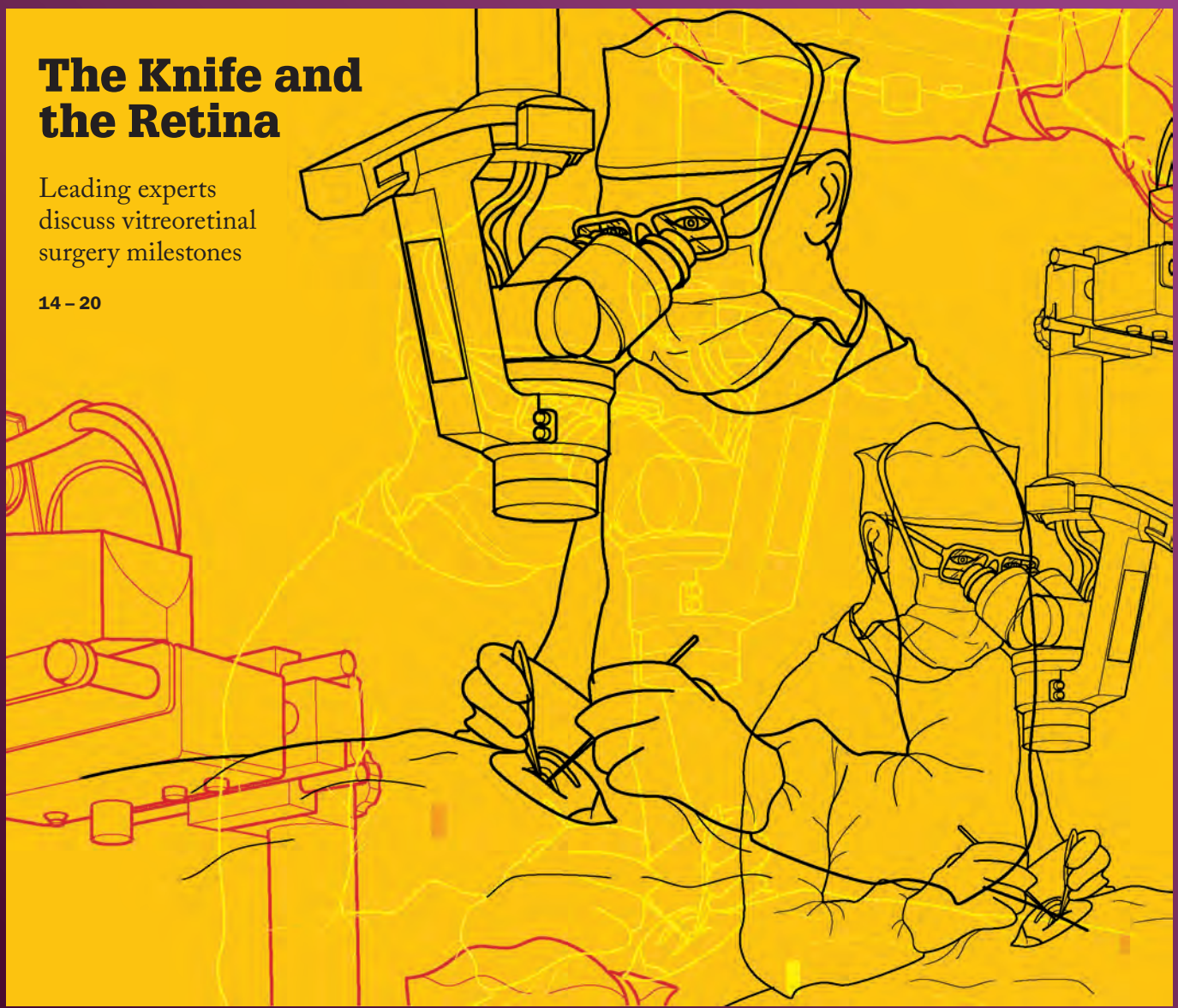
NOVEMBER 2020 # 49

the Ophthalmologist™



The Knife and the Retina

Leading experts discuss vitreoretinal surgery milestones

14 – 20

Alcon

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CAUTION: Federal (USA) law restricts this device to the sale by or on the order of a physician. **INDICATIONS:** The AcrySof® IQ PanOptix® Trifocal IOLs include AcrySof® IQ PanOptix® and AcrySof® IQ PanOptix® Toric IOLs and are indicated for primary implantation in the capsular bag in the posterior chamber of the eye for the visual correction of aphakia in adult patients, with less than 1 diopter of pre-existing corneal astigmatism, in whom a cataractous lens has been removed. The lens mitigates the effects of presbyopia by providing improved intermediate and near visual acuity, while maintaining comparable distance visual acuity with a reduced need for eyeglasses, compared to a monofocal IOL. In addition, the AcrySof® IQ PanOptix® Toric Trifocal IOL is indicated for the reduction of residual refractive astigmatism. **WARNINGS/PRECAUTIONS:** Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting a lens in a patient with any of the conditions described in the Directions for Use labeling. Physicians should target emmetropia and ensure that IOL centration is achieved. For the AcrySof® IQ PanOptix® Toric Trifocal IOL, the lens should not be implanted if the posterior capsule is ruptured, if the zonules are damaged or if a primary posterior capsulotomy is planned. Rotation can reduce astigmatic correction. If necessary, lens repositioning should occur as early as possible prior to lens encapsulation. Some visual effects may be expected due to the superposition of focused and unfocused multiple images. These may include some perceptions of halos or starbursts, as well as other visual symptoms. As with other multifocal IOLs, there is a possibility that visual symptoms may be significant enough that the patient will request explant of the multifocal IOL. A reduction in contrast sensitivity as compared to a monofocal IOL may be experienced by some patients and may be more prevalent in low lighting conditions. Therefore, patients implanted with multifocal IOLs should exercise caution when driving at night or in poor visibility conditions. Patients should be advised that unexpected outcomes could lead to continued spectacle dependence or the need for secondary surgical intervention (e.g., intraocular lens replacement or repositioning). As with other multifocal IOLs, patients may need glasses when reading small print or looking at small objects. Posterior capsule opacification (PCO) may significantly affect the vision of patients with multifocal IOLs sooner in its progression than patients with monofocal IOLs. Prior to surgery, physicians should provide prospective patients with a copy of the Patient Information Brochure, available from Alcon, informing them of possible risks and benefits associated with the AcrySof® IQ PanOptix® Trifocal IOLs. **ATTENTION:** Reference the Directions for Use labeling for each IOL for a complete listing of indications, warnings and precautions.

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the Ophthalmologist®

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On Kindness

We remember a giant of ophthalmology, Alan S. Crandall

On October 2, 2020, renowned surgeon and humanitarian Alan S. Crandall passed away following a sudden illness. Born June 13, 1947, Crandall graduated from the University of Utah School of Medicine in 1973. Over the course of his career, he focused on glaucoma, cataract, and complex anterior segment surgery and was involved in clinical research studies and the training of hundreds of surgeons worldwide.

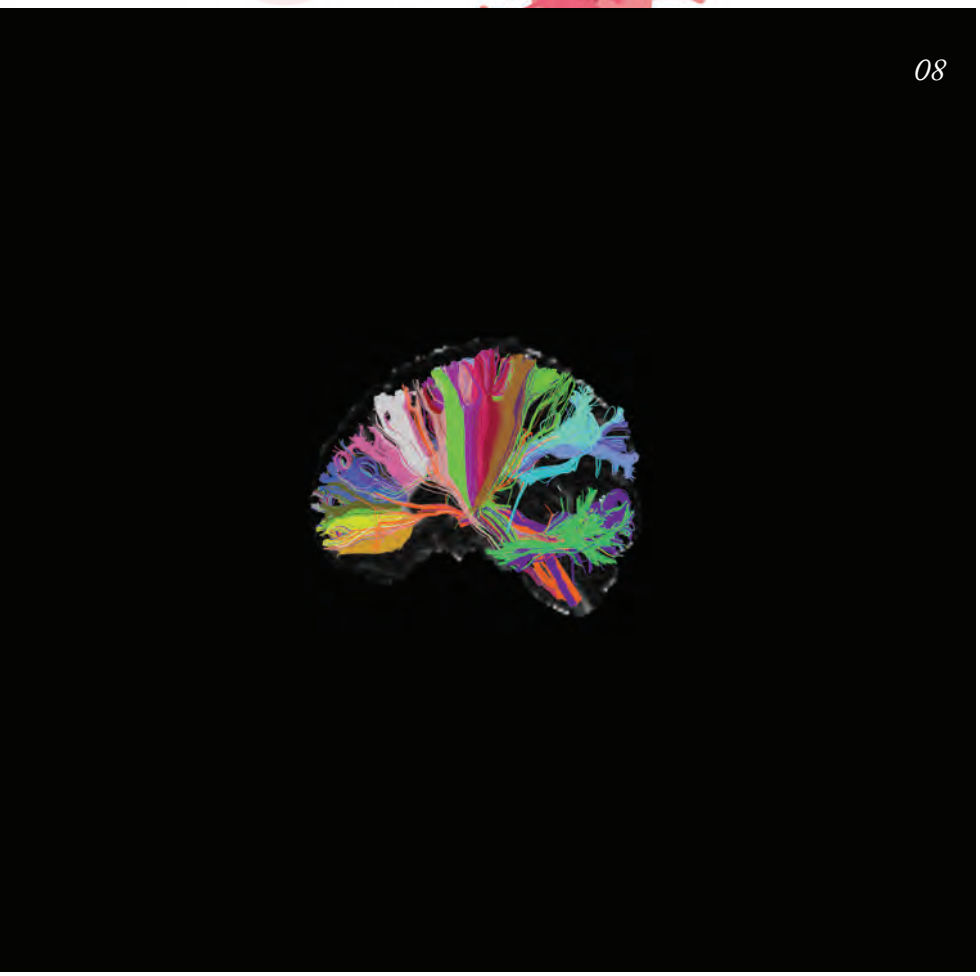
The Ophthalmologist had the pleasure of interviewing Crandall in 2018. When asked what drives his work in developing countries, he answered: "I have always been passionate about helping others. When you fix somebody's eyes in the developing world, you free up two people: the blind person and their caregiver. It makes a massive difference in those countries, and I think it will benefit the developed world too, eventually. It's like the concept of a butterfly's wings starting a wind that goes far; I believe that kindness to individuals ultimately helps society as a whole." The desire to help others is what made Crandall special – and it is his kindness that will be remembered by the ophthalmic community.

We spoke to Crandall again in April to tell him he'd been included in our 2020 Power List; we asked for a piece of advice he would give to himself in his younger days: "Enjoy what you do, look for ways to improve your outcomes, and treat everyone like they are family." I think the latter point shows us all a path towards becoming kinder human beings.

You can find our memoriam to Crandall, with tributes from members of our community, on page 10 and online, at top.txp.to/on-kindness. We encourage you to share your own memories in the comments.

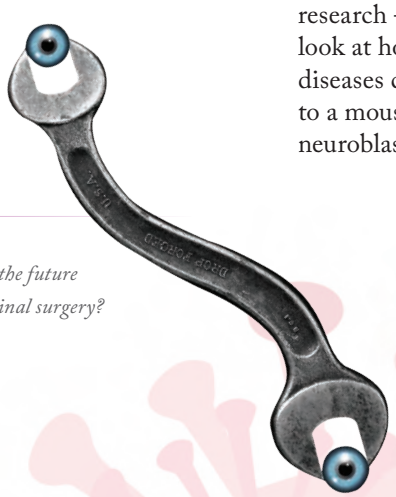
Phoebe Harkin
Deputy Editor

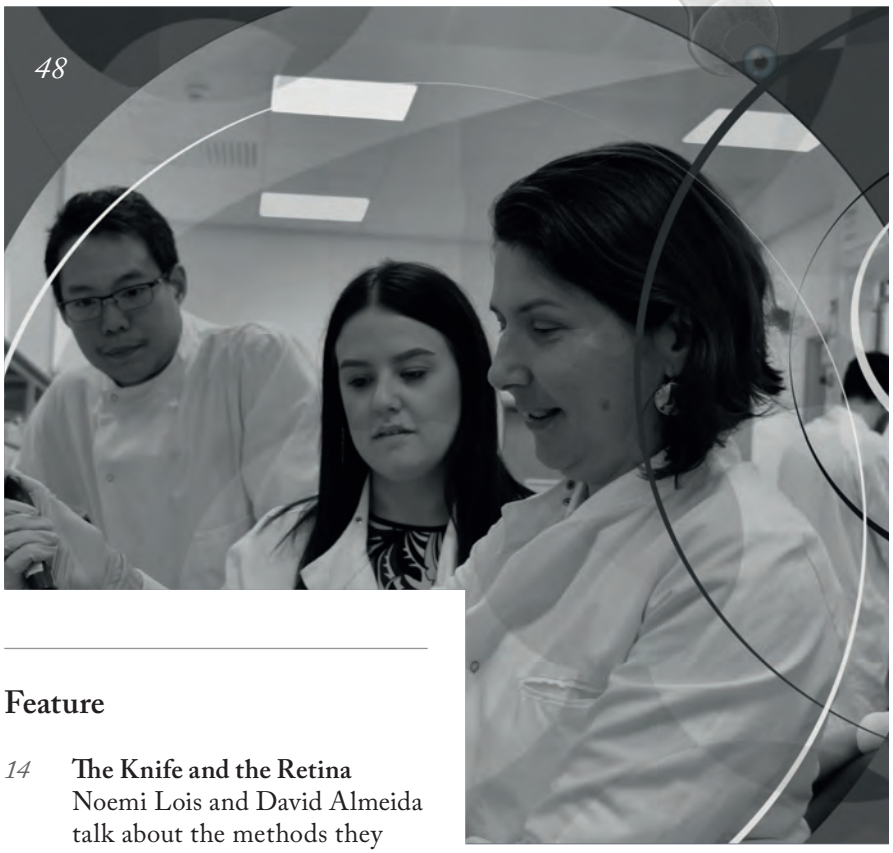
Contents



On The Cover

What does the future hold for retinal surgery?





Feature

In Practice

NextGen

Sitting Down With

the Ophthalmologist

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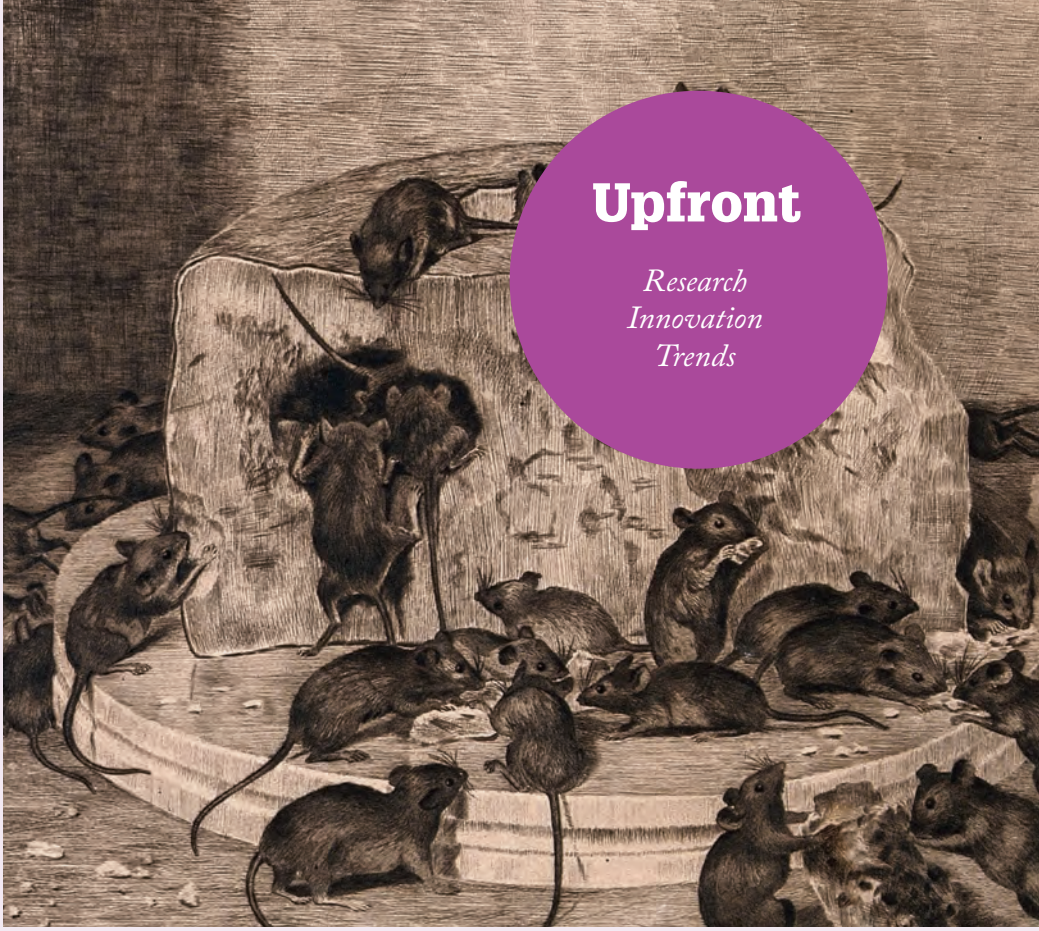

Credit: Robert Hicks, 1888. Courtesy of the Wellcome Collection.

