coming back after five or 10 years asking for an enhancement, as opposed to patients who just had their LASIK within the past year asking for a re-do. Either way, physicians say to make sure the enhancement is necessary.

"You want to make sure the best-corrected vision is good and they don't have a significant cataract, retinal disease or any other factor that would be significantly limiting the vision," says Beverly Hills, Calif., surgeon Andrew Caster. "You also want to make sure that the other factors that will lead to a successful procedure are present: good tear film; no significant lid disease; and sufficient stroma on topography and tomography."

Majid Moshirfar, MD, director of refractive surgery and cornea at the University of Utah's Moran Eye Center, says that he also makes sure the refraction is stable. "They need two consecutive acuity measurements performed three to six months apart and a cycloplegic refraction," he says. "They also need tomography to determine if the refractive error is consistent with early keratoconus or if it's lenticular myopia. The patient may also have developed epithelial hyperplasia from ocular surface dryness that led to the development of myopia."

If the patient legitimately needs an enhancement, Dr. Caster likes to simulate what the resulting vision will be for the patient. "You want to show the patient the anticipated correction with spectacles," he says. "If it's a person of presbyopic age, make sure he understands the ramifications of both far and near vision, and that he thoroughly tests his far and near vision with the trial glasses. If it's a myopic enhancement, I emphasize to presbyopic patients how this will have a negative impact on their near vision. If I'm creating monovision, I emphasize how it's going to negatively impact their distance vision. I emphasize that this won't solve all their vision needs but will make their vision better."

PRK or Lift the Flap?

Surgeons say they usually go one of two routes for LASIK enhancement: Re-lift the flap and do LASIK or do PRK on top of the flap. Surgeons say the decision comes down to weighing the risk of epithelial ingrowth with LASIK vs. the slow visual recovery and risk of haze associated with PRK.

• ***Ingrowth concerns.*** "In a study at my practice, I found that my risk for epithelial ingrowth with primary LASIK was 1/1,440," says Alan Carlson, MD, chief of corneal and refractive surgery services at the Duke Eye Center. "But it was 1/40 with LASIK enhancements. So I looked carefully at who to avoid with a flap lift: epithelial basement membrane dystrophy;

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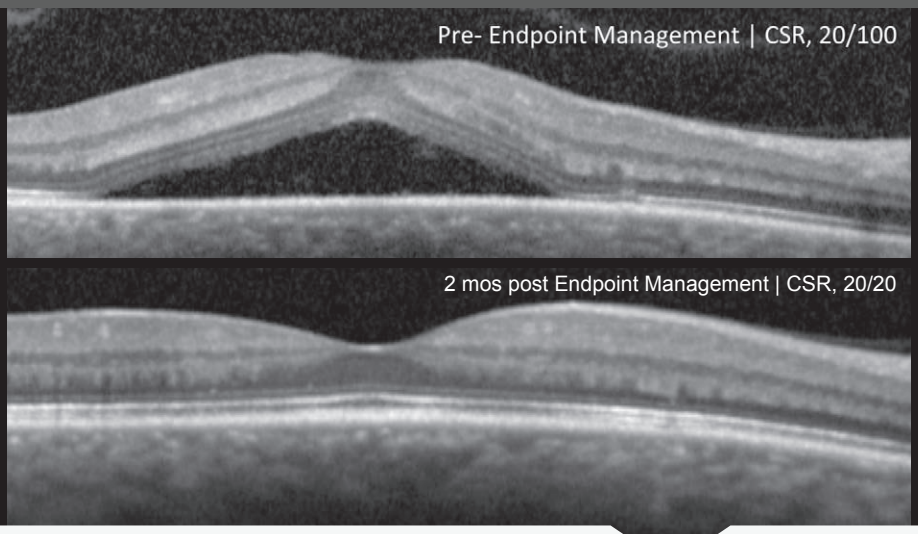

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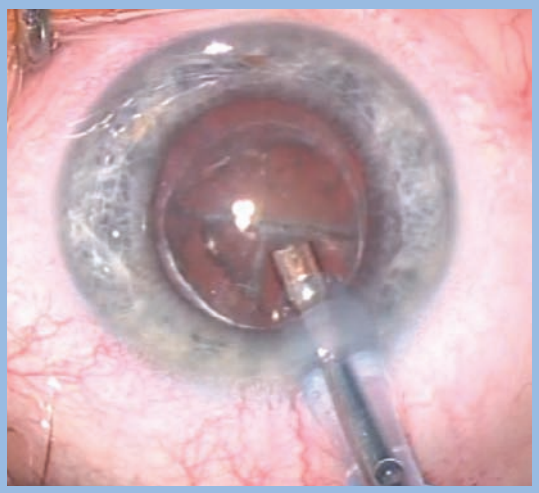

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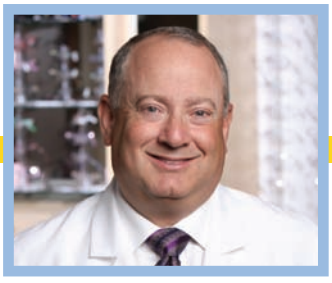

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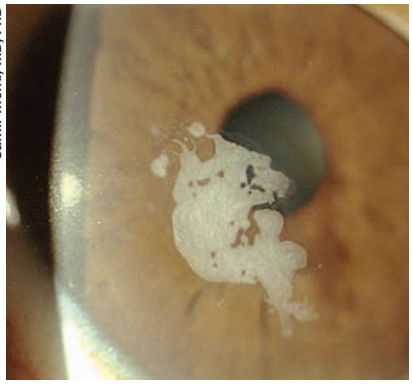
neovascularization, especially across the flap edge; a history of ingrowth either in this eye or the other; if I had done a previous myopic LASIK; and situations where travel might be a problem for the patient in terms of postop follow-up."

Dr. Caster published a study on epithelial ingrowth that's of interest to surgeons contemplating enhancements.[1] In it, he found that when an enhancement was performed within three years of the initial procedure, there was an epithelial ingrowth rate of around 1 percent. "If it was performed after three years, though," Dr. Caster explains, "the ingrowth rate from a LASIK enhancement increased to about 7 percent and remained constant at 7 percent during that longer period. So, a 10-year post-LASIK flap lift didn't have a higher incidence of ingrowth than a four-year flap lift."

Dr. Caster says surgeons use this data in different ways. Some recommend a flap lift enhancement if it's within the three-year period, but will do PRK if it's been longer than that. "I take a different approach," he says. "I recommend a LASIK enhancement for most of my patients who originally had LASIK with the understanding of the ingrowth risk if it's longer than three years out. I carefully explain this to the patient, and say he's got the option of PRK, but that I'm prepared to deal with the complication of ingrowth, because it's a very rare patient in whom the first treatment for ingrowth doesn't solve the problem. I feel the morbidity from the epithelial ingrowth and the subsequent ingrowth removal is less than the morbidity from a PRK procedure. PRK is also a different experience for patients; what they really dislike is the slow recovery of vision. People just don't like a PRK enhancement when they've had a previous LASIK."

• ***Surface ablation issues.*** Dr. Carlson acknowledges that surface ablation either takes away completely, or substantially reduces, the risk of ingrowth. "But the disadvantages are the medication usage is longer, there's an added risk of haze and there's what I call the mitomycin-C 'black box': It's a lot of variability in the recommendations of how to use it. We got recommendations initially to use it for 40 seconds, then it was 24 seconds, and now they recommend using it for 12 seconds. Who knows what it's going to be next year? Also, performing a flap lift conforms to patient expectations. If it goes well the healing is great and occurs at the LASIK interface, as opposed to the surface, where there could be some remodeling." Dr. Carlson says it may be good to avoid this epithelial remodeling from PRK in the long run. "If you have a LASIK flap, there's a good chance there are very fine irregularities in the flap," he says. "If the irregularities are mild, then they're typically not visually significant and the epithelium has remodeled to correct for them. If you perform a surface treatment—rather than lifting the flap, treating the bed, then placing the mild, accepted irregularity back down—you remove the epithelium and induce a new remodeling. The new epithelial remodeling could lead to a change in refraction."



Samir Melki, MD, PhD

Epithelial ingrowth is increased with a flap-lift enhancement compared to a primary LASIK, surgeons say.