Early Promise

The latest studies in vision science research – from treating retinoblastoma to developing therapies for retinopathy

Scientists from the Oklahoma Medical Research Foundation (OMRF) in Oklahoma City, have been studying the development of blood vessels, including one set that regresses and disappears in murine eyes after birth. The researchers discovered that down-regulation of a specific class of proteins called ETS transcription factors was responsible for this natural blood vessel loss in the eye. A compound called YK-4-279 acts as an inhibitor of these ETS transcription factors and appeared to be particularly effective in low-flow vessels. The researchers decided to test the effectiveness of YK-4-279 in an oxygen-induced retinopathy mouse model that mimics human disease (including diabetic retinopathy and retinopathy of prematurity) and found: i) YK-4-279 reduced the abnormal neovascular tufts associated with the model and ii) the compound did not appear to affect healthy retinal vessels. Together, these discoveries point to the therapeutic potential of ETS transcription factor inhibitors (1).

Meanwhile, researchers at the University of North Carolina Lineberger Comprehensive Cancer Care Center in Chapel Hill, implanted mice with retinoblastoma tissue to test a new treatment using CAR-T cells (ganglioside GD2-specific lymphocytes – GD2.CAR-Ts) injected into the retina. The result: delayed tumor development. They then combined the CAR-T cells with an immune-boosting interleukin (IL)-15 protein in a water-based gel, which was injected into the retinas of the mice, and found that the majority of treated mice remained tumor-free for up to 70 days. The therapy is currently being used in clinical trials for pediatric neuroblastoma, and the researchers are hoping to see further trials looking at the therapy's efficacy in retinoblastoma (2).

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1. *CM Schafer et al., Proc Natl Acad Sci USA, [Online ahead of print] (2020). PMID: 33020273.*
2. *K Wang et al., Nature Cancer, 1, 990 (2020).*

INFOGRAPHIC

Is #HopeInSight?

Johnson & Johnson Vision release results of their global eye health survey in time for World Sight Day

80%

of adults surveyed said they view an **eye exam** as **important** for their overall health.

46%

of respondents said they actually get an **EYE EXAM EACH YEAR.**

BUSINESS IN BRIEF

The latest industry news – in 60 words or less

- Samsung Bioepis and Biogen, Inc., announced that the European Medicines Agency has accepted for review its Marketing Authorisation Application for SB11. If approved, the drug – a proposed biosimilar for ranibizumab (Lucentis) – will join a growing number of biosimilars developed by Samsung Bioepis and commercialized by Biogen.
- The oldest optical organization in the world, The Worshipful Company of Spectacle Makers, has launched a new nonprofit, The Spectacle Makers' Charity. This initiative combines two previous grant-giving trusts, one promoting support for optical education and the other for organizations helping vision-impaired people. They have previously given over £70,000 a year to students, trainee ophthalmologists, and charities worldwide.
- At Euretina, Oculis presented positive results from its Phase II trial of OCS-01 in patients with DME. The study met its pre-specified efficacy endpoints, showing that OCS-01 eye drops were more effective than vehicle in reducing central macular thickness and improving visual acuity. No adverse side effects were observed.
- The IAPB has announced a record-breaking number of Eye Health Heroes to mark World Sight Day 2020. The 52 heroes hail from 27 countries and have been praised by IAPB Global Ambassador, HRH The Countess of Wessex, for their work on the frontline, "adapting to deliver vital services and support the response to this global pandemic."

- Jena-based medical technology manufacturer Imedos Systems GmbH has entered a new partnership with Aifei Electronic Technology Co., Ltd. The company now distributes RCrodent systems, which enabling contactless retinal imaging and vessel analysis in particularly small eyes (such as rodents and small animals), paving the way for lab-based research projects.

Credit: The Night Watch by Rembrandt van Rijn, the Rijksmuseum, Amsterdam, The Netherlands.

The Night Watch

Understanding retinal adaptation in photoreceptor degenerative diseases could inspire future treatments

The findings of a recent study of retinitis pigmentosa in mice could be useful in explaining why patients suffering from retinal disorders might be able to maintain their night vision. The possible mechanism? Homeostatic plasticity – when second-order neurons in the retina maintain their function even as rod photoreceptor degeneration continues.

Researchers from the University of California in Irvine and the University of Utah in Salt Lake City, USA, used whole-retina RNA sequencing, electrophysiology, and behavioral experiments to show that degeneration of rod photoreceptors causes changes to the retina at the genome level. It also increases electrical signaling between rod receptors and rod bipolar cells. An improved understanding of homeostatic plasticity of the inner retina could inform future treatments.

Reference

1. *H Leinonen et al., Elife [Online ahead of print] (2020). PMID: 32960171.*

The most **COMMON REASON** for skipping an eye exam is their **VISION HADN'T CHANGED (32 PERCENT)**.

25 percent of respondents were aware an eye exam could help detect **DIABETES**
10 percent knew it could detect **CARDIOVASCULAR DISEASE** and **9 percent** knew it could detect **CANCER**

47 percent of people surveyed believed they could prevent their eyesight from **DETERIORATING**; **46 percent** believed vision loss was an inevitable **PART OF AGING.**

Reference

1. *Prioritize Your Eyes Global Eye Health Survey (2020). Available at: https://bit.ly/3nWTpqf.*

A Life Well Lived

Celebrating the legacy of Alan S. Crandall

Figure: Alan Crandall, painted by Nilma Pacini Werner, pictured with Liliana Werner and Julie Crandall.

Alan S. Crandall was more than a masterful surgeon; he was a tireless humanitarian, a trusted teacher, and a much-loved friend. His career, spanning four decades at the John A. Moran Eye Center alone, was unique in both its reach and its impact. He is notably the only physician to have received four internationally recognized awards for his humanitarian contributions: the American Glaucoma Society Humanitarian Award, the AAO Humanitarian Award, the ASCRS Humanitarian Award, and the inaugural ASCRS Foundation Chang Humanitarian Award.

As the founder and Senior Medical Director of Moran's Global Outreach Division, Crandall worked tirelessly to not only increase access to eye care in developing countries, but also help those who could not afford care in his own community in Utah.

Robert H. Osher, Professor of Ophthalmology, University of Cincinnati College of Medicine and Medical Director Emeritus, Cincinnati Eye Institute, USA, remembers Crandall. "I was fortunate to have been close with Alan for four decades. Our friendship began in the early 1980s, when he was one of the original faculty of the Video Symposium, along with Dick Lindstrom, Roger Steinert, Sam Masket, and Doug Koch. Although he was the quiet one in the group, he was always the most experienced. A gifted surgeon, Alan traveled the world sharing his expertise with surgeons on every continent. He was also a bona fide innovator – the glaucoma surgeon who first adopted small incision cataract surgery. And his support for his younger colleagues, like Ike Ahmed and Bob Cionni, was truly inspiring.

Out of the operating room, Alan was an excellent athlete and fitness enthusiast. He was also a genuine humanitarian who willingly gave his time to help countless patients in developing countries recover or preserve sight. Yet despite his celebrity status, Alan was humble and approachable. He would stay long after our courses had ended, patiently answering question after question until the last attendee was satisfied. Alan was warm, kind, selfless, and a man of total integrity. He was a consummate gentleman, an ambassador, and a man good to the core. I will miss teaching and laughing with Alan. I will miss his friendship, his smile, his grace. Ophthalmology has lost one of our most respected and treasured colleagues."

Liliana Werner, Professor of Ophthalmology and Visual Sciences and Co-Director, Intermountain Ocular Research Center at John A. Moran Eye Center, comments, "In 2014, I had the great honor to present Alan and Julie Crandall with a painting by my mother, Nilma Pacini Werner, based on a photograph taken during an outreach trip to South Sudan. To me, this image shows the person Alan was. He always supported me professionally, he was someone I could call a friend, and I will simply miss him! It is a great loss for his family and for many around the world who had the opportunity to interact with him."

So Long, Lazy Eye

Is subanesthetic ketamine the cure for amblyopia?

There has long been evidence that subanesthetic ketamine, commonly used to treat depression and pain, may control how the nervous system makes structural changes in response to internal and external demands – a process known as neural plasticity. But how the drug works has remained elusive… until now. Researchers at the University of California, Irvine School of Medicine have demonstrated how a single dose of the drug can reactivate adult visual cortical plasticity and promote functional recovery of visual acuity defects – specifically amblyopia. "Our research team showed that ketamine downregulates NRG1 expression in PV inhibitory cells, resulting in sustained cortical disinhibition to enhance cortical plasticity in adult visual cortex," said Steven F. Grieco, a postdoctoral scholar and lead author of the study (1). "Through this neural plasticity-based mechanism, ketamine mediated functional recovery from adult amblyopia." The lab intends to continue further testing to determine the full implications of this discovery.

References

1. *UCI School of Medicine (2020). Available at: https://bit.ly/3iwtBxb.*

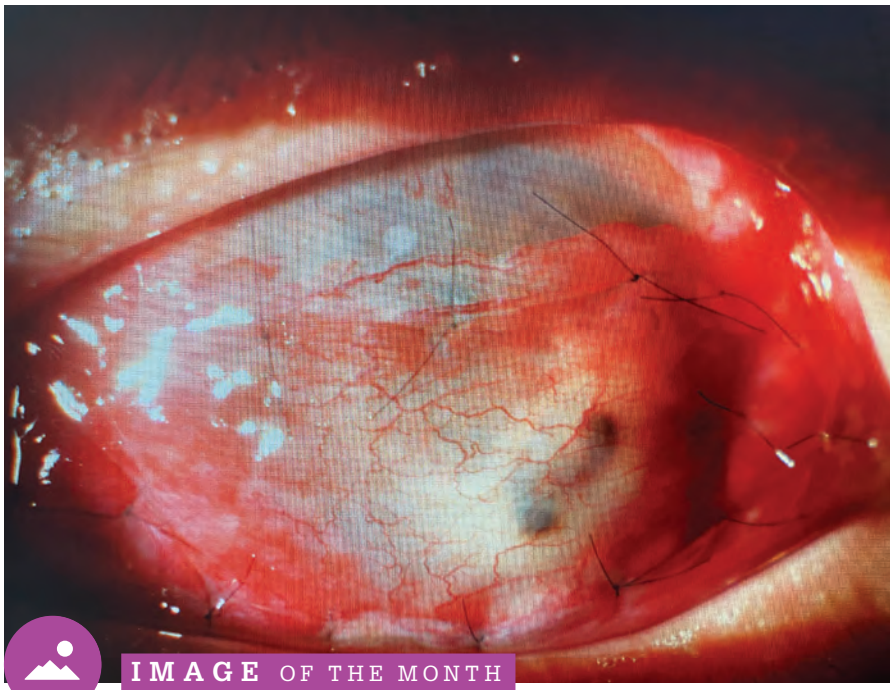

IMAGE OF THE MONTH

Under the Hood

This month's image shows Gundersen conjunctival hooding flap (partial) in an impending perforated corneal ulcer.

Credit: Channdarith Kith, Resident of Ophthalmology, University of Health Sciences, Cambodia.

Would you like your photo featured in Image of the Month? Send it to edit@theophthalmologist.com

QUOTE OF THE MONTH

"Retinal pigment epithelium is a fascinating tissue – and you have to be passionate about the tissue you work on! This monolayer of cells at the back of the eye is formed in utero and has to sustain our vision for our entire lives."

Luminita Paraoan, Department of Eye and Vision Science at the University of Liverpool, UK. Read more on page 48.

Figure 1. A 2D pathoconnectome image shows rod bipolar cell dendrites and their synapse locations with rod (red), cone (blue), and indeterminate (yellow) photoreceptors. Credit: John A. Moran Eye Center.

Live Wires

The pathoconnectome of retinitis pigmentosa shows how neurodegenerative diseases change retinal circuitry

In 2011, the NIH-funded Marclab for Connectomics from the John A. Moran Eye Center at the University of Utah, Salt Lake City, USA, created a diagram of retina circuitry – the retinal connectome for vision, showing how physiology and behavior might reflect synaptic networks and their topologies. The lab then moved on to researching network changes in retinal degeneration, and has recently published a paper presenting the first ultrastructural pathoconnectome of early neurodegeneration (1).

Though the pathoconnectome has been developed based on a model of early-stage retinitis pigmentosa, the neural network changes have implications extending beyond the eye and could be helpful in researching epilepsy, Alzheimer's, Parkinson's and Lou Gehrig's diseases, and even developing potential treatments. The data set used in the project is open for use by other researchers.

Reference

1. *RL Pfeiffer et al., Exp Eye Res, [Online ahead of print] (2020). PMID: 32810483.*

In My View

Experts from across the world share a single strongly held opinion or key idea.

No Magic Bullet

Using your voice shouldn't mean losing your vision – it's time we take a stand against sight-threatening munitions

By Ravi Goel, Ophthalmic Surgeon, Wills Eye Hospital, Philadelphia, Pennsylvania, USA

The term "rubber bullets" offers a false sense of security when it comes to the eye. A study into the type and severity of ocular and orbital injuries caused by rubber bullets found that orbital fractures are common: "The tissues of the orbit are easily penetrated. If the globe is hit, it is rarely salvageable (1)." Of the 42 patients the researchers assessed, 54 percent had lid or skin lacerations, 40 percent hyphemia, 38 percent ruptured globe, 33 percent orbital fracture, 26 percent retinal damage, and 21 percent retained rubber bullet in or around the orbit. Unfortunately, eye injuries of this kind are becoming increasingly common worldwide.

In 2019, Chilean protests saw Santiago's ophthalmologists treat more than 211 patients in the space of a month with severe eye injuries resulting from non-lethal rounds. Over a third of patients arrived with rubber, metal, or ceramic fragments still lodged in their eyes. Researchers at the University of Chile later conducted an analysis into the pellets and found that 80 percent are composed of denser materials – such as lead – that increase the projectile's velocity, making it as hard as a skateboard wheel (2). Do they still seem safe to you?

In 2016, a wave of protests against Indian military presence in Kashmir saw more than 570 patients report to the region's main government hospital between mid-July and late August alone. That year went on to be remembered as the "year of dead eyes" – and I fear 2020 will be ours (3).

Protests which started in late spring saw the use of rubber bullets as a crowd control and dispersal technique – and the effects were devastating. In a single week of unrest, 12 people were partially blinded – and eight were completely blinded (4). Chicago-based glaucoma specialist Steve Gieser has been posting poignant clinical vignettes of individuals affected by tear gas, rubber bullets, and other projectiles.

What can we do to stop this from happening? We can advise our patients to protect their eyes and seek medical attention in the case of physical or chemical trauma – but the truth is, until the use of these vision threatening instruments is curbed, we will continue to see these kinds of injuries. We have a responsibility as healthcare practitioners to protect our patients – and that means advocating against the use of rubber bullets.

In June, I joined the American Academy of Ophthalmology in asking physicians, public health officials, and the public to condemn this practice by supporting the #NoMoreRubberBullets campaign. The AAO said it best in the statement, "Americans have the right to speak and congregate publicly and should be able to exercise that right without the fear of blindness. You shouldn't have to choose between your vision and your voice (5)." Although nothing has changed (yet), we must continue to make our voices heard.

I realized a long time ago that a critical part of being a physician is being a citizen lobbyist. As ophthalmologists, it is our job to represent the best interests of our patients, whether in the exam room or the statehouse. We cannot let there be another year of dead eyes.

The Department of Ophthalmology at the University of California San Francisco has partnered with the AAO to collect information regarding ocular injuries surrounding civil protests. To add a case to this registry, please use the Google Form below.

bit.ly/340xerb

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3. *The New York Times, "An Epidemic of 'Dead Eyes' in Kashmir as India Uses Pellet Guns on Protesters" (2016). Available at: https://nyti.ms/3lkydsb.*
4. *The Washington Post, "Partially blinded by police" (2020). Available at: https://wapo.st/3nsEUKw.*
5. *AAO, "Nation's Ophthalmologists Condemn Use of Rubber Bullets" (2020). Available at: https://bit.ly/3nocfqc.*

When Nothing Is Normal

What is it like to start a new job in the midst of a pandemic?