Dr. Moshirfar is a surgeon who saw Dr. Caster's data and went in the direction of surface ablation for long-standing flaps. "I think the standard of care now for me, if someone comes in who's five to 10 years out, is to perform surface ablation for the enhancement," Dr. Moshirfar says. "But what about patients who had LASIK five or six months ago? If the surgeon knows the patient and is confident in the thickness of the residual stromal bed, and the refractive error makes sense and is stable, I think lifting is valid."

Though mitomycin-C has made haze less of an issue than it used to be with surface ablation, Dr. Moshirfar acknowledges that it's something to keep in mind. "There's still a chance you might cause PRK haze," he says. "For instance, say a LASIK patient who was -9 D before LASIK comes back and is -3 D. There's a chance you might get haze in this case due to the laser treatment inadvertently ablating the flap and then lasering through it. That event can cause haze. It's a small possibility.

"If the patient has a very small correction and PRK is being used for the enhancement, it makes sense to use mitomycin-C," Dr. Moshirfar adds. "If it's a -1.5 D virgin cornea, you don't need to use it. But for -1.5 D with an enhancement—there's a risk for haze with that, so I don't think it would be a bad idea to use mitomycin-C."

• ***Ectasia worries.*** Dr. Carlson agrees that it's crucial to get the stromal bed measurement right, since another complication of flap-lift enhancement—rarer than ingrowth but more devastating—is corneal ectasia. "The vast majority of patients who develop ectasia are those who have undergone a flap-lift enhancement," says Dr. Carlson. "And the largest settlements in LASIK court cases are those in which the patients went on to ectasia." REVIEW

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Amniotic Membrane's Therapeutic Action

New insights into amniotic membrane's potential to treat diseases in the eye and in other parts of the body.

By Hua He, PhD, Suzhen Zhang, PhD, and Scheffer C. G. Tseng, MD, PhD, Miami

Cumulative experimental and clinical evidence has demonstrated that cryopreserved human amniotic membrane possesses potent anti-inflammatory, anti-scarring and anti-angiogenic actions. In the past several years, our research studies have revealed new insights about the molecular candidate responsible for these actions. In this review, we will only focus on AM's anti-inflammatory action and its therapeutic implication.

HC-HA/PTX3 Complex in AM

In 2006, we first reported that AM stromal matrix exerts an anti-inflammatory action by inducing apoptosis of IFN-γ–activated monocyte/macrophage RAW264.7 cells *(See Figure 1)* and that such an action is not caused by nitric oxide but instead by the downregulation of anti-apoptotic NF-κB and Akt-FKHR signaling pathways.[1] Subsequently in 2008, we demonstrated that such an anti-inflammatory action is retained in soluble AM extract (AME). AME upregulates IL-10, downregulates TNF-α and IL-6, and suppresses the activation of RAW264.7 cells by IFN-γ, LPS and IFN-γ/LPS.[2] These findings suggest the key molecule(s) in AM responsible for its anti-inflammatory and other biological actions can be extracted and possibly be identified and isolated.

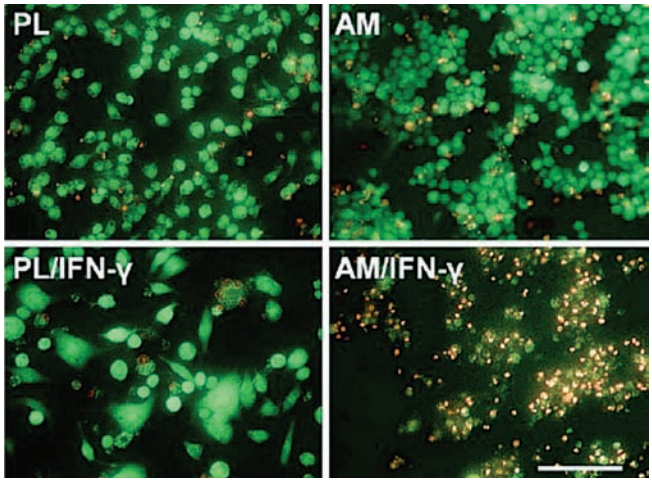
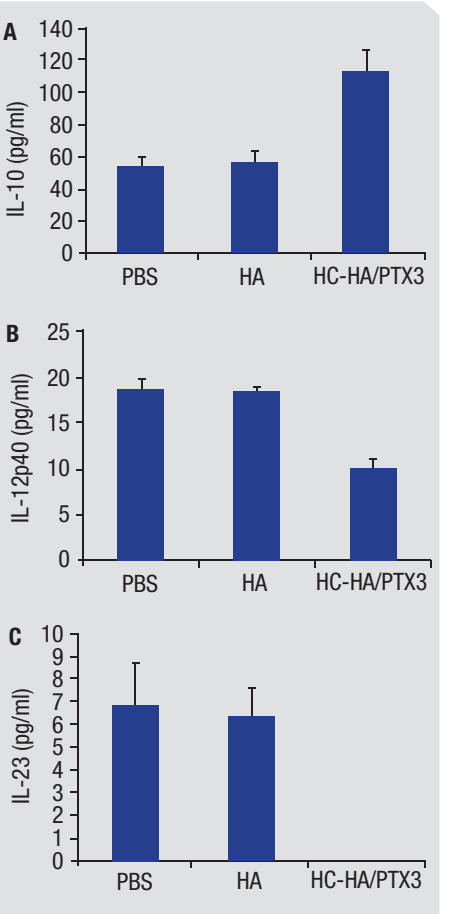


Figure 1. Amniotic membrane induces apoptosis in IFN-γ-activated RAW264.7 cells measured by LIVE/DEAD staining.[1]

Indeed, in 2009, we successfully purified a complex designated as "HC-HA/PTX3" from AME.[3] HC-HA/PTX3, first found in cumulus-oocyte complex (COC) surrounding the ovulated oocyte, is vital for subsequent fertilization.[4,5] It is formed by tight association between pentraxin 3 (PTX3) and HC-HA, which consists of high molecular weight hyaluronic acid covalently linked to heavy chain 1 (HC1) of inter-α-trypsin inhibitor. IαI is mainly secreted by the liver and present in the blood at considerably high concentrations (0.15 to 0.5 mg/ml).[6] It is composed of a common light chain and two heavy chains (HC1 and HC2). The light chain is a typical proteoglycan molecule having a single chondroitin four-sulfate chain. Its core protein, known as bikunin, contains two tandem Kunitz-type protease inhibitory domains that contribute to the protease inhibitory activity. In IαI, a bikunin molecule is linked to HC1 and HC2 via a unique ester bond.[6,7] IαI is usually

only found in serum and ingresses into tissue spaces as a consequence of increased vascular permeability at sites of inflammation. Because AM is an avascular tissue, we then investigated how AM cells can produce HC-HA/PTX3 without having a direct access to serum IαI. In 2012, our studies unraveled that human amniotic epithelial and stromal cells constitutively express the individual HCs (e.g., HC1 and HC2) as well as the bikunin, therefore producing IαI in AM locally.[8] Tumor necrosis factor-stimulated gene-6 (TSG-6) is a hyaluronic acid-binding protein normally only induced under inflammatory conditions.[9-11] It acts as a catalyst to transfer both HC1 and HC2 from IαI to HA for HC-HA complex formation. Our studies showed that human amniotic epithelial and stromal cells constitutively produce TSG-6 without requirement of stimulation by pro-inflammatory cytokines (e.g., IL-1 and TNF-α).[8] In addition, PTX3, a prototypic long pentraxin that plays a critical role in innate immunity,[12,13] is also an important structural component of COC. PTX3-deficient mice display a severe deficiency in female fertility due to defective assembly of the HA-rich matrix around the oocyte in the COC.[5] PTX3 can be produced by mouse cumulus cells during cumulus expansion and localized within the matrix.[5] It is believed that PTX3 makes multiple contacts to HCs of HC-HA complexes to provide structural integrity to the cumulus matrix,[14-16] implicating a nodal activity of PTX3 depending on its multimeric organization (i.e., octamers, tetramers and dimers). Interestingly, we have found PTX3 is also constitutively expressed and secreted by AM epithelial and stromal cells as an integral component of the HC-HA/PTX3 complex.[17] Collectively, for the first time our biochemical studies have shown that HC-HA/PTX3, which is originally found in COC,[5] is uniquely produced and can be purified from AM.