By Erin McEachren, Regional Vice President, Europe, Middle East & Africa, Johnson & Johnson Surgical Vision

To say it has been an interesting time to start in my role at Johnson & Johnson Surgical Vision would be an understatement. The process of onboarding in a new place is always going to have its ups and downs, whether it is in person or remote. Nevertheless, even in these difficult times, it has been a thrill to join the company, partly because it is so focused on people. I think we have all been feeling the need to show more empathy, and be more supportive of each other, and the team at J&J Vision has been very warm and welcoming, for which I am very grateful.

Have there been any silver linings to the dark cloud of the pandemic? I truly believe that COVID-19 is making us better leaders. We are letting our guard down and being more human. Seeing our co-workers — via Zoom — in their homes with spouses, kids and pets popping into view — has softened our interactions. It has also given us time to pause travel and spend more time at home with loved ones.

Not having the flow of communication that you achieve from face-to-face interactions has been a challenge for me – it takes longer to build deeper team relationships, but I have been encouraged by watching the willingness of my colleagues to support one another during this time, not just as a new leader of the team, but in working together at a unique time. I have approached this time with gratitude and have learned a great deal. And when I finally get to be in a room with my team, I am going to cherish it!

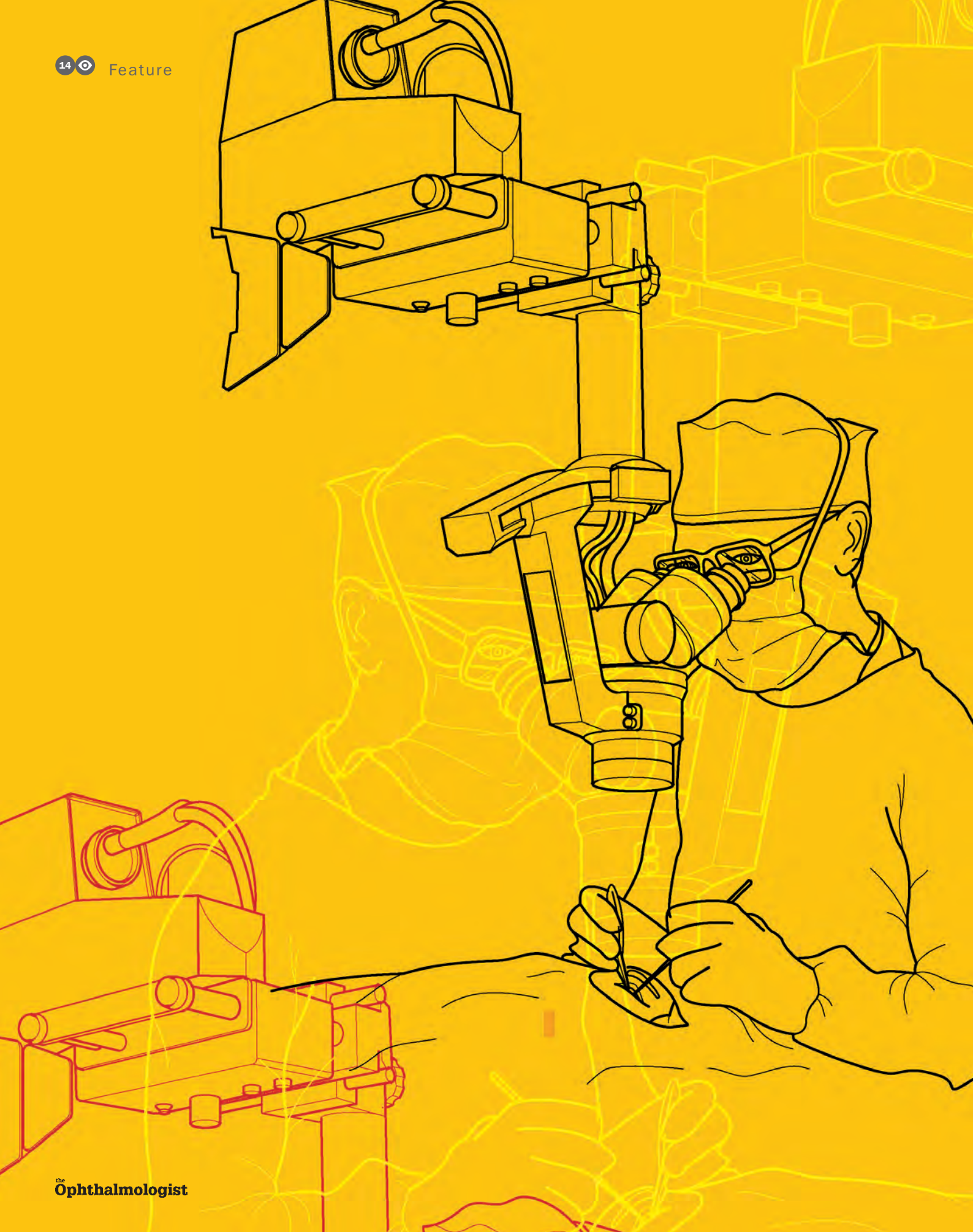
Our industry has been significantly challenged by COVID-19, as our main realm is elective surgery. It has been difficult to witness the dramatic effect this time has had on the elderly cataract population who have had to delay care. As a corporate partner, we have been listening carefully to our customers, as their future has also changed. We are looking at ways to build more efficient business models, using data and digital tools, and enabling stronger partnerships.

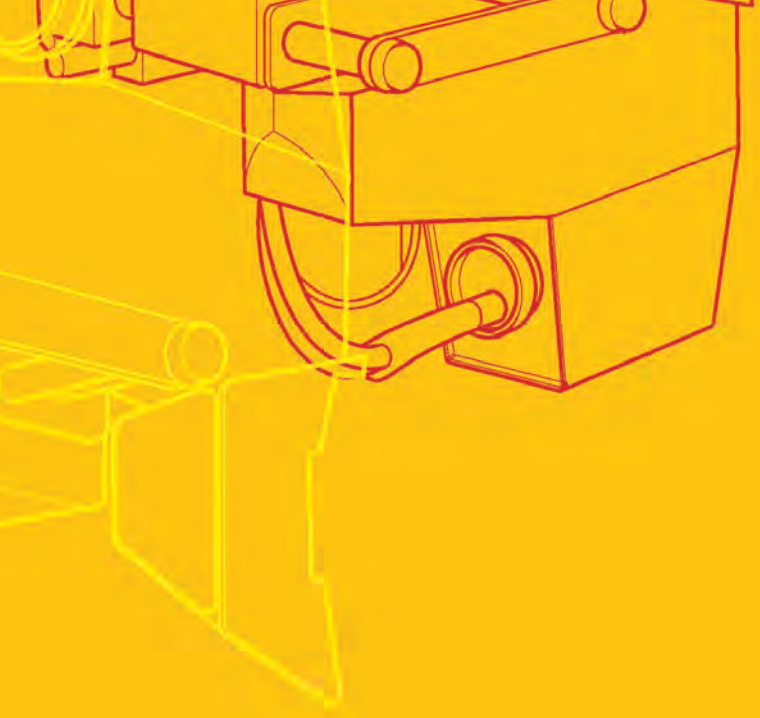
At J&J, our number one goal is to support our customer base and make sure that they can affect patient care. We also want to be bolder, with our sights set on innovation and customer support. We have had some remarkable, game-changing innovations — rare in our device world — in the past year that we've launched in the optical segment. My first launch since joining J&J Vision was at ESCRS recently, where we expanded our TECNIS Synergy range with a new TECNIS Synergy Toric lens. It has been exciting to watch the response of our surgeons who are implanting these advanced IOLs, for example, and the great results that they're achieving. We are always looking to improve as a business partner with ways we can better deliver our services and become easier to communicate with. Long term, we want to be able to have a profound effect on ophthalmic care throughout the stages of a patient's life.

"I have approached this time with gratitude and have learned a great deal."

I have a deeply personal reason for playing a role in a surgical, device-based organization because surgical technology has made a tremendous difference in my own life – I was affected at a young age. Many of us have had a family member undergo a surgery that changed their life for the better. And that's why I am so passionate and why I love healthcare. I am fortunate to not only be a part of a great organization with a powerful credo, but also be a part of the device world. I truly value the opportunity to produce technology that has an impact on people.

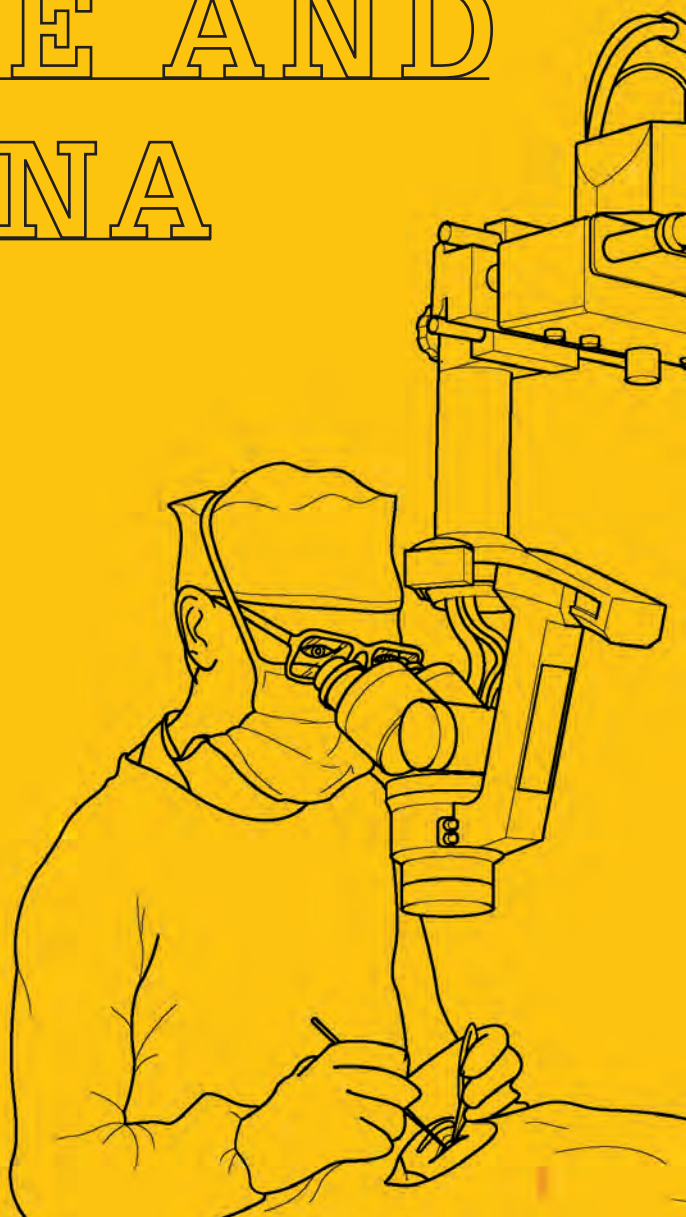
It has been a real privilege to come to J&J during the hard times because there's such a broad range of solutions, between pharma, consumer, and medical devices. In times of crisis, it is great to be part of a stable, large and diverse organization that can and does make a real difference — I think all of us here have gratitude for that. J&J was built for times like this; we are structured to be supportive and serve through challenging circumstances. It is now my role to help lead through these challenges.





THE KNIFE AND THE RETINA

Two leading vitreoretinal surgeons discuss the developments they've seen over the course of their careers, and share their hopes for the future of the field



MEET THE SURGEONS

Noemi Lois is Professor of Ophthalmology, Queen's University in Belfast, Honorary Consultant Ophthalmic and Vitreoretinal Surgeon, The Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK

Route to the Retina: I was lucky to do subspecialty training in vitreoretinal surgery at the Royal Liverpool University Hospital in the UK, with David Wong. He is an outstanding and gifted surgeon: innovative, enthusiastic, very humble, and a fantastic teacher. I am very grateful to him for everything he has taught me.

Before that, I'd done an Ocular Oncology Fellowship at Wills Eye Hospital in Philadelphia (under the direction of Jerry and Carol Shields), and a Medical Retina Fellowship at Moorfields Eye Hospital in London (under the direction of Alan Bird). I was also very lucky to be able to do training in phaco-chopping techniques with an amazing cataract surgeon, Carlos Figueiredo, in São José do Rio Preto, Brazil. This experience helped me with phacovitrectomy – a very efficient surgical approach (when needed), which I very much enjoy doing.

David Almeida is a vitreoretinal eye surgeon and director of clinical research at Erie Retinal Surgery, a retina-only private practice in Erie, Pennsylvania, USA

Route to the Retina: My circuitous route sometimes feels like an adventure race spanning two continents and three countries! I completed medical school and ophthalmology residency at Queen's University in Kingston, Ontario, Canada. Previously, I had finished a PhD in pharmaceutical chemistry at the University of Szeged in Hungary and an MBA in healthcare administration from The George Washington University School of Business. My aim was to blend my skill set and I was lucky enough to join the vitreoretinal service at the University of Iowa in Iowa City, Iowa for a two-year vitreoretinal surgery fellowship. Every day I am grateful for my journey to the retina and for the superb training and genuine friendships I developed along the way.

WHAT DO YOU CONSIDER TO BE THE BIGGEST MILESTONES IN SURGICAL RETINA?

David Almeida: With respect to my career, generally, the introduction of transconjunctival sutureless vitrectomy (1, see box on page 18) accelerated efficiency gains with improved safety. Specifically, macular surgery, with the advent of Kelly and Wendel's work on macular holes (2), provided opportunities for knowledge gains involving surgical approaches to membranectomy.

HOW HAVE RETINAL SURGERY METHODS CHANGED OVER THE COURSE OF YOUR CAREER?

Noemi Lois: During my residency in ophthalmology, contact-viewing systems were widely used and vitrectomy was being done using 20-gauge incisions. When I started my vitreoretinal fellowship, wide-angle viewing systems were in place. These not only allowed for an excellent view of the fundus but also for "independence" – we do not need to rely any longer on an assistant maintaining and moving the contact lens for us, which is an advantage. New techniques were developed and their use became generalized, such as chromovitrectomy (see box on page 19), which greatly facilitates surgical manoeuvers such as internal limiting membrane (ILM) peeling (see box on page 21). The use of ILM peeling was also generalized soon after I became a consultant vitreoretinal surgeon. It is incredible to think we are able to peel this extremely thin layer of the retina!

In recent years, small-bore vitrectomy was introduced. With this transconjunctival trocar system it is now hard to tell which eye has had a procedure even only a day or two following surgery, as there is minimal, if at all, chemosis and inflammation. Patients are very comfortable and the recovery is very fast. It has reduced our time to initiate and finalize the vitrectomy, allowing us to spend more time, if needed, inside the eye, doing the work.

David Almeida: I've enjoyed using valved trocar-cannulas (they provide excellent stability without the need for plugs) and lighted endolaser probes (allow for photocoagulation and scleral depression without an endoilluminator or assistant). Both of these solutions are simple, but they provide significant efficiency improvements; with a lighted endolaser probe, you can scleral depress for yourself and apply the laser at the same time without the need for an additional light source or assistant for scleral depression.

WHAT HAVE BEEN THE BIGGEST DEVELOPMENTS IN THIS FIELD OVER THE LAST FEW YEARS?

David Almeida: Over the last few years we've witnessed a myriad of refinements in vitrectomy for proliferative vitreoretinopathy and endophthalmitis. The challenges in these disease states require unique approaches, such as limbal vitrectomy (trocars placed in the corneal limbus; 5) and chromovitrectomy, which aid in addressing relevant pathology.

WHAT TECHNIQUES DO YOU CURRENTLY USE?

Noemi Lois: I probably use most techniques that are currently around, although I like to see a good evidence base before introducing new techniques to my clinical practice, unless I use them within the context of a research study. The one technique I still do – and which many of us consider to be at "risk of extinction" – is scleral buckling (SB, see box on page 20). I cannot think of anything else more rewarding than doing a scleral buckle for the appropriate retinal detachment. It is cheap and efficient: you can reattach the retina on the same day and, if that is the case, it is very unlikely the retina will detach later on. And the patient can go back to work right away, if needed. For the surgeon, it is fun to do, too.

David Almeida: I use the Alcon Constellation platform with either 25- or 27-gauge valved trocar-cannulas. I prefer the end-grasping ILM-type forceps which facilitate pinch-and-peel membrane removal of epimacular and peripheral membranes. I also use adjuvants like triamcinolone, methotrexate, and foscarnet for complex pathologies.

WHAT ARE THE BIGGEST CONTROVERSIES OR UNCERTAINTIES IN SURGICAL RETINA?