Figure 2A Through C



Retains Anti-inflammatory Action

Our studies have also shown that HC-HA/PTX3 purified from AM retains AM's anti-inflammatory action by exerting the following effects:

1) HC-HA/PTX3 promotes apoptosis of pro-inflammatory but not resting neutrophils and macrophages. During inflammation, neutrophils are among the first recruited to engulf pathogens and damaged tissues before their eventual apoptosis.[18-20] Pathologically, delayed neutrophil apoptosis leads to a prolonged inflammation, which is a hallmark of many inflammatory diseases.[21,22] We have reported that apoptosis of freshly-isolated neutrophils activated by fMLP or LPS is promoted only when they are treated by soluble HC-HA/PTX3, but not HA or PBS control.[23] We also report that soluble HC-HA/PTX3, the same as AM and AME, dose-dependently promotes apoptosis of RAW264.7 cells activated by IFN-γ, LPS, or IFN-γ/LPS.[2,3,23]

2) HC-HA/PTX3 enhances phagocytosis of apoptotic neutrophils by macrophages. Clearance of apoptotic neutrophils by macrophages is essential for inflammation resolution.[24-26] We have reported that soluble HC-HA/PTX3, but not HA, is effective in enhancing phagocytosis of apoptotic neutrophils by resting macrophages (about sevenfold vs. PBS control). Meanwhile, immobilized HC-HA/PTX3 is more potent in promoting phagocytosis of apoptotic neutrophils by LPS-activated macrophages (about 2.5-fold).[23]

3) HC-HA/PTX3 polarizes M2 macrophages. Macrophages may undergo classical M1 activation to express pro-inflammatory IL-12, which together with IL-23 activates Th1 and Th17 lymphocytes.[27] Consequently, M1 polarization leads to many chronic inflammatory diseases such as arthritis, atherosclerosis and diabetes. In contrast, they may also undergo alternative M2 activation, which expresses anti-inflammatory IL-10, activates T regulatory cells (Tregs) and promotes wound healing without fibrosis.[28-30] We have demonstrated that immobilized HC-HA/PTX3 polarizes LPS and IFN-γ/LPS-activated macrophages toward the M2 phenotype.[17,23,31] In short, immobilized HC-HA/PTX3, but not HA, upregulates transcript and protein expression of M2 markers (e.g., IL-10 and TGF-β1) and downregulates M1 markers (e.g., IL-12p40 and TNF-α) in activated RAW264.7 cells *(See Figures 2A & B)*. In addition, such M2 polarization is coupled with notable downregulation of IL-23 *(See Figure 2C)*, which is the cytokine produced by activated macrophages and dendritic cells to activate Th17 cells.[32,33]

4) HC-HA/PTX3 suppresses activation of CD4+ T cells. Naïve CD4+ T cells can be activated to proliferate and

differentiate into Th1, Th2, Th17 or Tregs.[34-36] Th1 cells secrete IFN-γ and IL-2 to enhance pro-inflammatory responses.[37,38] This action can be downregulated by Tregs that is activated by M2 macrophages.[39] Our study shows the soluble HC-HA/PTX3 suppresses the proliferation and production of IFN-γ and IL-2 and expression of T cell activation markers (CD25 and CD69) while significantly promoting the expansion of CD25+/FOXP3+ T cells.[31] These data strongly suggest that HC-HA/PTX3 suppresses activation of CD4+ T cells into Th1 cells.

5) HC-HA/PTX3 suppresses the macrophage influx to LPS-elicited corneas and prolongs survival of corneal allografts. While intrastromal injection of LPS elicited notable influx of EGFP+ macrophages to the corneal periphery in Mafia mice from day one to day five,[40,41] subconjunctival injection of HC-HA/PTX3 significantly suppresses the infiltrated macrophages. Further, the infiltrated macrophages are polarized towards an M2 phenotype by expressing higher M2 markers (Arg-1 and IL-10) but lower M1 markers (IL-12p35 and IL-12p40).[31] Using a murine orthotropic corneal transplantation model,[42-45] we have found that subconjunctival injection of HC-HA/PTX3 prolongs the significant survival of allografts compared to PBS injection.[31] These data suggest that HC-HA/PTX3 may be used to exert a potent anti-inflammatory action leading to suppression of (alloreactive) immune activation *in vivo*.

HC-HA/PTX3, a unique matrix component purified from human AM, retains AM's multifactorial anti-inflammatory actions. It is foreseeable that HC-HA/PTX3 can be used as a new class of biologics to treat ocular inflammatory diseases (e.g., proliferative diabetic retinopathy, trauma and subretinal fibrosis secondary to age-related macular degeneration and other choroidal neovascular processes) as well as similar pathological processes in other parts of the body. REVIEW

Dr. Tseng is a physician scientist and the chief scientific officer of TissueTech Inc, where both Dr. He and Dr. Zhang serve as research scientists. Contact Dr. Tseng at Ocular Surface Center, 7000 SW 97 Ave., Ste. 213, Miami, Fla. 33173. Phone: (305) 274-1299; fax: (305) 274-1297; e-mail: stseng@ocularsurface.com. *Supported in part by grants from National Institute of Health, National Eye Institute. Additional support is from a research grant from TissueTech Inc. and an unrestricted grant from Ocular Surface Research & Education Foundation, Miami.*

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OCTOBER 18-21 TO LEARN MORE ABOUT NANOTEARS®

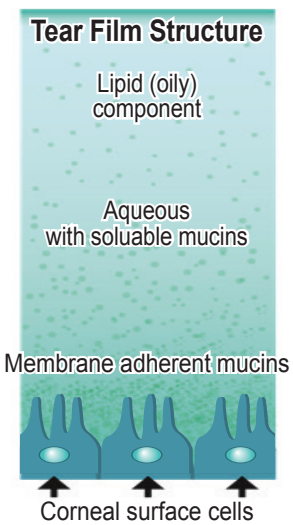
iSolutions®

NanoTears®

New Nano-Phased Lipid Technology Represents Advancement in Restoring the Pre-corneal Tear Film (PCTF)

We have tried many treatments for dry eye disease (DED) and, for the most part, found them all lacking. Older, more traditional wetting agents are insufficient when it comes to attacking the root causes of this multifactorial condition, particularly as it affects patient comfort. Some newer, more complex agents have been developed and seem to be a step forward. We recently had the opportunity to try a new formulation containing a proprietary blend of nano-phased lipids and an in-situ gelling agent and were pleasantly rewarded with positive findings, clinically and in patient satisfaction.

One key component of DED is a breakdown of the mucin layer that is responsible for converting the hydrophobic corneal surface of the eye to one that is hydrophilic. This allows the pre-corneal tear film (PCTF) to coat the surface of the eye filling in surface irregularities and providing optimal coverage. Patient comfort is often a direct result of the range of sufficient coverage afforded by the PCTF. NanoTears™ contain natural mucomimetic characteristics which help the patient become more comfortable almost immediately upon instilling the drop.



Another, very important component of DED is a deficiency of the lipid component of the PCTF, leading to evaporative dry eye disease (EDED). This evaporation causes the aqueous component of the tears to increase in osmolarity, which ultimately may be the final common pathway in dry eye pathology. The eye abhors the higher osmolarity and seeks natural ways of dilution. This leads to drawing water up through the surface cells of the eye, damaging them and leading to the clinical finding of conjunctival staining, and subsequently, corneal staining.

Sometimes Meibomian Gland Dysfunction (MGD) leads to secretion of what ultimately breaks down into fatty acids, which are toxic and destabilizing to the tear film. Controlling MGD is critical, but beyond that, reconstructing a healthy PCTF is essential to controlling the disease and making the patient comfortable again.

The nano-phased lipid component in NanoTears™ helps lower tear osmolarity by repairing and restoring the surface lipid layer, reducing tear evaporation and allowing for proper aqueous buildup and dilution. Other attempts have been made to develop an ophthalmic solution containing a lipid component to rebuild or restore the lipid layer of the PCTF. Nevertheless, almost by necessity, these preparations consist of a cloudy, somewhat opaque fluid, causing blurring that may last for several minutes after instillation. NanoTears™ have helped to alleviate this problem by using its proprietary NanoPid™ technology, allowing the drop to be clear, permitting immediate relief without causing the blur commonly associated with other products.