Noemi Lois: There are still many uncertainties. However, our field continues to advance, and we have more evidence with regard to benefits and potential harms of our interventions than other fields of surgery. It is a complex area as there is a great deal of variability among people presenting with vitreoretinal disorders, which represents a challenge when designing randomized controlled trials. Despite this, we have managed to pursue them, and complete them successfully. For example, trials evaluating internal limiting membrane peeling and posturing for the treatment of idiopathic macular hole; trials comparing buckle or vitrectomy with pneumatic retinopexy and comparing buckle with vitrectomy for certain types of rhegmatogenous retinal detachment, just to mention a few. Nevertheless, there is still a great deal of work to do. I think it is essential that we put together our efforts through collaboration to ensure we will be able to address even the not so common problems (such as trauma, giant retinal tears, proliferative vitreoretinopathy).

David Almeida: Although not strictly a controversy, I worry about the decreasing use of scleral buckling – either as a primary technique or combined with vitrectomy – for retinal detachment repair. For some cases (such as young patients, high myopes, absence of posterior vitreous detachment), scleral buckling offers significant advantages. We actually published a "Scleral Buckling 101" article in The Ophthalmologist back in 2018 (6) to highlight case selection and pearls for successfully using the technique. I hope scleral buckling remains a fundamental tenet of vitreoretinal surgical training and remains relevant in the surgical literature.

WHAT ARE THE UNMET NEEDS IN SURGICAL RETINA – AND THE MAIN BARRIERS TO ADDRESSING THEM?

Noemi Lois: Although challenges do remain when it comes to anatomically restoring the retina with surgery in various vitreoretinal conditions, a major challenge we face is to restore function and vision. For many years, I have concentrated on the repair of tractional retinal detachments and the removal of proliferative membranes in people with diabetes. I think this is one of the most challenging problems we face in vitreoretinal surgery today. Here, better intraoperative imaging technologies, including optical coherence tomography, would be very helpful; for example, to better discern planes for delamination. Robotic surgery may also allow improved control of surgical dissections and may provide input with regard to forces being applied to the retina, providing immediate feedback to the surgeon to avoid iatrogenic damage. However, in these cases, the successful removal of membranes and reattachment of the retina does not always equate to improved function and vision. Retinal ischaemia is a major event triggering the proliferation of diabetic membranes, which, through its growth and contraction, lead to tractional retinal detachment. Currently, there is no means to revascularize the retina. At the Wellcome-Wolfson Institute for Experimental Medicine in Northern Ireland, UK, I work with scientists to try to improve our understanding of retinal ischaemia and to develop therapies that may allow retinal blood vessel regeneration.

David Almeida: Implantation of retinal prosthetic devices, pioneered by Humayun and colleagues (11), represents an important advancement in retinal surgery. However, this is limited to a few sites, given the surgical learning curve and technical requirements. I expect there will be additional retina prosthetic devices, along with stem cell products, approved in the future, and these will require further refinements to how vitreoretinal specialists approach surgery.

> "For many years, I have concentrated on the repair of tractional retinal detachments and the removal of proliferative membranes in people with diabetes."

HAVE YOU APPLIED ROBOTICS IN YOUR PRACTICE?

David Almeida: A fascinating question. I do not currently use robotics as a means of executing procedures, but this may change. I foresee a major limitation being the three-dimensional spherical nature of the eye and the unique challenges of working in spaces such as the anterior chamber or posterior segment. I am interested in the concept of robotics employed as surgical assistants, and I envision vitrectomy platforms with robotic components to directly aid retina surgeons with respect to instruments, tamponade agents, and similar aspects of retinal procedures.

TRANSCONJUNCTIVAL SUTURELESS VITRECTOMY SURGERY (TVS)

At the American Academy of Ophthalmology meeting in New Orleans, Louisiana, USA, in 2001 Gildo Y Fujii and colleagues presented a new 25-gauge instrument system for TSV (3). Based on the results of an experimental, comparative interventional in vitro study, they aimed to evaluate the infusion and aspiration rates and operative times of the surgery using 20- and 25-gauge vitrectomy system. They found that using 25-gauge TVS effectively reduced operative times that didn't require full vitrectomy. In 2005, Claus Eckardt argued that 25-gauge instruments were too flexible for many of the complicated retina and vitreous body procedures, and proposed using a 23-gauge system (1).

HOW ABOUT YOUR BIGGEST FRUSTRATIONS AS A RETINA SURGEON?

Noemi Lois: As for any surgeon, I guess it is not being able to help all patients. Not being able to always successfully reattach a retina with a single surgery. Not being able to understand why, for example, despite doing a good vitrectomy and closing all visible retinal breaks or holes, a retina still re-detaches. Frustration is unhelpful, however, so we should ensure we turn "frustration" into "challenge." A challenge is stimulating and will lead us to success.

David Almeida: To avoid a downward spiral, I will say "valuation" of vitreoretinal surgery is a major frustration I have. How retinal surgery is evaluated, remunerated and coded is incongruent with the skill and intensity required. And that creates a disincentive for retina specialists to perform surgery and hinders innovation in new techniques and products.

WHAT EXCITING PROJECTS, RESEARCH OR DEVELOPMENTS ARE YOU FOLLOWING? HOW ARE THEY LIKELY TO CHANGE THE FIELD?

David Almeida: I'm interested in the use of adjuvants to aid vitrectomy for complex pathologies; for example, triamcinolone chromovitrectomy for retinal detachment repair (12), foscarnet for complex retinal detachments secondary to viral retinitis (13), and fibrin glue for optic disc pit maculopathy (14). I believe adjuvants like foscarnet or methotrexate have the ability to significantly mitigate complex pathology that surgery alone may be insufficient for. We are currently working on methotrexate for proliferative vitreoretinopathy.

WHAT DO YOU SEE FOR THE FIELD'S THE FUTURE?

David Almeida: In the short term, I believe we will see further improvements in enhanced surgical visualization along the lines of the Ngenuity 3D Visualization system (Alcon) and intraoperative optical coherence tomography imaging. Moreover, surgically implanted delivery devices for vascular endothelial growth factor inhibitors and surgical approaches for stem cell delivery will provide new insights in how we can modulate the eye to affect different disease states. In the longer term, efforts will continue to be directed at improving the efficiency of retina surgery with respect to operating room design, technology aids, and logistical integration.

WHAT IS YOUR ULTIMATE WISH LIST FOR THE FIELD OF SURGICAL RETINA?

Noemi Lois: The ability to undertake "regenerative" surgery. As I mentioned above, being able to regenerate retinal blood vessels would transform outcomes for people with proliferative vascular disorders, including proliferative diabetic retinopathy. The ability to transplant retinal cells, of any kind, with the goal of regenerating damaged or lost ones is exciting. Induced pluripotent stem cell technology makes this a real possibility, bypassing problems related to the harvesting of cells and rejection. However, whatever we do – and whichever surgical technique we develop – we need to ensure they are easy enough for any trained vitreoretinal surgeon to perform, safe and efficacious and, very importantly, acceptable to patients. Ticking those three boxes would guarantee their implementation in clinical practice and their accessibility to patients.

David Almeida: I have two! First, preservation of robust training programs to ensure ongoing innovation in vitreoretinal surgical techniques and retainment of key procedure skills. Second, productive collaboration on patient needs between surgeons and industry is fundamental to facilitating new surgical approaches (such as stem cell delivery), which I am hoping will flourish.

CHROMOVITRECTOMY

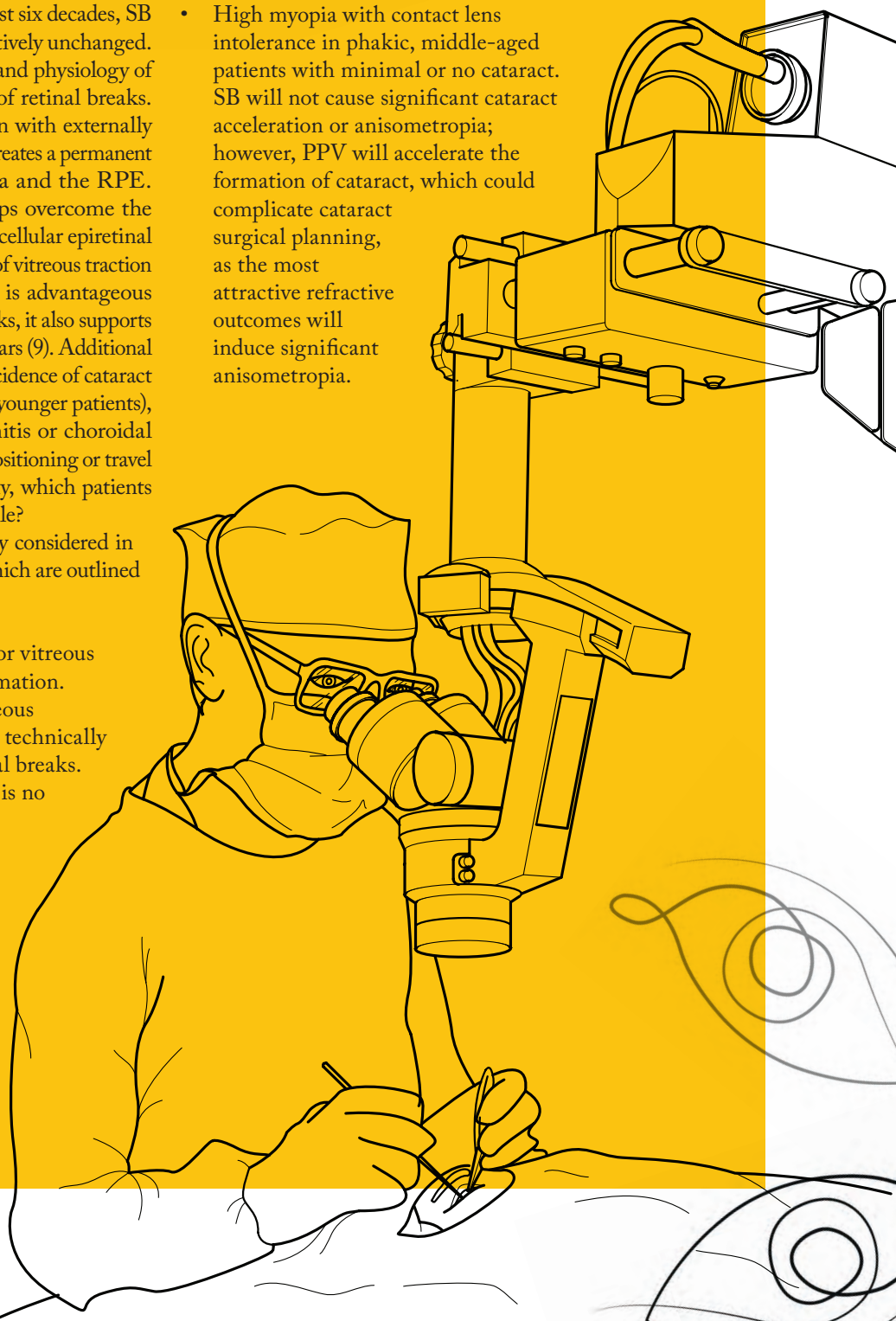
In chromovitrectomy, the vitreoretina specialist uses dyes to better visualize diseases, such as macular holes and macular traction maculopathy, to achieve better postoperative outcomes. Blue and green dyes provide good contrast against the retinal pigment epithelium (RPE) natural color. Indications for chromovitrectomy include pars plana vitrectomy, ILM peek, ERM peel, macular hole repair, retinal detachment repair, and anterior vitrectomy. Dyes are normally injected intravitreally, either following removal of the intravitreal fluid through fluid-gas exchange, or straight into the intravitreal fluid (6).

SCLERAL BUCKLING (7)

Scleral buckling (SB) was first described in 1949 by Ernst Custodis, and was further popularized by Charles Schepens and Harvey Lincoff in the 1950s. Over the past six decades, SB principles and techniques have remained relatively unchanged. The technique favorably alters the geometry and physiology of the eye to help close and maintain closure of retinal breaks. Inward indentation of the eye in conjunction with externally applied cryotherapy or laser photocoagulation creates a permanent adhesion between the neurosensory retina and the RPE. Furthermore, SB-induced indentation helps overcome the forces tending to detach the retina, including cellular epiretinal proliferation and the magnitude and direction of vitreous traction on the neurosensory retina (8). SB surgery is advantageous because, as well as treating existing retinal breaks, it also supports the vitreous base, which prevents new retinal tears (9). Additional advantages of SB over PPV include a lower incidence of cataract (which may help preserve accommodation in younger patients), fewer complications (such as endophthalmitis or choroidal hemorrhage), and no need for post-operative positioning or travel restrictions (10). But in this age of vitrectomy, which patients are best candidates for a primary scleral buckle?

Scleral buckling surgery should be strongly considered in patients presenting with specific scenarios, which are outlined below with our reasoning:

- Young, phakic patients with no posterior vitreous detachment. Why? Avoids cataract formation. Moreover, induction of a posterior vitreous detachment (PVD) during PPV can be technically challenging and create iatrogenic retinal breaks.
- Retinal dialysis. Why? Typically, there is no associated PVD with dialysis. Further, given its anterior location, it can be difficult to visualize and therefore perform adequate vitrectomy in the area of dialysis.
- Very anterior break(s). Again, it is challenging to treat anterior retina with PPV.
- Patients with extensive lattice or multiple retinal breaks at the vitreous base. SB provides 360° support to the vitreous base and peripheral retina thereby preventing future tears.
- High myopia with contact lens intolerance in phakic, middle-aged patients with minimal or no cataract. SB will not cause significant cataract acceleration or anisometropia; however, PPV will accelerate the formation of cataract, which could complicate cataract surgical planning, as the most attractive refractive outcomes will induce significant anisometropia.



"Do not worry about spending time training and working hard to pursue the best possible learning experience. It will be worth it and the benefits will be long lasting."

IF YOU COULD GO BACK AND GIVE YOURSELF ONE PIECE OF ADVICE AT THE START OF YOUR CAREER, WHAT WOULD IT BE?

Noemi Lois: The one I gave myself so many years ago: "Do not worry about spending time training and working hard to pursue the best possible learning experience. It will be worth it and the benefits will be long lasting."

David Almeida: "Never use two steps when one will do!" Economical surgical manoeuvers will not only improve your efficiency in the operating room, it benefits patient safety by minimizing surgical time. Additionally, a focus on eliminating surgical redundancy provides vantage of "pain points" inherent in current surgical approaches and techniques – and that aids innovation (15).

To see the full list of David Almeida's disclosures, visit top.tx.to/the-knife-and-the-retina

INTERNAL LIMITING MEMBRANE (ILM) PEELING (4)

Over the last couple of decades, ILM peeling has become a very common procedure. A combination of new microsurgical instruments and the availability of different dyes to stain the membrane have boosted the performance of ILM peeling, reducing both the time and trauma associated. ILM peeling has been used to treat various retinal pathologies, including full-thickness macular hole, epiretinal membrane, macular edema, vitreomacular traction syndrome, and Terson syndrome. ILM peeling is associated with better anatomical and visual outcomes after retinal surgery for the above conditions.

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COVID-19 and the Ophthalmic Industry

We asked business leaders to open up about their experiences during the pandemic. What operational adjustments did they have to make? How have they helped clinicians get through this crisis? Did they learn any lessons? Here's what they told us.

Charles Holmes
Associate Vice President, Head of Global Marketing, Eyecare

How has Allergan adapted to meet physicians' needs during the pandemic?

Our customers and their patients are our highest priority. When it became apparent that congresses were being canceled, travel between countries restricted or stopped, we knew that it was critical to continue to support the community – eyecare professionals and patient groups – during this unprecedented time. Facilitating the coming together of the community on a virtual level to share learnings, experiences, ideas, and fears was essential. Furthermore, the role of patient groups was becoming more critical than ever as access to care in many countries became restricted due to local regulations.

We proactively reached out to experts, patient groups, and trade media to better understand their needs. We were sensitive to the fact that our community may be impacted personally by the pandemic.

Once we had a good understanding of what the community needed, we conducted carefully timed webinars with content driven by our external experts, we moved quickly to turn our face-to-face meetings into engaging virtual content, and worked with congress organizers to deliver virtual satellite symposia. The timings of those webinars were optimized to allow for work and family commitments in lockdown situations and the content was created to specifically meet the needs of the community.

Are there any silver linings to this dark cloud?

The acceleration of virtual care models or telemedicine has been a positive impact of the pandemic, as has the rapid adoption of virtual meeting technologies for educating a wider group of people. We have also seen many stories of courage, empathy, and generosity over the last few months.

www.allergan.com

Allergan

Jim Mazzo
Member of the Board of Directors

How has the world of ophthalmology changed in the wake of COVID-19?