I used this product in a preliminary study and was immediately struck with the effectiveness of the product. Among the questions posed to patients in the study was one asking whether they had immediate blurring of vision. This was not a problem, and the vision remained clear even after instillation. Many of the study patients had a long history of dry eye and ocular discomfort, so they were a good test for the response to this drop. I was impressed with the marked improvement in the Ocular Surface Discomfort Score, and with how many patients spontaneously commented that their eye felt more comfortable almost immediately, and that the eye seemed to "cool off" with this drop. In a subsequent study, I followed patients for two months and even in that short time was able to document a substantive increase in Tear Break-Up Time (TBUT) and reduction in corneal staining.

Some of the responses to the product from my patients participating in the study:

"Usually my drops blur my vision for 30 seconds or so. With this drop I could see clearly almost right away."

"My usual drops make my eye feel wetter, but there's still an underlying scratchy feeling. These drops were soothing and made my eyes feel better."

"These drops are very comfortable. I could tell right away they were working."

All in all I was impressed with this drop, and believe that the proprietary combination of nano-phased lipids, demulcent, and in-situ gelling agent seem to provide long term desiccation protection without the blurring typically found with more traditional ophthalmic gels.

Dr. Paul S. Koch, M.D
Warwick, RI

Mfd. by: ALTAIRE Pharmaceuticals, Inc. Aquebogue, N.Y. • Telephone: 800.258.2471 • www.NanoTearsEyeDrops.com

Sustained Visual Acuity Loss Rare in CATT

Newly published results from the Comparison of Age-related Macular Degeneration Treatment Trials show that sustained visual acuity loss was relatively rare in CATT participants. While the risk was 3 percent higher among eyes treated with bevacizumab, the development of foveal scar, pigmentary abnormalities or geographic atrophy contributed to most of the sustained visual acuity loss.

Participants in the CATT clinical trial were randomized to treatment with ranibizumab or bevacizumab and to two years of monthly or p.r.n. injections, or monthly injections for one year and p.r.n. injections for the following year. Within this group, 1,030 participants were selected for a cohort study to determine the incidence, characteristics, causes and baseline predictors of sustained visual acuity loss. Sustained visual acuity loss was defined as loss of 15 or more letters from baseline at weeks 88 and 104.

Sixty-one eyes (5.9 percent) developed sustained visual acuity loss in two years. Within this group, visual acuity decreased gradually over time, with a mean decrease of two letters from baseline at four weeks, 19 letters at one year, and 33 letters at two years. At two years, eyes with sustained visual acuity loss had more scarring (60 percent vs. 41.4 percent, p=0.007), more geographic atrophy (31.6 percent vs. 20.7 percent, p=0.004), larger lesions (16 vs. 8 mm^2, p<0.001) and higher proportions of: intraretinal fluid (82.5 percent vs. 51 percent, p<0.001); subretinal hyperreflective material (84.5 percent vs. 44.2 percent, p<0.001); retinal thinning (43.3 percent vs. 23 percent, p<0.001); and thickening (20 percent vs. 12.1 percent, p<0.001). The likely causes of sustained visual acuity loss include foveal scarring (44.3 percent), pigmentary abnormalities (27.9 percent) and foveal GA (11.5 percent). Baseline factors independently associated with a higher incidence of sustained visual acuity loss were the presence of nonfoveal GA (odds ratio: 2.86; 95 percent confidence interval, 1.35 to 6.08; p=0.006); larger area of choroidal neovascularization (OR for a >4-disc area vs. ≤1-disc area: 3.91; 95 percent confidence interval, 1.7 to 9.03; p=0.007); and bevacizumab treatment (OR: 1.83; 95 percent confidence interval, 1.07 to 3.14; p=0.03).

JAMA Ophthalmol 2014;132:915-921.

Ying G, Kim B, Maguire M, Huang J, et al.

Following Suggested Diet Reduces Visual Impairment Risk

Australian researchers utilized a population-based cohort composed of participants from the Blue Mountains Eye Study to determine that adherence to dietary guidelines is associated with a decreased long-term risk of visual impairment in suburban Australian patients aged 65+ years.

Participants were examined at baseline, five and 10 years. The incidence of visual impairment was defined as best-corrected visual acuity <20/40 at follow-up in one or both eyes. Dietary information was obtained at baseline using a validated food frequency questionnaire. Total Diet Score was calculated based on the Australian diet quality index. TDS includes components of diet quality, poor dietary habits and energy balance. Discrete logistic regression models with time-dependent outcome variables were used to calculate hazard risk ratios and 95 percent confidence intervals associated with the incidence of visual impairment for each unit/quartile increase in TDS, adjusting for potential confounders.

Of the baseline participants in the study (n=3,654), 1,963 had up to 10 years follow-up with completed FFQs. With each unit increase in TDS, the risk of visual impairment decreased (HR 0.94; 95 percent confidence interval, 0.88 to 1.0). The risk of developing visual impairment was lower among persons in the highest

compared to the lowest TDS quartile (HR 0.71; 95 percent confidence interval, 0.41 to 1.05). This association was significant among persons aged 65+ years (HR 0.63; 95 percent confidence interval 0.38 to 0.98) but not among those aged <65 years (HR 0.95; 95 percent confidence interval, 0.46 to 1.97).

Am J Ophthalmol 2014;158:302-308.

Hong T, Flood V, Rochtchina E, Mitchell P, et al.

Evaluation of MIGS with iStents And Travoprost in OAG

Researchers enrolled 39 phakic patients with open-angle glaucoma not controlled on two medications preoperatively in a prospective, open-label, non-randomized trial to evaluate the IOP-lowering effect of two trabecular microbypass stents (iStent, Glaukos Corp.) and postoperative travoprost. Patients achieved a significant and sustained reduction in IOP and medication through 18 months.

The patients had a medicated IOP between 18 mmHg and 30 mmHg, with an unmedicated baseline IOP (after washout) between 22 mmHg and 38 mmHg. Patients received two iStents through a clear corneal incision and were prescribed travoprost starting the night of postoperative day one. Complications, IOP and various safety measures were assessed at examinations through 18 months and planned for every six months after until month 60. A washout of medications was performed 13 months postop.

All patients achieved an IOP reduction of 20 percent or more from baseline to 12 months with reduction of one medication and with IOP of 18 mmHg or less. Follow-up through 18 months showed that medicated IOP decreased from 22.2 ±2 mmHg (standard deviation) on two medications preoperatively to 14 mmHg or less on one medication at the postop visits. The mean unmedicated IOP decreased from 25.3 ±1.8 mmHg preoperatively to 17.1 ±2.2 mmHg 13 months postop. No intraoperative or serious device-related adverse events occurred.

J Cataract Refract Surg 2014; 40:1295-1300.

Ahmed I, Katz L, Chang D, Donnenfeld E, et al.

New Index to Monitor Central VF Progression in Glaucoma

Researchers in New York have developed and validated a new index to monitor central visual field progression that is minimally affected by the presence or removal of cataract: the central field index.

The researchers employed a retrospective cohort of glaucoma patients (176 eyes of 142 patients) with paracentral defects seen on 24-2 perimetry and followed up with at least five 10-2 visual tests to calculate an age-corrected defect depth at test points that were obtained during the 10-2 examinations. The sensitivities at these points were scored as percentages similar to the method described for the visual field index: 100-[(|total deviation|/age-corrected normal threshold)x100]. A weighting procedure was applied based on published estimates of the occipital cortical spatial magnification.

For validation, researchers performed mixed linear model testing for the association between CFI rates of change (percent per year) and known risk factors for glaucoma progression in a population with established glaucoma and at least five 10-2 VF tests. To determine whether the CFI was affected by cataract, as is known to occur with mean deviation, the researchers conducted a pilot evaluation comparing rates of CFI change in three groups: eyes with cataract; pseudophakic eyes; and eyes in which cataract surgery was performed in the middle of the series. The mean rate of CFI change of the entire sample was -1.1 percent per year (95 percent confidence interval, -1.03 to -1.16 percent per year). Elevated intraocular pressure ($p<0.001$) was associated significantly with faster CFI change, whereas lens status did not influence CFI rates of change ($p>0.1$).

Ophthalmology 2014;121:1531-1538.

De Moraes C, Furlanetto R, Ritch R, Liebmann J.

Predictors of Sustained IOP in Eyes Receiving IVI Anti-VEGF

New York researchers asked 530 retina specialists, spanning both private and academic practice, about their current anti-VEGF protocols, including anti-VEGF drug of choice, needle gauge, injection volume, injection technique and self-reported prevalence of sustained intraocular pressure elevation. Based on survey data, it appears that serial anti-VEGF injections using higher injection volumes with a rapid injection technique may potentially lead to sustained IOP elevation.