Physicians have had to adjust to managing patients using telemedicine instead of figuring out ways to get patients into the office – this probably should have happened years ago, but COVID-19 has been the catalyst. Some practices are finding a way to balance this change, reporting more refractive and elective procedures than last year. On the industry side, there is still plenty of innovation and entrepreneurial activity, albeit slowed down or delayed due to lack of funding or inability to conduct clinical studies under lockdown conditions.

How have Avellino's operations changed as a result?

We changed our entire business! Avellino was very excited about bringing AvaGen to the market after our launch event at the 2019 AAO in San Francisco. Just as we were ramping up, COVID-19 shutdowns came all across the USA. We pivoted, using our expertise in molecular testing, and focused on taking the pandemic head on. We designed a test for our own employees and applied for authorization through the FDA, which we received in March. Since then, we have used our Active Coronavirus Testing & Safety (ACTS) program to help clinics and surgery centers implement testing to keep employees and patients safe as they reopened, with detailed step-by-step guidelines. We have also helped first responders, nursing homes, schools, employers, and community screening sites provide testing to those most at risk. We have performed over 350,000 tests since March, and are growing every week. This growth will power our expansion in ophthalmology and R&D work in other genetic diagnostics and therapies.

We will keep working on and providing testing solutions for SARS-CoV-2, until the market opens up and we can relaunch our core genetic testing product, AvaGen – the first genetic test for corneal dystrophy diagnosis and keratoconus risk.

www.avellino.com

AVELLINO

Shervin Korangy
President and CEO

How have you adapted to meet physicians' needs during this period?

We have been doing our part by repurposing our products and redirecting supplies in response to the COVID-19 crisis, including significant donations of PPE to healthcare facilities in some of the hardest-hit areas. Surgical gowns and gloves are a vital part of BVI®'s ophthalmic surgical business and, with the global surge in demand for these items, it is unclear when more supplies can be expected. To help, BVI® partnered with Haywood Vocational Opportunities (HVO) in late spring to provide isolation gowns to US healthcare workers on the front lines of the pandemic. HVO is a US-based medical product manufacturer that provides vocational training and employment opportunities for adults with disadvantages and disabilities. Through outstanding teamwork between the organizations, an isolation gown was designed, tested, manufactured, and released to the market in less than three months, which is unprecedented for a company in the ophthalmic industry.

What further plans do you have in store?

As well as donating to frontline workers, we have quickly adapted to meet customers' needs and continue providing innovative products to ophthalmic surgeons. This means that, when patients return to hospital centers or offices for treatment, they will benefit from an extended range of options to improve their sight and quality of life. Launches included products that support surgical procedures, such as CryoTreq® and IPure®, as well as the US expansion of Malosa® single-use and Patient Packs, which are individually packaged for added patient confidence in returning for routine office visits and check-ups. BVI continues to consistently innovate, adapting to support our customers and their patients in ever-changing circumstances.

www.bvimedical.com

BVI

Warren Foust
Worldwide President, Surgical

What changed for J&J Vision in the wake of COVID-19?

COVID-19 has undoubtedly changed the landscape of 2020, but we were built for times like these. We knew that our industry was hurting – so we mobilized quickly to partner with our customers and their practices. We provided compliant ways to help ease the financial burdens brought on by halting elective procedures, guidance for reopening safely, and educational programs to keep practitioners' skills sharp. We have hosted over 200 hours of professional education projects in the US and trained over 50,000 HCPs worldwide since January, and we will continue this trend post-COVID-19. Our teams created a digital ECP toolkit that includes Reconnect and Rebuild Guide, compiling all the government and trade association guidance available in one place to support successful and safe re-openings.

How have your operations had to change?

At J&J, we are all-in on vision, and we are passionate about changing the trajectory of eye health worldwide. And that hasn't changed. But as we navigated the unique challenges our customers, patients, and own business faced due to the pandemic, we had to reassess our priorities and focus on what we can impact now, while ensuring our long-term focus continues to be shaped by the needs of our customers and their patients. Our near-term focus is on supporting our customers, patients, and employees – safely – throughout all stages of reopening and rebuilding their practices. Our long-term focus right now is on innovation. We have done a lot of listening to make sure we deliver what our customers and their patients need in the future.

www.jjvision.com

Johnson & Johnson VISION

Euan S. Thomson

President of Ophthalmic Devices and Head of the Digital Business Unit of Carl Zeiss Meditec

How has ZEISS adapted to meet physicians' needs in the wake of COVID-19?

The pandemic has been a disruptive force for us globally. We engaged with thousands of customers to understand their challenges and short- and long-term needs. There were some clear themes across the world: extra pressures on surgical procedures, additional sterilization protocols, social distancing between patients and clinicians, and the need to adjust workflows to increase efficiency and improve clinical outcomes.

In response, we launched the "MED Support Now" website to provide resources such as social distancing and remote-care solutions, patient COVID-19 communication packages, guidelines for optimizing diagnostic exams for adapted workflows, personal treatment outcome analysis tools, cleaning and disinfecting guidelines, and we donated over 100,000 breath shields globally. Our professional education team put together more than 270 webinars and other digital formats for continuing education and eLearning.

We have now shifted our focus to providing solution enhancements across the full spectrum of care – from assessment, diagnosis, to treatment.

How have your own operations changed as a result?

We continue to focus on providing technologies and solutions to help address the problems for the physician. We launched workflow solutions for cataract, corneal refractive, retina and glaucoma at ESCRS and introduced our future product FORUM Cloud Viewer, which will provide access to patient data easily and quickly from anywhere to support doctors in delivering better patient care through secure sharing of complex cases with their colleagues. ZEISS will continue to invest in digital solutions to capture and integrate data across clinical workflows to help improve patients' quality of life and drive progress, efficiency and access to quality healthcare.

www.zeiss.com

Jeannette Bankes

President and General Manager, Global Surgical Franchise

How has Alcon adapted to meet physicians' needs during the pandemic?

Early on in the pandemic, we wanted to understand the challenges of our customers, so we listened a lot. We stepped up our efforts to collaborate with industry societies and the medical community as new protocols were developed to safely serve patients. We developed resources needed during this unprecedented time, including virtual customer support, online assets and training, and reimbursement tools for telemedicine, while also raising customer awareness of available government funding mechanisms. Our website is a hub of information resources to help our customers weather this environment and successfully reopen their practices.

How have your operations had to change as a result?

Our immediate focus was on implementing extensive measures to keep our associates safe – whether they be essential employees in our manufacturing and distribution facilities or our office-based associates who worked from home. Throughout this disruption, we found our workforce to be as collaborative as ever – enabling Alcon to continue to innovate and deliver the products that surgeons and their patients need. We adapted our approach to leverage virtual opportunities. For example, to launch Vivity – a first-of-its-kind PC-IOL – throughout Europe, we'll be virtually hosting an array of events with ophthalmologists to generate excitement. We also offer remote account management by our sales and customer service teams in lieu of in-person visits. And our emphasis on digital technology is further exemplified by our commitment to launch the SMART Suite by Alcon – a comprehensive cloud-based platform designed exclusively for ophthalmology to seamlessly connect devices and data systems from the clinic to the OR.

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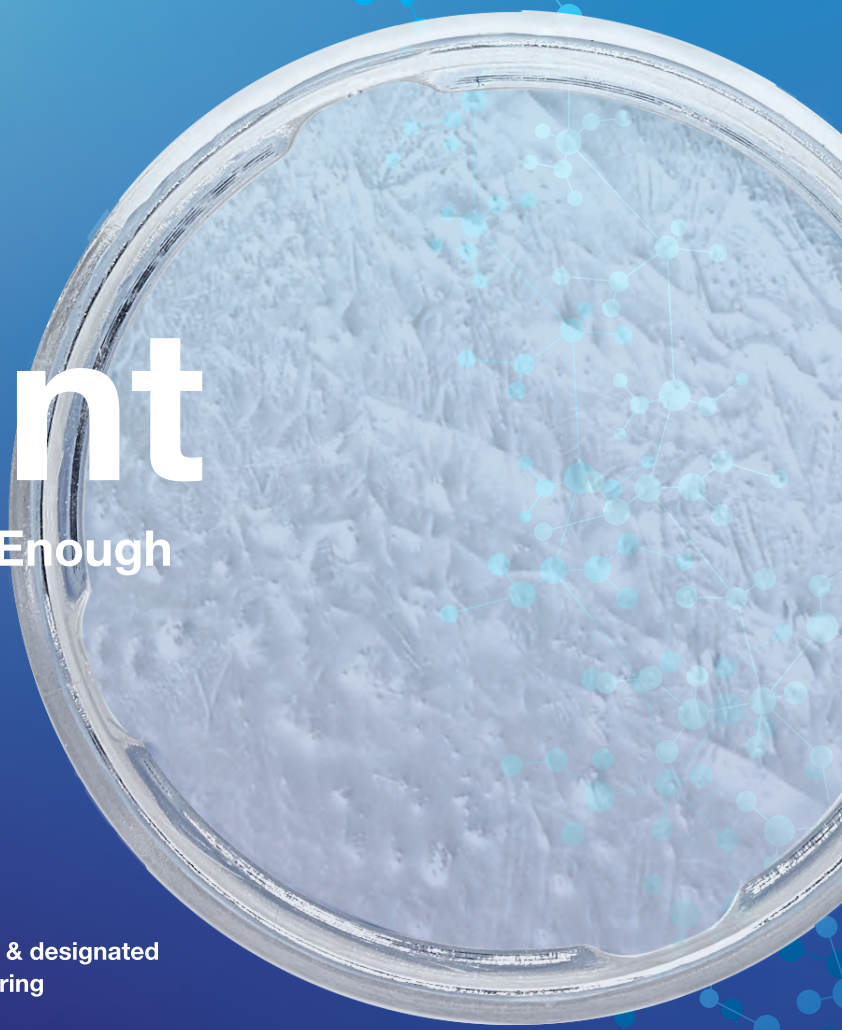

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In Practice

Surgical Procedures
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New Drugs

Safety First

The pandemic has forced physicians to rethink glaucoma treatment – starting with updated tools and protocols for safety-conscious encounters

By Jason Bacharach

Physicians are living in a new reality. Every day, we are being called on to do incredible, creative things in increasingly complex conditions. The situation is evolving in real-time and the impetus is on us to make sound decisions that keep ourselves and our patients safe – all while providing the best possible care. We must do more than simply take precautions; we must find innovative approaches to treatment as well – and glaucoma is no exception.

Challenges to treating right now

Though hospitals and surgical centers are reopening, many continue to experience major backlogs as there is a lack of OR time available for incisional glaucoma treatments. In many locales, equipment is unavailable as resources are being reallocated for emergent care. Patients' fear of COVID-19 exposure also continues to be a major concern, particularly for the elderly and vulnerable. This issue is compounded by many nursing homes and long-term care facilities still being in mandatory lockdown, which prevents patients from getting to the doctor or to the pharmacy.

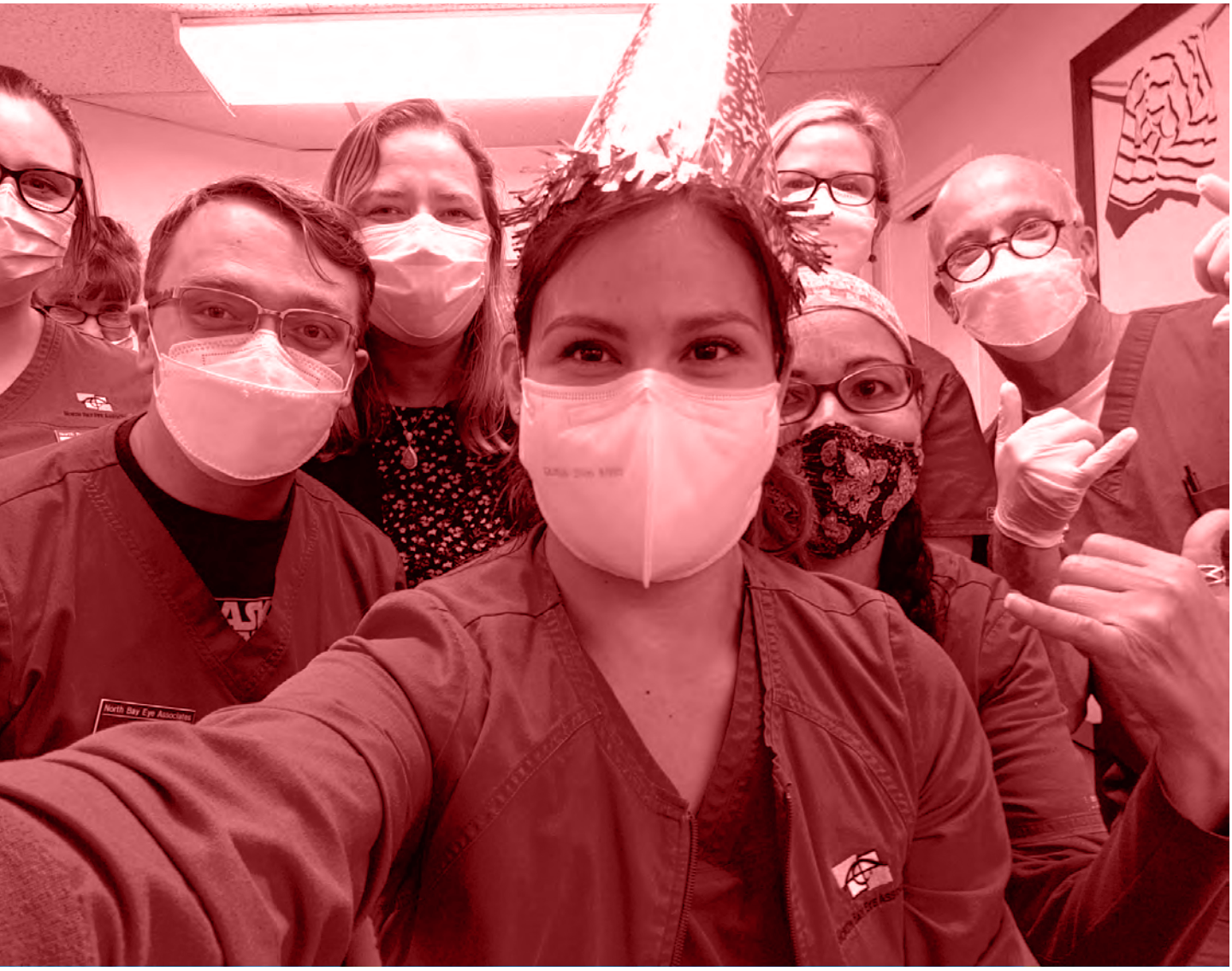
To overcome these challenges, there are a few ideas to consider: implement office-based procedures to move your patient from the OR backlog to the front of the line; choose procedures that are safe and durable with minimal post-op care to reduce follow-up visits; and incorporate new office operating procedures to keep yourself, your staff, your patients and your business safe.

New standard operating procedures (or the "new normal")

Providers have a principal responsibility: not being vectors for disease. Our duty is to help people, not put them at risk. With that in mind, my practice has reimagined everyday logistics and implemented a series of thorough safety protocols.

These new operating procedures begin well before a patient arrives, with intake paperwork, patient history, and pre-screening completed over the phone where possible. Patients are also triaged virtually to see if they have been out of the country or to any hotspots recently, and to make sure they haven't had a fever or exposure to a COVID-19-positive patient. At the time of appointment, a staff member – wearing a face shield and other appropriate PPE – greets the patient at the door with sanitizer and a mask, if one is needed, and a temperature check is performed. Once a patient passes the pre-screening and temperature check, they wait outside (weather permitting) or in their vehicle until they are called to be seen. Check-in, temperature, and IOP checks can be performed car-side as well. Patients only wait inside our waiting room in extenuating

"Patients' fear of COVID-19 exposure also continues to be a major concern, particularly for the elderly and vulnerable."



circumstances. Even then, the waiting room is arranged to allow for proper distancing. It is free of all magazines and print materials, and thoroughly sanitized on a regular basis.

Patient flow within the practice is also optimized for efficiency and linearity. Patients enter through one door and exit through another, creating unidirectional flow. Thinking in a completely different logistical fashion is a big change, but it is critical to the economics of the practice. In the past, we would bring the patient into the exam lane, maybe take some history, then escort the patient to another room for testing and then back to the exam lane to see the doctor. Now, each room the patient visits remains empty until they have been re-sterilized, which requires extra time and labor. Currently, most testing is performed prior to the patient entering the exam lane. This reduces patient movement around the office, contributes to a linear flow, reduces the need for unnecessary sanitation and keeps exam lanes open.

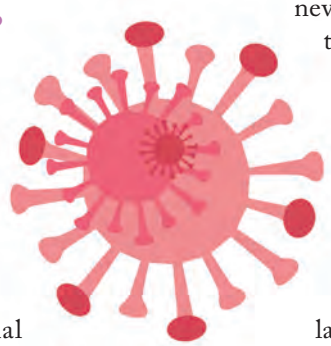
We have also experimented with hybrid models. For example, after a patient is tested and leaves the clinic, I speak to them over the phone to discuss their test results. This combination of tele-health with an in-person component

"As a provider and business owner, it is extremely important to me that my staff, and our patients, feel confident that we're doing everything within our power to protect them."

Fortunately, we have received nothing but positive feedback so far – not a single complaint or negative review – as patients are generally appreciative of the protocol changes to reduce exposure. Once they've experienced the safety precautions we've implemented, they feel extremely gratified and, in many cases, are more inclined to return feeling more comfortable and are less concerned about exposure to COVID-19. As a provider and business owner, it is extremely important to me that my staff, and our patients, feel confident that we're doing everything within our power to protect them.

Rethinking treatment options

After being severely restricted for several months, surgery centers are left with a backlog of cases – it has never been more valuable to have safe and durable treatment options that can be performed in the clinic.



When safety is paramount and when flexibility and durability are key, MicroPulse transscleral laser therapy (TLT) with the MicroPulse P3 Delivery Device (Iridex) is an excellent tool. I've used it in both the office and the surgical center for many years. Many patients, particularly seniors, are scared to come to the hospital or clinics. So, when I tell them I can treat their glaucoma with an efficient procedure that can be performed in the office with no cutting and reduced risk of infection, they are all ears. I make sure they understand that MicroPulse TLT does not decrease the success of subsequent procedures, so it can be considered earlier on the glaucoma continuum. The procedure is quick, and standardized to 100 seconds per eye. The relatively has become very useful for us.

During all face-to-face patient interactions, proper PPE is maintained, as well as some additional precautions. We developed our own shields that fit over the slit lamps as an extra barrier early on in the pandemic. Now, we have switched to commercially available shields that are specifically designed to reduce exposure for slit lamps. We also try to limit conversation as much as possible to prevent any viral transfer during close interactions, with the overall goal of keeping facetime to six minutes or less.

All of these logistical alterations have reduced facetime by 25-30 percent, but the key is to not make patients feel rushed or neglected. We help them understand that these amendments are designed to reduce risk for them and for our staff.

short procedure time allows us to reduce facetime and move patients through the clinic efficiently. More than that, the durability of MicroPulse TLT allows us to push out follow-ups, further reducing face-to-face interaction – a boon in COVID-19 times.

Another benefit of MicroPulse TLT is the reduced impact on activity level after the procedure. We patch the eye and send patients home with a topical steroid; the next morning, they remove the patch and resume normal activities. In these times, patients are understandably reluctant to invest in any procedure that requires a great deal of follow-up or restricts their activity or exercise. With MicroPulse TLT, patient downtime is negligible, requiring minimal in-office follow-ups after the procedure.

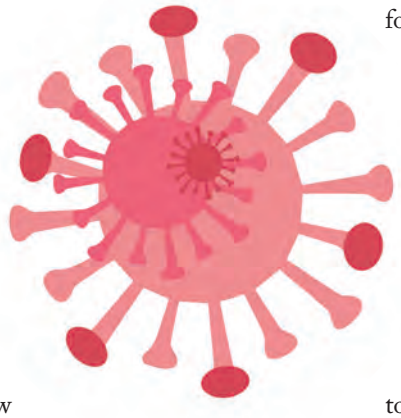
As my understanding and experience with MicroPulse TLT evolves, my patient outcomes have improved, becoming more consistent and predictable. Iridex recently introduced a revised MicroPulse P3 Delivery Device that, in my opinion, offers improved ergonomics, greater stability and better light coupling to the tissue than the original device. I'd say the revised design has reduced the learning curve for quick implementation into practice. Although it may not be right for every patient, it is a useful tool to have in your armamentarium, especially if you have no access or limited access to an ASC.

Online pharmacies and telemedicine

Complete lockdowns are still in effect at many nursing homes and care facilities. Here, telemedicine and online pharmacies help reduce patient burden and unnecessary exposure, especially for high-risk patients. So, we've employed a variety of mechanisms for patients to get their medications directly. Even before COVID-19, we transitioned to a considerable number of mail-order acquisition modalities, rather than making patients go to a brick-and-mortar pharmacy. We've also created new accounts with online pharmacies to reduce the office burden of ensuring patients get their medications directly.

In normal circumstances, we are quite strict about requiring patients to come in for a visit before renewing their glaucoma medication. We like to ensure that a person's IOP is well controlled; however, circumstances have forced us to become more flexible on our rigid posture on refills. Consider a patient who's been stable for several years but is running low on medications

"In addition to expanding to mail-order and online pharmacy options, we have also employed larger bottles where possible or more refills to reduce patient visits to physical pharmacies."



and can't physically come to the office because they are in lockdown. This patient would be an excellent candidate for a telemedicine visit. We schedule a phone or video chat, review their medications, reinforce compliance, and then forward their prescription refill to their local pharmacy or online pharmacy, extending the length between visits.

In addition to expanding to mail-order and online pharmacy options, we have also employed larger bottles where possible or more refills to reduce patient visits to physical pharmacies. We have also sought partnerships with other eye care practitioners who are in closer proximity to the patient for more timely care when needed. Commonly, a comprehensive ophthalmologist or optometrist might have passed a patient on to us so that the totality of glaucoma care could be under our control. Now, we may partner with them to make sure the patient has a local touch point or if they just need a follow-up pressure check or basic testing. Partnerships of this nature have become even more important than ever and will continue to be in the coming months.

Lasting lessons

As the COVID-19 situation gradually subsides, some of these approaches may start to disappear and our practices will gradually return to normal. The telehealth component, however, will most likely stay. It's become an incredibly valuable tool and though it will never fully replace in-person visits, there is certainly a place for it in today's world. So, where does that leave us now? This pandemic has forced us to adapt our practices and protocols in creative ways – for the better. Let us take these new lessons and tools with us into the future, so we may strive to continually evolve and offer our patients the best possible treatment options – and the best possible care.

Jason Bacharach is the Medical Director and Founding Partner at North Bay Eye Associates in Sonoma, California, and Director of the Glaucoma Division at the California Pacific Medical Center in San Francisco, California, USA.

He is a consultant for Iridex.

To (Pre)serve and Protect

How can cryopreserved amniotic membrane help herpetic keratitis patients?

By Marjan Farid

Herpes simplex virus (HSV) can be the most difficult corneal infectious disease to diagnose and manage despite its prevalence: at least 90 percent of the world's population is infected with latent HSV-1 by the age of 60 (1). Herpetic keratitis (HK) is surprisingly common – in fact, it is the leading cause of corneal disease and blindness in humans worldwide (1). HSV keratitis is recurrent and, if not treated effectively and in a timely manner, can result in corneal nerve damage, which could lead to neurotrophic keratopathy with persistent epithelial defects. Untreated HSV keratitis can also contribute to the development of corneal scarring, corneal melting, potential corneal perforation, and permanent vision loss (2).

Clinical diagnosis

The HSV keratitis diagnosis is primarily based on characteristic features of the corneal lesion (3). We're all familiar with the red flags, but a complete ocular history and a thorough slit lamp examination go a long way toward identifying and confirming a herpetic keratitis infection. Patients with epithelial herpetic keratitis may complain of pain, photophobia, blurred vision, tearing, and redness. The earliest sign of active disease is the development of small, raised, clear vesicular lesions on the cornea that will often stain with Rose Bengal. Dendritic ulcers are actually the most common presentation of herpetic keratitis. Prominent features of a dendritic ulcer include a linear branching pattern with terminal bulbs at the ends of the branches, swollen epithelial borders of the branches and central ulceration through the basement membrane. Fluorescein and Rose Bengal staining can aid in visualization of epithelial dendriform lesions with stippling of terminal endbulbs typical for HSV keratitis (4). Subbasal corneal nerves are also a telltale sign of HSV keratitis (5).

Recurrent disease

Though it's true that most people have a herpes virus in their system at some point in their life, the number of those in whom it manifests and becomes symptomatic is much smaller. Those are the people we see coming in with recurrent herpetic keratitis of the eye. In a lot of these cases, when patients have their first ocular outbreak, they don't know what's happening. Often times they'll present at optometry or general ophthalmology practices, but in cases where it becomes a recurrent issue for the patient, they often get referred to a cornea specialist. It's a common enough occurrence that general ophthalmologists encounter it frequently; however, in a tertiary care referral cornea practice like mine, I always have a sizable percentage of patients who have herpetic keratitis.

There are patients who will have only one or two episodes of HSV keratitis throughout their life, but a large percentage of patients will have recurrent disease. During periods of stress, or if the eye undergoes surgical intervention, for instance, the virus might make a return

appearance. Recurrent disease can cause scarring to settle in. Most cases resolve spontaneously within three weeks but, if not treated early, can go on to have irreversible subepithelial haze and scarring. In those that persist, the rationale for treatment is to minimize scarring and neovascularization, which are more common in recurrent disease.

Treatment options

Adequate prophylaxis and timely treatment are crucial to prevent corneal nerve damage, neurotrophic keratopathy, corneal scarring, corneal melting, corneal perforation, and vision loss (2). Gentle epithelial debridement may be performed to remove infectious virus and viral antigens that may induce stromal keratitis; antiviral therapy – topical or oral – can be effective treatments as well (6). The first effective drug used for HSV keratitis was idoxuridine (a pyrimidine analogue) way back in 1962 (7). Since then, the treatment options have primarily been a variety of nucleoside analogues and DNA-synthesis inhibitors (8).

The conventional drugs of choice for HK treatment tend to be acyclovir (ACV) and gancyclovir (GCV), which are nucleoside analogues and, less frequently, foscarnet (FOS) and cidofovir, which are DNA-synthesis inhibitors. These treatments, along with corticosteroids, have resulted in a significant reduction of HSV-induced corneal blindness (9).

The older, more traditional antiviral known as Viroptic (trifluridine) kills the active replication of the virus when it is on the surface of the eye, but it also wreaks havoc on the ocular surface, which can cause significant limbal stem cell deficiency. What's more, preservatives in the drop can cause a significant epitheliopathy of the surface of the eye; in short, the cure is almost worse than the disease. Clinicians often start the patient on trifluridine and then continue it for too long, which is one of the reasons why we see a lot of the secondary side effects occur on the ocular surface.

Now we have better topical antivirals; for example, Zirgan (ganciclovir ophthalmic gel 0.15%, Bausch & Lomb), a gel used five times a day – but even that should be used for a limited time. It is effective at stopping viral replication on the surface of the cornea and is usually not needed any longer than two weeks. Beyond two weeks, it too can cause epitheliopathy, punctate keratitis, and ocular surface disease.

Conventional therapy includes treatment of the viral infection, which may be followed by topical steroids and other methods to heal the cornea. But there are limitations to this regimen; for instance, topical steroids may enhance viral replication and delay resolution in epithelial HK (10).

Biological healing

Cryopreserved amniotic membrane (CAM) is an innovative solution that I've come to rely on with great success for many of my herpetic keratitis patients.

Several amniotic membrane options are available for ophthalmic purposes, including Prokera (BioTissue), AmbioDisk (Katena), and BioDOptix (Integra LifeSciences). AmbioDisk is a processed, dehydrated amniotic allograft intended for overlay use on the ocular surface. BioDOptix is also a dehydrated allograft, and its dehydration is facilitated via DryFlex, a proprietary process that preserves the amniotic tissue's

Infectious keratitis and CAM treatment pearls

- Many epithelial herpetic infectious keratitis patients are good candidates for CAM.
- Use CAM as soon as possible after identifying the infectious keratitis and initiating anti-microbial therapy, particularly when it is associated with significant inflammation.
- CAM can be used on an active viral infection because of its anti-microbial properties and because the infection can be monitored with fluorescein through the AM.
- CAM may warrant replacement if it turns from translucent to opaque or partially or completely dissolves in highly inflammatory cases.
- In patients with suspected protozoan or fungal keratitis, consider the use of CAM only after a diagnosis can be confirmed by culture, Gram stain, confocal microscopy or after a response to topical therapy is observed.

"A serious consequence of recurrent herpetic keratitis is the death of corneal nerves, resulting in neurotrophic keratitis."

extracellular matrix, growth factors, and cytokines, all of which are instrumental in ocular tissue repair. Prokera is a cryopreserved amniotic tissue, and studies have shown that its preservation process, known as CryoTek, helps prevent, slow, or decrease scarring (11).

CAM has anti-inflammatory, anti-scarring, and anti-angiogenesis properties that are particularly important for this disease; they help improve epithelial healing; prevent perforation, scarring and irregular astigmatism; and regenerate corneal nerves (12, 13, 14). Data presented by Cooke and colleagues suggests that cryopreservation effectively preserves the structural and biochemical integrity of AM matrix components that are essential for the anti-inflammatory and anti-scarring effects that are observed clinically. Cooke's study also showed that the absence of those components within dehydrated AM may contribute to the decreased effectiveness of the dehydrated tissue in reducing inflammation and fibrosis (15).

The CAM that I use for patients with HK is Prokera from BioTissue. Prokera is bound by a clear polymer ring and inserted into the eye in a manner similar to contact lens placement. CAM manages healing via the presence of collagen and growth factors. It also counteracts the potentially cytotoxic effects of topical antibiotics and provides antimicrobial effects over and above those of first-line antibiotics. Ultimately, CAM acts as both a bandage that protects the cornea and allows a microenvironment for healing. And, as a disease-modifying therapy that promotes regenerative wound-healing (12, 13, 14, 15), I find that post-herpetic scarring is reduced when I use CAM in these eyes.

How CAM works

CAM suppresses inflammation by facilitating neutrophil apoptosis, polarizing M1 to M2 macrophages and suppressing Th1 and Th17 lymphocyte activation. It inhibits scarring by preventing myofibroblast differentiation and reprogramming into progenitor cells, and promotes regenerative healing by supporting and augmenting stem cell function and maintaining stem cell quiescence (12).

The cryopreservation process allows CAM to retain heavy chain peptide (HC) covalently conjugated with high molecular weight hyaluronic acid (HA), which is noncovalently complexed with pentraxin-3 (PTX3). HC-HA/PTX3 is the biologic matrix that is responsible for CAM's anti-inflammatory and regenerative healing properties. HA and PTX3 are involved in tissue repair and remodeling; and HC components of immunoglobulin form complexes with HA. Each component of CAM is found broadly in the human body but exist together as a complex in the amniotic membrane (12, 13, 14, 16, 17). This complex is what provides the regenerative healing that is maintained in cryopreservation, but lost in dehydration (15).

Therapeutic management

The two major visual sequelae of infectious keratitis, especially involving

"In the acute phase of an active viral replication, CAM along with oral antivirals will help speed up the time to resolution."

Brief case

- *Patient:* 32-year-old woman
- *History:* Recurrent herpes simplex virus on her right cornea. Responds to topical Zirgan and oral ACV, but is having significant punctate keratitis and epitheliopathy from the topical toxicity of the Zirgan. The cornea is also starting to develop visually significant subepithelial haze.
- *Examination:* Central corneal haze and severe 3-4+ punctate keratitis.
- *Diagnosis:* Resolved post herpetic disease with early scarring and epithelial toxicity
- *Treatment:* Prokera CAM slim placed on the right eye. Instructed to stop Zirgan and continue oral ACV. Prokera remains in place for 5 days.
- *Follow-Up:* Superficial punctate keratitis completely resolved after five days of Prokera. No active viral disease seen and significant reduction of the subeithelial haze/scarring. The patient's best-uncorrected visual acuity improved while avoiding previously ineffective or irritating medications. The regenerative and anti-inflammatory effects of CAM produced desirable surface healing while avoiding topical steroid toxicity or risk of reactivating the herpetic disease.

the visual axis, are scarring and ectasia; and both can be prevented, reduced or remediated with CAM (13, 17, 18, 19). It provides effective anti-inflammatory therapy with a better safety profile than topical steroids, which can delay healing, reactivate a viral infection, cause cataract formation, and elevate intraocular pressure (IOP) (20, 21).

A serious consequence of recurrent herpetic keratitis is the death of corneal nerves, resulting in neurotrophic keratitis. In fact, the most common cause of neurotrophic keratitis is herpetic eye disease. Neurotrophic keratitis is difficult to manage and often associated with non-healing and scar formation; CAM is especially effective for these cases. The cryopreserved membrane provides a milieu of anti-inflammatory substrates and regenerative cytokines to help heal the corneal surface when it is neurotrophic, and it has been shown in the literature and anecdotally to actually help regenerate nerves in the cornea (14).