Two hundred ninety-two specialists (55 percent) reported believing that intravitreal anti-VEGF therapy may cause sustained IOP elevation. Of these responses, the most common reported prevalence was 1 to 2 percent (48 percent), followed by 3 to 5 percent (34 percent). There was no relationship between frequency of sustained IOP elevation and anti-VEGF drug of choice. Physicians who injected more than 0.05 cc in less than one second were 5.56 times more likely to observe a high frequency of sustained IOP elevation ($p=0.006$; 95 percent confidence interval, 1.64 to 18.89). The underlying mechanism for this complication may be injury to the trabecular meshwork resulting from rapid elevation in IOP.

AM J Ophthalmol 2014;158:319-327.

Yannuzzi N, Patel S, Bhavsar K, Sugiguchi F, Freund K.

REVIEW Calendar

OCTOBER

16 - 17
CHICAGO
The American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) will host its 45th Annual Fall Science Symposium at the Sheraton in Chicago. For more information, visit asoprs.org.

18 - 21
CHICAGO
The American Academy of Ophthalmology and the European Society of Ophthalmology will hold their annual meetings in conjunction in Chicago, at McCormick Place West Convention Center. The annual meeting will be preceded by subspecialty days that will focus on cornea, glaucoma, ocular oncology and pathology, oculofacial plastic surgery, pediatric ophthalmology, refractive surgery, retina and uveitis. CME hours will be available. For more information, visit aao.org.

24 - 25
BOSTON
The 3rd International Biennial Symposium on Age-related Macular Degeneration will take place at the Starr Center in the Schepens Eye Research Institute. International AMD experts, along with leaders from related disciplines outside ophthalmology, will come together in an interactive format to discuss current and future topics in AMD research. For more information, visit schepens.harvard.edu/amd2014.

NOVEMBER

22 - 26
BRISBANE, AUSTRALIA
The Royal Australian and New Zealand College of Ophthalmologists' 46th Annual Scientific Congress will be held at the Brisbane Convention and Exhibition Centre, and feature an international lineup of speakers covering most specialties. Additionally, RANZCO and the International Council of Ophthalmologists will discuss setting international surgical standards. For more information, visit ranzco2014.com.au.

28 - 30
OSAKA, JAPAN
The 53rd Annual meeting of the Japanese Retina and Vitreous Society will be held in conjunction with the 31st Annual Meeting of the Japanese Society for Ocular Circulation in the Osaka International Convention Center in Osaka, Japan. Topics will include anti-VEGF therapies, retinal degenerative diseases and subthreshold laser therapies for macular edema. For more information, email vitreoretina@jtbcom.co.jp or visit convention.jtbcom.co.jp/rvoc2014/index.html.

DECEMBER

1 - 4
KYOTO, JAPAN
The International Strabismological Association meeting is held every four years; the 2014 meeting will be hosted by the Japanese Association of Strabismus and Amblyopia at the Kyoto International Conference Center. The meeting is a chance for those with a special interest in strabismus from all around the world to gather to present topics in this sub-specialty area of ophthalmology and to share experiences in a smaller, more personal setting. The scientific program will feature a large international group of speakers focusing on all sensory and motor aspects of strabismus, as well as other disorders of ocular motility, and promoting clinical research. For more information, visit isa2014.jp.

4 - 6
BALTIMORE
The Wilmer Eye Institute's 27th Annual Current Concepts in Ophthalmology will be held on campus in the Turner Auditorium at Johns Hopkins University. Expert faculty will present the latest developments in the management of ocular conditions, with a specific concentration on the most advanced medical and surgical treatment options within glaucoma, retina, anterior segment and refractive surgery. CME is available. For more information, phone (410) 955-2959 or visit hopkinscme.edu/pdfs/80034487pc.pdf.

JANUARY 2015

17 - 23
MAUI, HAWAII
More than 1,200 comprehensive ophthalmologists, retina specialists, nurses/technicians and administrators will come together for Hawaiian Eye and Retina 2015. The first two days of the meeting are designed for the entire practice and are spent together in the same room to offer insight from all viewpoints. The rest of the week, each profession has separate general sessions where they discuss relevant updates and emerging data. The comprehensive ophthalmologist program will cover today's hot topics, practice management, cataract/IOL technique and technology, cataract and refractive surgery complications, vitreoretinal issues, glaucoma, medical retina, ocular surface management and refractive surgery. The retina program will feature a fast-paced mix of scientific and clinical presentations along with dynamic panel discussions and question and answer sessions. Each day will offer a different focus area, exploring the latest information about new therapeutic agents, surgical techniques and clinical trial results. CME is available. For more information, email meetings@registrationams.com or visit hawaiianeyemeeting.com.

FEBRUARY

5 - 8
HO CHI MINH CITY, VIETNAM
The Inaugural Asia-Australia Congress on Controversies in Ophthalmology will raise the most dynamic and controversial topics facing clinicians in the field, with the aim of reaching up-to-date and agreed-upon answers to ongoing debates in ophthalmology through evidence-based medicine and expert opinion. The Congress will emphasize issues related to the region in terms of retina, anterior segment, glaucoma, diagnostics, typical complications and distinctive responses to treatments. The official conference language is English. For more information, email cophyaa@comtecmed.com or visit comtecmed.com/cophy/AA/2015.

12 - 15
AVENTURA, FLA.
The American Society of Cataract and Refractive Surgery and American Society of Ophthalmic Administrator's Side X Side Conference, formerly known as Winter Update, will take place at Turnberry Isle Miami hotel and spa, in Aventura, Fla. This newly designed meeting has been specifically created for anterior segment eye surgeons and busy ophthalmic practice administrators who need in-depth, focused information on key topics that will allow them to integrate advanced techniques into their practices. Each year, Side X Side will focus on key innovations in the ophthalmic practice, providing in-depth "how to's" on all aspects, from discussions with patients, to preoperative screening and planning, to technique adjustments. Side X Side will incorporate the relaxed atmosphere and extensive interaction between faculty and attendees, both within sessions and at networking events, that the ASCRS/ASOA Winter Update made its own. CME and CE are available. For more information, call (703) 591-2220 or visit sidexside.ascrs.org.

MARCH

26 - 29
SORRENTO, ITALY
The 6th World Congress on Controversies in Ophthalmology will take place at the Hilton Sorrento Palace in Sorrento, Italy. This educational Congress will continue to focus on anterior segment, glaucoma and retina sections, and will also discuss controversies in other areas of ophthalmology, such as neuro-ophthalmology. The scientific program will include state-of-the-art lectures and controversial debates; outstanding world leaders as faculty will present both pro and con positions while further challenging and exploring what the optimal treatments for patients are, with emphasis on the appropriate use of new and emerging drugs. This format includes a substantial allocation of time for interactive debates and questions from the audience to each panel of experts. The official language of the Congress is English. For more information, email cophy@comtecmed.com or visit comtecmed.com/cophy/2015.

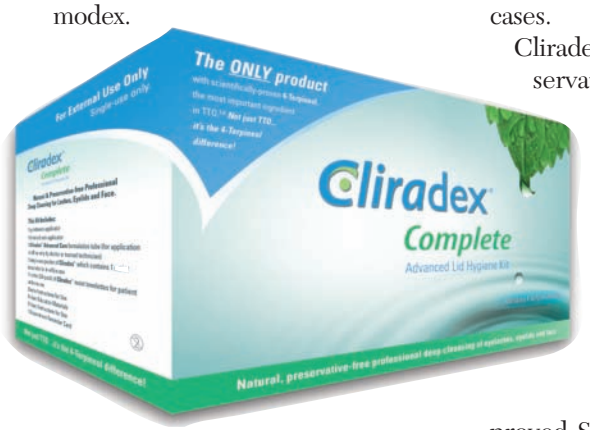
APRIL

15 - 17
SAN DIEGO
The World Cornea Congress highlights the international corneal community's endeavors in clinical and research areas. It is held every five years and is sponsored by the Cornea Society. The three-day meeting will include both invited speakers and a call for papers, as well as a poster session each day and an exhibit hall. The Congress will immediately precede the American Society of Cataract and Refractive Surgery and the American Society of Ophthalmic Administrators Symposium and Congress. For more information, visit corneasociety.org.