Speedy resolution

CAM is a valuable adjunct in the acute phase of active herpetic disease, as well as in the neurotrophic phase. In the acute phase of an active viral replication, CAM along with oral antivirals will help speed up the time to resolution. It also helps heal the underlying scarring and haze that we typically see during the resolution of the virus.

In conclusion, I continue to use oral therapy or topical drops in many cases of herpetic keratitis in an effort to eliminate active disease and prevent disease recurrence. However, if the patient has had underlying dry eye or ocular surface disease, I veer away from topical therapeutics because they will further irritate the ocular surface. For those patients, CAM can be a first line treatment, and I do not necessarily need to add a topical antiviral to the oral regimen. Of course, each case needs to be assessed and treated based on the best clinical judgement for that patient.

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Marjan Farid has consulted for and been a speaker for BioTissue.

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INDICATION

DEXTENZA is a corticosteroid indicated for the treatment of ocular inflammation and pain following ophthalmic surgery.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DEXTENZA is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella; mycobacterial infections; fungal diseases of the eye, and dacryocystitis.

WARNINGS AND PRECAUTIONS

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. Intraocular pressure should be monitored during treatment.

Corticosteroids may suppress the host response and thus increase the hazard for secondary ocular infections. In acute purulent conditions, steroids may mask infection and enhance existing infection.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

ADVERSE REACTIONS

The most common ocular adverse reactions that occurred in patients treated with DEXTENZA were: anterior chamber inflammation including iritis and iridocyclitis (10%); intraocular pressure increased (6%); visual acuity reduced (2%); cystoid macular edema (1%); corneal edema (1%); eye pain (1%) and conjunctival hyperemia (1%).

The most common non-ocular adverse reaction that occurred in patients treated with DEXTENZA was headache (1%).

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. Sawhney AS, Jarrett P, Bassett M, Blizzard C, inventors; Incept, LLC, assignee. Drug delivery through hydrogel plugs. US patent 8,409,606 B2. April 2, 2013.
2. DEXTENZA [package insert). Bedford. MA: Ocular Therapeutlx, Inc: 2019.

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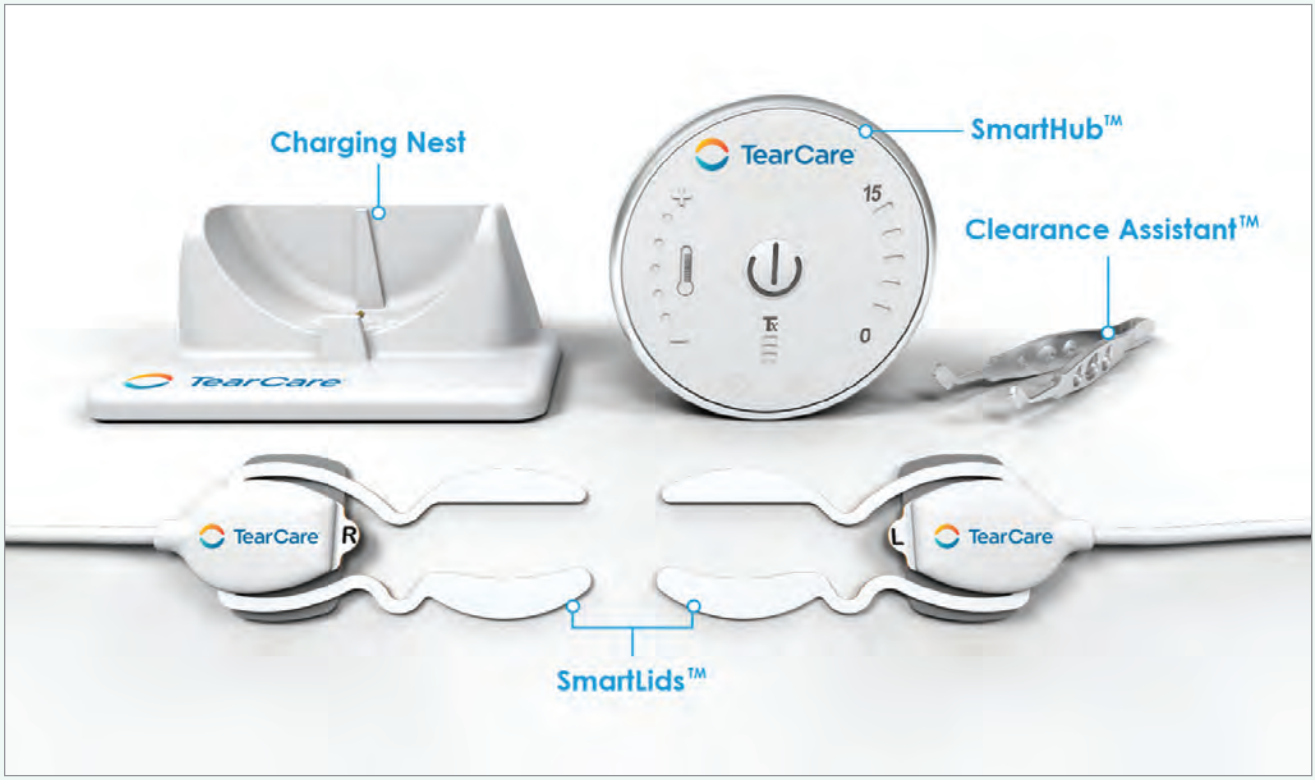

HOT PROPERTY

How a smart system turns up the heat on obstructed meibomian glands

Most eye care providers acknowledge and treat inflammatory dry eye with prescription medications; relatively few of those providers use specific methods to address obstructive meibomian gland dysfunction (MGD), which affects 86 percent of dry eye patients in the US (1). Obstructive Meibomian glands result in reduced meibum secretion and a compromised tear lipid layer that causes accelerated tear evaporation.

Traditionally, practitioners have advised MGD, dry eye disease (DED), and blepharitis patients to use warm compresses – but an optimal effect on obstructed glands cannot be achieved with a warm compress or anti-inflammatory drugs. Active heating at a precisely-measured temperature – and successful evacuation of meibum from the glands – are key aspects of effective care.

Enter two brothers – David Badawi, corneal specialist in Chicago, Illinois, and Paul Badawi, a former NIH scientist based in Menlo Park, California – who worked together to develop TearCare® – an intelligent device designed for

TearCare

patients suffering from conditions such as MGD. The wearable and fully customizable technology helps deliver the right levels of thermal energy to the eyelids – all while allowing patients to keep their eyes open and blink.

The TearCare system from Sight Sciences is composed of four elements: a reusable, software-driven SmartHub, which generates electrothermal energy; a SmartHub charging nest; a single-use treatment assembly, with a flexible pair of eyelid devices – SmartLids – that conform to each patient's eyelids; and a sterile, single-use meibum Clearance Assistant instrument. The SmartLids feature multiple temperature sensors, which communicate with the SmartHub 240 times times per second to make sure the thermal therapy is closely controlled and consistent throughout the procedure. Notably, temperature can be manually lowered at any point.

TearCare enables tight control of eyelid temperature (up to 45°C) for 15 minutes, making it the first and only non-invasive technology that delivers heat to the outside of the eyelid while achieving the 41°C inner eyelid temperature required to sufficiently liquify hardened meibum and aid in the clearance of gland obstructions. After the thermal therapy, the ophthalmologist removes the SmartLids and uses the Clearance Assistant forcep to gently but thoroughly evacuate the unhealthy meibum from the glands.

TearCare can be used during a normal office visit, and can be repeated as often as needed over time, providing eye care professionals with a technologically-advanced and automated tool that addresses their patients' obstructive MGD – with pricing that allows all interested practices to become engaged in advanced dry eye care.

Right now, TearCare is commercially available in the US with limited insurance coverage based on CPT code (0563T). Assistance with insurance submissions is available through the Sight Sciences reimbursement team.

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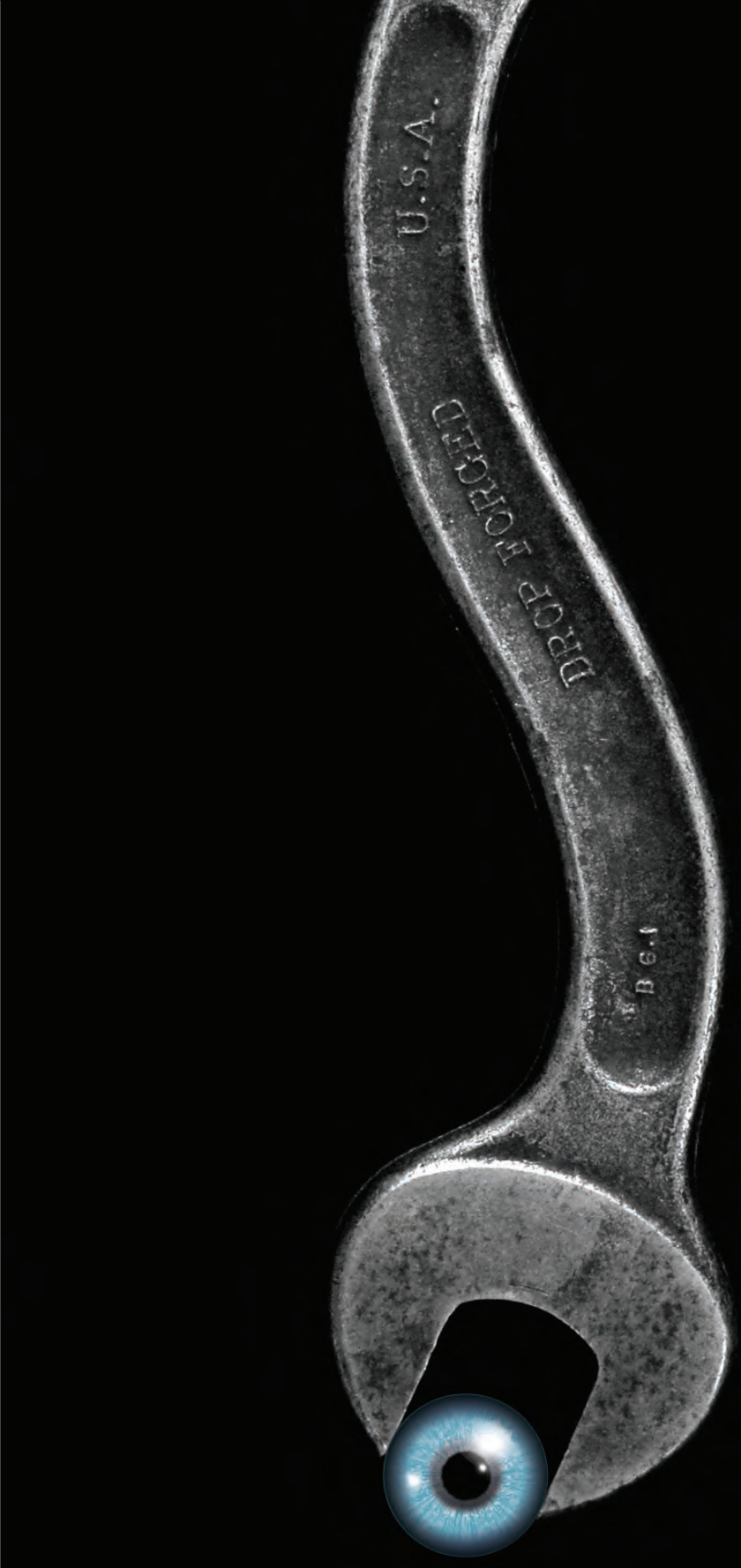


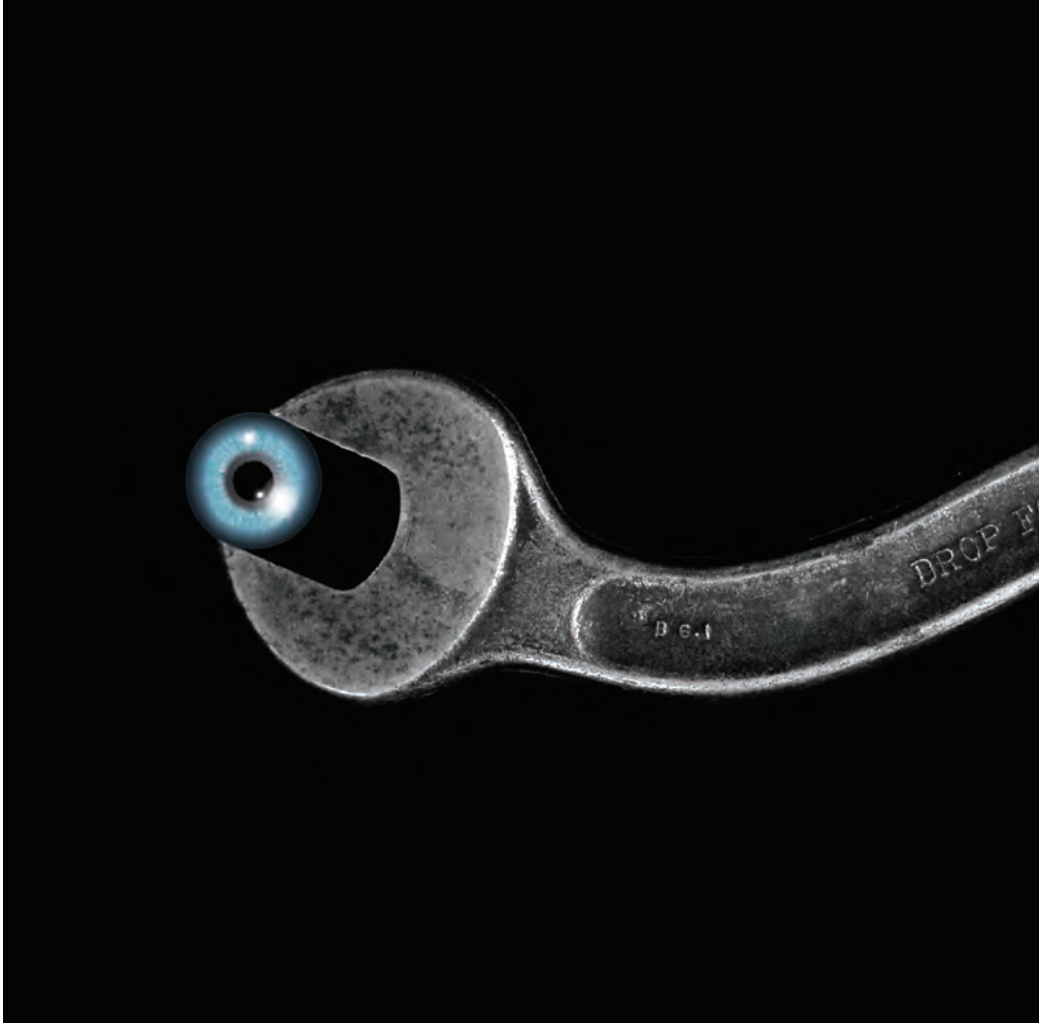
NextGen

Research advances
Experimental treatments
Drug/device pipelines

The Long Haul

Three glaucoma specialists assess the potential of the FDA-approved bimatoprost implant

With E. Randy Craven, Felipe Medeiros, and I. Paul Singh



The sustained-release bimatoprost implant – marketed by the trade name of Durysta – is indicated for open angle glaucoma and ocular hypertension patients who require intraocular pressure reduction. Following the FDA approval of this new drug delivery system in March 2020, we talk to three glaucoma surgery gurus: Felipe Medeiros, who was the lead investigator in the bimatoprost implant's clinical trials, as well as E. Randy Craven and I. Paul Singh, who view the technology as a practice-changing innovation. The big question: will glaucoma treatment be transformed? Let us know what your experience with the sustained-release implant has been like.

Felipe Medeiros, Distinguished Professor of Ophthalmology and Vice-Chair for Technology, Director Clinical Research Unit, Department of Ophthalmology, Duke University, Durham, North Carolina, USA

The burden

It is universally acknowledged that daily glaucoma eye drops constitute a treatment burden for many patients, causing issues with compliance and adherence to prescribed therapies – studies show that over 50 percent of patients don't follow their prescribed topical medication regimes over 75 percent of the time (1). Eye drops can also contribute to ocular surface disease, with side effects such as itching or stinging. One of the innovations attempting to provide long-term lowering of glaucoma patients' intraocular pressure – without the worry of poor adherence – is the slow-release implant.