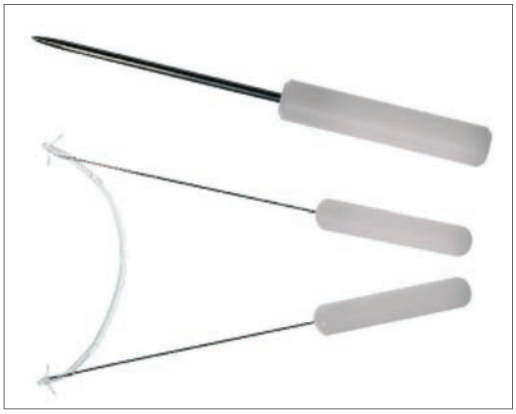
17 - 21
SAN DIEGO
The American Society of Cataract and Refractive Surgery and the American Society of Ophthalmic Administrators' annual Symposium and Congress will take place in San Diego at the San Diego Convention Center. The ASCRS Annual Symposium is the largest U.S. meeting dedicated exclusively to the needs of the anterior segment specialist. The simultaneous ASOA Annual Congress is the leading practice management program for comprehensive ophthalmology and subspecialties. The meeting will be preceded by a glaucoma subspecialty day covering critical updates, robust debates and interactive case studies on what comprehensive ophthalmologists and anterior segment surgeons need to know about glaucoma management. CME hours will be available. For more information, visit annualmeeting.ascrs.org.

Bio-Tissue's Cliradex Kit Expands Lid-Care Line

Bio-Tissue, which specializes in regenerative tissue therapies and ocular hygiene products for lid margin and ocular surface diseases, has launched Cliradex Complete Advanced Lid Hygiene Kit, the newest addition to the Cliradex product line. These products sisolate 4-Terpineol, the most important ingredient in tea tree oil, which the company says is scientifically proven to help manage symptoms of lid margin diseases, including blepharitis, meibomian gland dysfunction, rosacea, dry eye and demodex.



The kit is a professional, comprehensive lid hygiene protocol featuring a formulation gel called Cliradex Advanced Care that includes a stronger concentration of 4-Terpineol for in-office application by a doctor or trained technician. This new formulation also contains ingredients for easy removal of lid margin debris and makeup. The kit comes with a dual-sided applicator, doctor and patient materials, and a carton of Cliradex lid wipes for patients to use at home for management of their symptoms. This new addition to the Cliradex product line is used for moderate to severe cases of lid margin diseases, while the current Cliradex lid wipes can be used by patients at home for mild to moderate cases.



Cliradex products are natural, preservative-free lid, lash and facial cleansers, and are the only commercially-available products that isolate 4-Terpineol. For information, visit biotissue.com.

FCI Debuts Canaliculus Intubation Set

FCI Ophthalmics announces a new and improved Self-Retaining Bicanaliculus Intubation Set, designed by Pierre Bigé, MD. The SRSII allows the physician to intubate the canaliculi in the office with just topical anesthetic drops and enables intubation of the upper and lower canaliculi without having to enter through the nasal passageway.

The 0.64-mm wide tube is made of medical grade silicone and is available in 25-mm, 30-mm and 35-mm lengths. Each end of the tube has an anchor-shaped head with two flexible winglets that fold inward during insertion through the punctum. Pre-loaded introducers on each end make insertion easier. After passage through the common canaliculus, the winglets open in the lacrimal sac for secure fixation. A centrally placed marking on the tube acts as a reference point and allows verification of proper stent positioning.

Primary indications for the SRSII include horizontal lacrimal duct stricture or punctal stenosis. Special consideration should be given to cancer patients on constricting drug therapies such as Taxotere.

For information, call FCI Ophthalmics at 1 (800) 932-4202 or visit fci-ophthalmics.com.

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Rick Bay served as the publisher of The *Review* Group since 1991.

To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.

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Non-Detergent Dry-Eye Product

NovaBay Pharmaceuticals, Inc. will initiate a major marketing campaign and commercialization effort for the company's new product, i-Lid Cleanser. The marketing campaign will explain why i-Lid Cleanser is a significant advance in the care of dry eye and blepharitis. It is estimated that 23 million Americans chronically suffer from inflammation of the eyelids, known as blepharitis, and another 13 million struggle with meibomian gland dysfunction. NovaBay says its i-Lid Cleanser is the first non-detergent, non-irritating product to be prescribed for these conditions. For information, call 1 (800) 890-0329 or visit ilidcleanser.com.

A New View from Sony

Sony Medical has introduced two new products: the Sony MCC-500MD medical video camera and the HVO-550MD medical recorder with DVD optical drive.

Sony says that the MCC-500MD medical video camera is affordable, and features the latest-generation image sensor technology for better low-light sensitivity than traditional 1/3-inch image sensor technology to allow for superb image reproduction capability. The company says that the technology offers maximum flexibility with connectivity options such as high-definition multimedia interface, HD-serial digital interface (1080P), S-video and composite. Sony adds that all outputs are active simultaneously, ideal for multiple views in the operating room. Surgeons can capture full HD quality surgical video when the camera is paired with the HVO-550MD recorder, which features MPEG-4 recording, universal serial bus connectivity and network recording capabilities.

The company says that users will be able to simultaneously record to an internal hard drive and to a USB thumb or portable drive. The recorder's 500GB internal hard drive will store up to 85 hours of HD video with rapid access to previously recorded cases. For information visit http://pro.sony.com/bbsc/ssr/mkt-medical/.

Compact Washer-Disinfector For Ophthalmic Instruments

Miele Professional has introduced a new product for hospitals seeking to reduce the incidence of postoperative eye inflammations. The G7899 Washer-Disinfector is equipped with baskets, trays and racks designed specifically to clean delicate microsurgical instruments used in cataract and other ophthalmic surgeries. As a free-standing system, the G7899 allows hospitals to follow industry guidelines and manufacturer's directions for use (DFU), recommending the separation of ophthalmic instruments from other surgical tools during reprocessing. Compact and automated, Miele G7899 Washer-Disinfectors free hospital staff from manual soaking and scrubbing prior to sterilization.

Miele G7899 Washer-Disinfectors use specialized injectors to effectively remove soil and debris from the narrow lumens in phacoemulsification and other cannulated instruments used in ophthalmic surgery. The low spray pressure combined with high-volume water circulation provides gentle yet powerful cleaning and rinsing. Six preinstalled programs, including a specialized ophthalmology program, simplify operation for users and a variety of alarms and safety devices are built-in.

Miele Washer-Disinfectors are rated for intermediate-level disinfection prior to sterilization. The systems assist hospital infection control departments to conform to industry best practices, such as AAMI ST79. Engineered for durability, Miele systems are designed to perform optimally for 15,000 hours, providing years of continuous service. Miele includes installation of the washer with verification documentation and a two-year warranty on parts and labor. For information, contact: medical@mieleusa.com or call 1 (800) 991-9380, or visit miele-pro.com. REVIEW

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1. Publication Title	2. Publication Number	3. Filing Date
Review of Ophthalmology	0 1 2 - 3 4 5	10/1/14
4. Issue Frequency	**5. Number of Issues Published Annually**	**6. Annual Subscription Price (if any)**
Monthly	12	$63.00

7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP+4®)
Jobson Medical Information
100 Avenue of the Americas
New York, NY 10013

Contact Person: Hamilton Maher
Telephone (Include area code): (212) 219-7870

8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer)
Same As Above

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank)

Publisher (Name and complete mailing address)
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Jobson Medical Information
11 Campus Blvd., Suite 100, Newtown Square, PA 19073

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13. Publication Title: Review of Ophthalmology			14. Issue Date for Circulation Data Below: October 2014	
15. Extent and Nature of Circulation			**Average No. Copies Each Issue During Preceding 12 Months**	**No. Copies of Single Issue Published Nearest to Filing Date**
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f. Total Distribution (Sum of 15c and e) ▶			25,078	23,244
g. Copies not Distributed (See Instructions to Publishers #4, (page #3)) ▶			438	374
h. Total (Sum of 15f and g)			25,516	23,618
i. Percent Paid and/or Requested Circulation (15c divided by f times 100) ▶			64.87%	93.49%

16. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the October 2014 issue of this publication.

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PS Form **3526-R**, September 2007 (Page 2 of 3)

REVIEW Advertising Index

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Awakening with severe, acute vision loss in the left eye prompts a patient to seek evaluation at the Wills Eye Emergency Department.

Spenser Morton, BS, and Murtaza Adam, MD

Presentation

A 59-year-old Cambodian male presented to the Wills Eye Emergency Department with a one-day history of vision loss in the left eye. The patient stated he previously had equal vision in both eyes and awoke with significantly decreased vision in the left eye on the day of presentation. He denied any history of trauma, straining, coughing, lifting, pain, headache or neurologic symptoms.

Medical History

The patient's past ocular history was only significant for mild cataracts in both eyes. His past medical history was significant for hypertension. His medications included amlodipine, indapamide, low-dose aspirin and fish oil supplements. Allergies included shellfish derivatives. He denied any recent travel and had no pets at home. Social history was negative for tobacco, alcohol or drug use.

Examination

The patient's corrected visual acuity was 20/25 in the right eye and count fingers in the left without improvement on pinhole. Pupils were normal without afferent pupillary defect. Confrontational visual fields were full to finger counting in both eyes. Amsler grid testing revealed a significant central scotoma in the left eye. Motility was full in both eyes. There was no proptosis. Intraocular pressure was within normal range and equal in both eyes. Nuclear sclerotic changes were present. His funduscopic exam was significant for some macular retinal pigment epithelium changes in the right eye consistent with a pigment epithelium detachment. A large subretinal hemorrhage involving the macula and peripapillary region without peripheral pathology was noted in the left eye *(See Figure 1)*. Blood pressure was 130/70. Neurologic exam was unremarkable without weakness, paresthesias, loss of reflexes or ataxia.

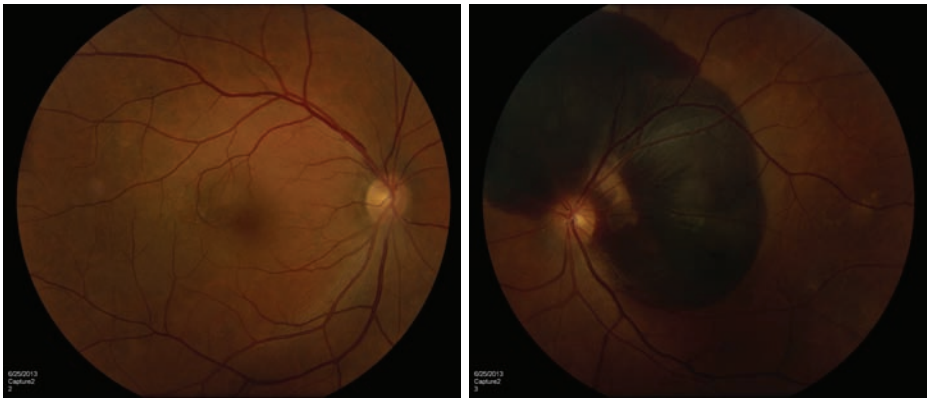

Figure 1. Fundus photos of the right eye (left) and left eye (right) on presentation. Juxtafoveal retinal pigment epithelium changes are consistent with a pigment epithelial detachment in the right eye. A large, elevated subretinal hemorrhage involving the macula and superior peripapillary region is noted in the left eye.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 68

Diagnosis, Workup and Treatment

Prior to discharge from the Wills Eye Emergency Department, a complete blood count with differential, PT and PTT were reviewed and were unremarkable. The patient was subsequently referred to the Retina Service of Wills Eye Hospital for further workup and treatment.

Optical coherence tomography disclosed a macular serous pigment epithelial detachment in the right eye and a large submacular hemorrhage without subretinal fluid in the left eye *(See Figure 2)*. Fluorescein angiography revealed diffuse mottled hyperfluorescence with focal hyperfluorescence localized to the PED in the right eye and diffuse choroidal fluorescein blockage due to subretinal hemorrhage in the left eye.

Although indocyanine green angiography was not performed, the overall clinical picture and diagnostic testing were consistent with a diagnosis of idiopathic polypoidal choroidal vasculopathy (IPCV). Given the degree of submacular hemorrhage, the patient underwent pars plana vitrectomy with injection of subretinal tissue plasminogen activator and intraocular sulfahexafluoride (SF6) gas bubble tamponade. With gas tamponade, inferior displacement of the subretinal hemorrhage was achieved.

Four months following surgery, the patient experienced a markedly improved anatomic *(See Figure 4)* and visual outcome with corrected visual acuity of 20/25 in the left eye. Throughout this time, the previously noted extrafoveal PED was monitored and remained stable without intervention in the right eye.

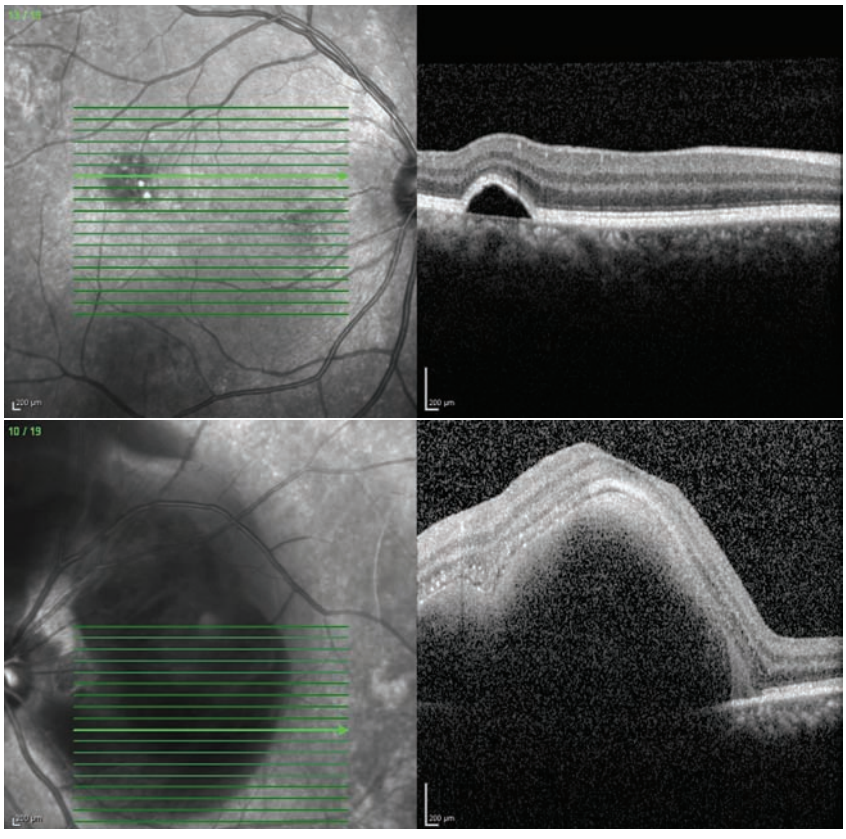

Figure 2. Optical coherence tomography of the right eye (top) and left eye (bottom) on presentation. A macular pigment epithelial detachment is noted in the right eye. A large, elevated hemorrhage appearing above the retinal pigment epithelium without subretinal fluid is observed in the left eye.

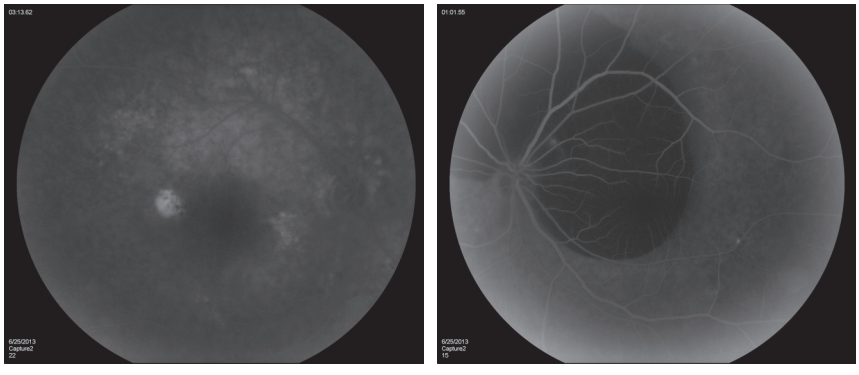

Figure 3. Late-phase fluorescein angiography of the right eye (left) and left eye (right). Patchy mottled hyperfluorescence is diffusely noted in the right eye with an area of focal subretinal hyperfluorescence in the region of a serous PED. Choroidal blockage due to the large submacular hemorrhage is observed in the left eye with two focal areas of subretinal hyperfluorescence.

Discussion

IPCV as first described by Lawrence Yannuzi, MD, and colleagues is a rare variant of age-related macular degeneration.[1] It is seen most commonly in Asians and African Americans and has a preference for

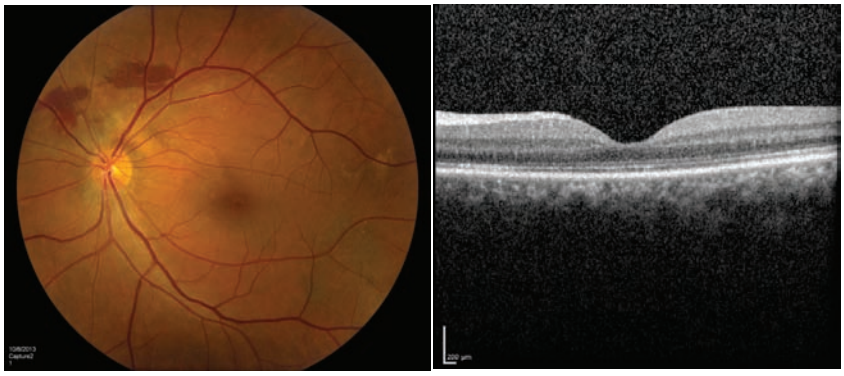

Figure 4. Fundus photo of the left eye and optical coherence tomography of the left macula four months following pars plana vitrectomy with injection of subretinal tissue plasminogen activator and intraocular sulfahexafluoride gas bubble tamponade. Near total displacement of subretinal hemorrhage and restoration of macular anatomy is observed.

females with a ratio of about 4:1, and an average age of onset between 60 and 70 years of age.[2,3] A recent study by Stephen J. Davis, MD, and colleagues showed that among Caucasians with presumed AMD, the rates of IPCV were between 4 percent and 9.8 percent, while in Asians the rates of IPCV are between 24 percent and 55 percent.[4] In general, patients with IPCV have better visual outcomes than patients with choroidal neovascularization with AMD.[4]

Aptly described by its name, IPCV is a vascular disease process characterized by lesions produced by a network of branching choroidal vessels with terminal, polyp-like aneurysmal dilations. On ophthalmoscopic examination, this can manifest as orange to red lesions protruding from the choroid into the subretinal space. Patients with IPCV experience multiple, recurrent, serosanguinous PEDs and neurosensory retinal detachment secondary to leakage and/or hemorrhage from the abnormal choroidal vasculature.[5] Both the etiology and pathophysiology of the IPCV disease process are still poorly understood.

AMD patients unresponsive to standard therapeutic measures with anti-vascular endothelial growth factor agents are nominees for IPCV workup, especially if the findings are unilateral and patient demographics align. While no universally accepted criteria for definitive diagnosis of IPCV exist, the current gold standard for diagnosis is visualization of polypoidal lesions on indocyanine green angiography.[6] ICGA is the preferable angiographic study because IPCV lesions can closely mimic CNV membranes on FA. En face OCT has been shown to be effective in detecting not only subretinal and sub-RPE fluid, but polypoidal lesions as well, making it another potentially helpful diagnostic tool in IPCV.[7]

Following diagnosis, several factors may dictate the treatment algorithm. Several studies have established that the best visual and anatomic outcomes for PEDs or subretinal fluid have been achieved with use of photodynamic therapy (PDT) coupled with periodic intravitreal injections of anti-VEGF agents.[3,8] In a study by Kaoruko Tomita and colleagues, it was shown that PDT used in combination with ranibizumab led to significant visual recovery in eyes previously untreated with PDT, but failed to show the same benefits in eyes that had demonstrated recurrence after previous PDT treatment.[9] More recent data on three-year visual outcomes of treatment-naïve patients comparing treatment with PDT and intravitreal bevacizumab (double therapy) to PDT, intravitreal bevacizumab and subtenon triamcinolone acetonide injections (triple therapy) showed superiority of the triple therapy treatment regimen.[10]

While not necessarily applicable to IPCV, the Submacular Surgery Trial examined the utility of submacular surgery versus laser photocoagulation in the treatment of recurrent subfoveal neovascular lesions in AMD and found no difference in visual outcomes for patients who underwent submacular surgery or laser photocoagulation.[11] However, in the setting of massive subretinal hemorrhage associated with AMD and its variant IPCV, surgical treatment options predominate. A multicenter interventional case series highlighted the utility of PPV, subretinal injection of tPA, and gas bubble tamponade for displacement of submacular hemorrhage in AMD with associated improved visual outcomes.[12] In a study examining the use of intravitreal tPA injection and pneumatic displacement for treatment of submacular hemorrhage, the hemorrhage attributed to IPCV was completely displaced in all 11 study eyes.[13] Interestingly, it was further noted that eyes with IPCV treated in this manner had better visual outcomes than eyes where submacular hemorrhage was attributed to "classic" AMD. A case series from Fumio Shiraga and colleagues reported improved visual outcomes with multiple surgical treatments including submacular removal of neovascular membranes, PPV combined with subretinal tPA, or SF6 gas bubble tamponade alone.[14]

Despite its similarities to AMD, the diagnosis and management of IPCV has its own challenges and the search for optimal multimodal treatment regimens continues. With PDT, anti-VEGF agents and numerous surgical interventions at the

ophthalmologist's disposal, the prognosis for most IPCV patients remains generally good. However, patients with excellent visual outcomes, as in our case, should be continually monitored for pigment epithelial hyperplasia, atrophic degeneration and subretinal fibrosis.[15] REVIEW

The authors would like to thank Joseph Maguire, MD, of the Wills Retina Service for his time and assistance in preparing this case report.

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too onerous to make a living and have a practice, given all the regulations and shrinking reimbursements they have to deal with. Now they're more anxious to become part of hospital networks.

"The question is, will this happen to ophthalmology practices?" he continues. "Will we see a trend of ophthalmologists selling their practices to health-care systems, hospitals and accountable care organizations? And if so, what will this mean for our field? Can general ophthalmologists stay in practice under these conditions? And even if they could stay in practice, would they want to?"

Dr. Blecher notes it's difficult to predict where the pressures on comprehensive ophthalmologists—and the field as a whole—are going to lead. "The situation may slowly evolve, with some ophthalmologists surviving and becoming part of the next version of delivering health care, whatever that turns out to be," he says. "Or the health care delivery system will hit a crisis and collapse and have to be rebuilt from the ground up. When a system is being pushed so hard from so many directions, it really could collapse, at least in certain areas. I think there's a chance of that."

Dr. Grayson believes that if there is a role for the comprehensive ophthalmologist in the future, it won't be in urban areas. "The only place it makes sense to do a little of everything is in a part of the country where there really are no specialists available," he says. "Even in that situation, some patients will need to be seen by a specialist, whether it's convenient or not. So I think there will still be a role for a comprehensive ophthalmologist in this country, but you'll have to know your limitations. In metropolitan areas, I think the future will be consolidation into large groups, including hospital-based groups."

Still in the Game

Despite all of the obstacles, Dr. Gossage says he believes there's still room for a comprehensive ophthalmologist. "I think there's a lot of pressure to specialize, though," he says, "including pressure from outside insurance carriers and from some super-subspecialists, saying general ophthalmologists shouldn't be doing some particular procedure; only they should be offering it. The reality is that traveling an hour and a half to get intravitreal injections is very inconvenient for a lot of elderly patients when those injections can be done locally by a general ophthalmologist such as myself. And I feel perfectly comfortable doing them. I did my first intravitreal injection the day after Macugen became available in 2004. We'd previously been giving steroid injections, so when anti-VEGF injections appeared it made sense for our patients to be locally treated.

"Of course, I do refer to retina specialists," he adds. "We often share patients. If there's something that doesn't seem normal for a specific disease process, I'll send the patient to the retina specialist. And the retina folks often send patients back to me to continue treatment, because my practice is much closer to the patients and they don't have to travel so far."

Despite all the pressures currently affecting comprehensive ophthalmologists, Dr. Gossage is still happy to be in that category. "You have to understand that this is what I wanted to do," he says. "This is what I love, and I want to continue doing it. Yes, over time it has become harder and more of a burden, but factors such as government reimbursement issues are being addressed every year with the help of advocates from the American Academy of Ophthalmology and other organizations. I used to participate in that myself. So I'm hopeful that many of these issues will be resolved in our favor." REVIEW

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