Durysta is the first FDA-approved sustained-release intracameral implant tackling intraocular pressure in glaucoma. It is indicated for any patient suffering from open angle glaucoma or ocular hypertension who requires an IOP reduction, as long as they don't have any contraindications (such as a history of angle closure or corneal diseases that decrease the number of endothelial cells).

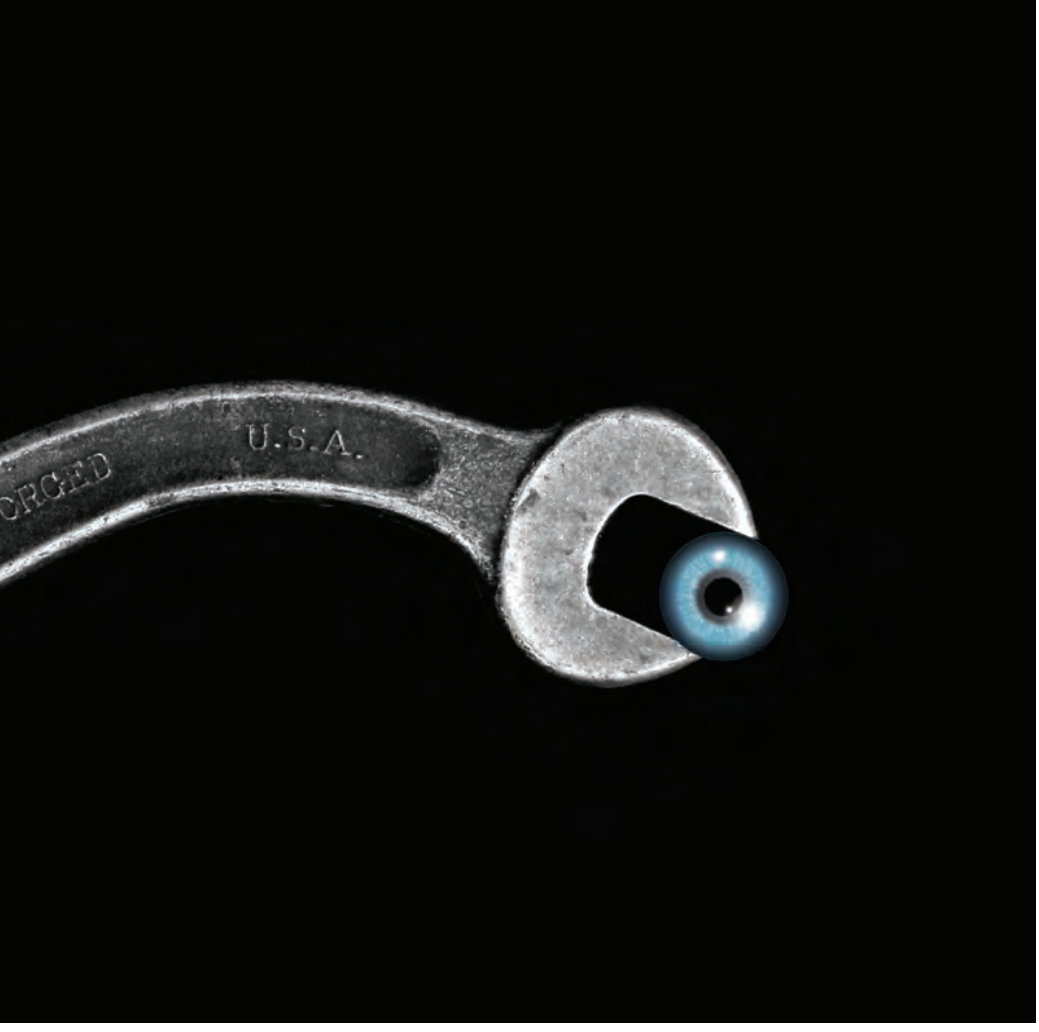
The patients

I can see the implant having broad applications, and working very well for patients who have trouble with compliance to topical medications, and where the glaucoma specialist believes there is a possibility of lowering the IOP before reaching for more invasive interventions, such as a surgery (MIGS or trabeculectomy). The idea is that, by using a slow-release mechanism, the medication will achieve more sustained pressure control, avoiding peaks and fluctuations that can potentially lead to more optic nerve damage and vision loss.

Many of my patients don't tolerate topical medications well and their ocular surface suffers. There are also those with limited mobility, including elderly patients suffering from rheumatoid arthritis, who have to rely on others to apply eye drops – the slow-release implant works well for them.

The trials

I was the lead investigator in the ARTEMIS clinical trials for Durysta, in which we evaluated 1,122 patients from 108 centers in 14 countries, comparing the implant's safety and efficacy with that of twice daily timolol-containing eye drops. We found that Durysta lowered the patients' IOP by around 30 percent, and the effect lasted through the chosen 12-week period (2). We designed the trials as non-inferiority studies and aimed to show that the implant did



not perform any worse than timolol eye drops. However, what the trials actually showed is that the pressure lowering by the implant is greater than that of timolol, and comparable to what can be seen with a topical application of a prostaglandin analog like bimatoprost. In other words – its effect is similar to that of the eye drops, without the significant treatment burden, and with a longer-term pressure reduction.

The implantation

The implantation procedure is quite simple and only takes a few minutes. The implant is inserted with the use of an applicator, with a 28-gauge needle, which is inserted into the anterior chamber. The implant is released and settles in the angle of the eye.

The future

For now, the implant is FDA-approved for a single application, which will last for a limited time. There are additional trials taking place, and in the planning stages, to support an extension of the FDA approval for multiple applications, which I hope will greatly improve patient outcomes.

The Phase 3 clinical trials that I led included three applications of the implant, each lasting four months. We observed that after the final application approximately 80 percent of patients did not need any additional treatment for up to a year – a crucial finding that shows the potential long-term response.

We also observed that the rate of visual field loss for the implant group was slower than for the group using timolol topical medication. This news is huge; preserving visual function is the ultimate goal of glaucoma therapy – lowering or maintaining pressure is just a surrogate result. I consider these to be very powerful results and they give me hope for the future of glaucoma management.

E. Randy Craven, Associate Professor of Ophthalmology at Johns Hopkins University, and Chief of Wilmer Eye Institute in Bethesda, Maryland, USA

The trials

I have a long track record with Durysta. When it was first being developed, I was one of the first consultants who took part in running test models, and in conducting the first in-human trials. I have been part of Phase 1, 2, and 3 trials – and I've watched the implant develop over that time.

We found that many patients had an extended pressure-lowering effect after just one implantation – for 28 percent of patients, this lasted up to 24 months, and for 68 percent of patients, it lasted for six months (2). The FDA approved it for a single injection based partly on that, and partly on the need to further evaluate long-term corneal safety with multiple injections, when multiple implants touch the endothelium.

The patients

My colleagues and I have been identifying patients with open angle glaucoma and healthy corneas, who suffer from corneal irritation caused by preservatives in topical medications, or who have issues with adherence. Some of them have a tremor, which makes instilling eye drops difficult; some suffer from early dementia and forget to use their medication. Those patients are usually on one or two medications, and they are excited to hear that there is now another option available in the form of an implant.

The implantation

Many of my colleagues perform the procedure at the slit lamp, with topical anesthetic, using the same protocols as for intravitreal injections. The patient looks straight ahead and the physician comes in from the side, with the applicator needle gently entering the anterior chamber, before pushing the button to release the implant.

I use the minor procedure room for the

implantation, but it is purely down to my personal preference. The patient lies back and I insert the implant – for the right eye, I sit above their head, and for the left eye, I sit temporal to them – then sit them back up and check the implant. I look for any leakages and ensure the implant is in the right position. I follow up with patients after a week and after a month, and then check their IOP every three months.

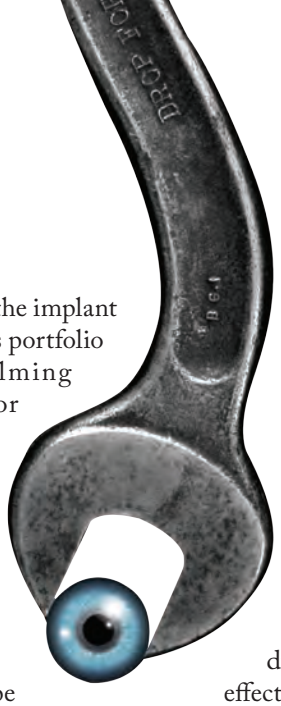
The pandemic

From what I have seen in the last few months, the COVID-19 pandemic has had a huge impact on the severity of glaucoma in patients reporting to ophthalmic practices. Patients classed as glaucoma suspects have not been coming in for check-ups, as the risk was deemed too great. Now, we are back in the clinic, and I'm seeing many more of these patients. It gives me a little more comfort knowing that with the slow-release implant, patients are not required to visit the ophthalmic practice as often, and the medication is still being delivered to the eye, for months at a time. However, I can see an issue with not knowing how long the pressure will be kept in check if patients are not seen regularly. Right now, it is difficult to see patients implanted with Durysta every three months, as my schedule is very full, and we are not back to full capacity due to COVID-19 safety protocols.

The practice

Glaucoma specialists who haven't tried the implant yet, should be encouraged to use it in their practice. My advice is to allocate time at the end of the day or half a day in the week when they can perform a few of these implantations, as it can be difficult to find the time to start implementing a new strategy in the middle of a busy clinic. I have a "Durysta day" when the room is ready, the patients scheduled, and I can focus on implantations, without worrying that I'm going to lose time meant for my other patients.

The logistics of adding the implant to the particular practice's portfolio might seem overwhelming at first: there are prior authorization issues, working out insurance billing, buying the implant and keeping it in stock, but it is worth the initial hassle. For the procedure itself, practice protocols already used for injections will generally be applicable and very safe.



"It's effect is similar to that of the eye drops, without the significant treatment burden, and with a longer-term pressure reduction."

The future

I'm really looking forward to future, larger studies. We have noticed during the clinical trials that visual field sensitivity decreased for control patients using timolol eye drops – a fairly typical outcome for people with mild glaucoma. For the patients implanted with Durysta, visual field sensitivity remained stable. The around-the-clock action seems to have a better mechanism for pressure control. This is very encouraging, and I'm looking forward to seeing further evidence of this from upcoming trials.

I. Paul Singh, President of The Eye Centers of Racine & Kenosha, Wisconsin, USA

The toolbox

The most difficult issue I face in the management of glaucoma is trying to maintain stable IOP. We are seeing a huge emphasis on improving compliance – problematic due to medication costs, side effects, or simply patients forgetting to instill eye drops – often with a surgical intervention mindset. And I think that's why MIGS and SLT are generating such a buzz of excitement. Early intervention is now seen as crucial.

Durysta is a new addition to the glaucoma specialist's toolbox, helping us intervene earlier and maintain a stable IOP, while overcoming compliance issues. It is a very flexible solution that can be used in a variety of different settings, from a hospital to a community-based practice or office (differentiating it favorably from MIGS). Provided there is good head stabilization, good magnification, and good aseptic conditions, the procedure is safe to be performed anywhere.

Expectations for a standalone procedure, as opposed to a MIGS procedure combined with cataract surgery, are high – and the implant delivers on its promise of lowering the IOP. It is applicable to any type of disease state, from mild to advanced glaucoma.

Durysta helps surgeons hedge their bets and attempt to achieve freedom from eye drops for patients before or after reaching for MIGS. It can also be an intermediary step to give patients' ocular surface a rest from topical medications containing preservatives. I use Durysta for my cataract surgery candidates with an unhealthy ocular surface to give it a chance to restore, so that I can obtain better biometrics and get better results after the surgery.

For some glaucoma specialists, not keen on using MIGS or glaucoma surgery in general, trying the implant might be the first step towards the interventional mindset. Implanting Durysta is a very straightforward process that any ophthalmologist can learn very quickly.

Additionally, Durysta does not cause the adverse effects typically associated with topical prostaglandin analogs, such as periorbital changes in pigmentation, meibomian gland dysfunction, and other issues.

The patients

I have been surprised by the uptake and the wide adoption of the implant, but it makes sense when I consider compliance issues and the fact that it is fully covered by insurance (it can be cheaper for the patient than using generic glaucoma medications). As many specialists now perform the implantation at the slit lamp, from the patient's perspective it is a very straightforward procedure, and it brings down their defense mechanisms – it is seen more like a regular check-up than a surgical procedure.

As with all glaucoma interventions that do not rely on patient compliance – such as MIGS or SLT – with the implant, the patients' visual field mean deviation is better (2). Even if the effect is not obvious straight away, over months and years it is improved, compared with the cohort using topical medication. For some patients there might not even be a big change in the IOP, but there is clearly more stability in the visual function.

I feel comfortable implanting Durysta in phakic patients – in fact, 75 percent of patients in the Phase 3 trial were phakic. The procedure is great for younger patients, where we want to avoid using topical drops altogether for as long as possible, and keep the ocular surface healthy.

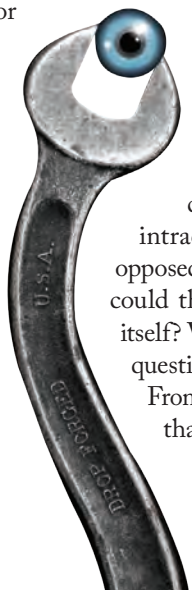
The pandemic

Many of my patients are now afraid to apply their eye drops, or even to go to the pharmacy to pick up a prescription. Many of the more vulnerable patients relied on others to instill medication, and those relatives or friends might not be able to see them in person at the moment. The slow-release implant removes many of these pandemic-related worries out of the equation. Patients don't have to worry whether they've washed their hands well enough before applying eye drops, or whether their relatives might not be able to visit because they work in high-risk settings or they're having to self-isolate.

As a care provider, I don't have to worry about compliance, whether my patients can get a refill or if they decide to buy a generic drug rather than a specific brand. All these variables can result in intraocular pressure fluctuating. And that's why I have appreciated being able to offer Durysta to my patients during the COVID-19 pandemic.

The future

I'm excited to see how Durysta works before or after SLT. Only 5 percent of patients in the trials had previously had SLT, so there are many unanswered questions on how this might affect the disease state itself.



Getting the implant approved by the FDA for multiple applications will be a great next step. It will give us a new understanding of how long the implant can last for. If there is constant, slow release of medicine intracamerally 24 hours a day, as opposed to once or twice a day topically, could this be changing the pathology itself? We might be able to answer that question soon, which is very exciting. From the clinical trial results, it seems that the more implants we use, the more longevity the therapy has, and only a smaller percentage of patients might require rescue therapy.

I'm already implanting a variety of my patients – from mild to advanced glaucoma – and monitoring the duration of the implant's effect very closely. For some patients, pressure might be lowered for four months; for others, the effect lasts for two years. Once multiple implantations are approved, the experience of using the implant in many different scenarios will give me a better plan of action for each individual patient – making it easier to work out how much time I should leave between check-ups, and between implantations.

Having Durysta as a new tool in our armamentarium is another step in the direction of wider adoption of the idea of early intervention, taking the issue of compliance out of the equation. This change of glaucoma specialists' mindsets will result in better IOP stability for our patients, and – ultimately – greatly improved outcomes.

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1. *A Robin, DS Grover, "Compliance and adherence in glaucoma management," Indian J Ophthalmol, 59, S93 (2011). PMID: 21150041.*
2. *FA Medeiros et al., "Phase 3, randomized, 20-month study of bimatoprost implant in open-angle glaucoma and ocular hypertension (ARTEMIS 1)," Ophthalmology, [Online ahead of print] (2020). PMID: 32544560.*

Solving the RPE Puzzle

Sitting Down With…
Luminita Paraoan, Chair of the Ocular Molecular Biology and Mechanisms of Disease Group in the Department of Eye and Vision Science at the University of Liverpool, UK

What inspired you to choose a research career?

The main inspiration for choosing my degree was my mother, a PhD biologist who combined her career with family life brilliantly. Watching her in the lab, doing her research and overcoming various challenges, influenced me greatly throughout my childhood. Even though I chose a slightly different subject, she gave me the inspiration for my postgraduate degrees and pursue an academic career.

I have met various inspirational people along the way, and the one thing they have in common is the passion for their field and the desire to get to the bottom of things by asking interesting questions. This still excites me greatly – some of these questions now come from my students, and make me stop and think, "What an interesting perspective!" If I'm not sure how to answer, I develop a hypothesis and think about practical ways of addressing the problem. I have been very lucky to find people who knew how to ask questions that weren't immediately obvious, which started interesting conversations, rewarding projects that in turn led to exciting discoveries.

How has your career developed?

I did my undergraduate degree at the University of Bucharest in Romania. It was a very competitive course, I enjoyed it greatly and finished first in my class; I then soon joined my department as a junior faculty member. I was awarded a Fulbright scholarship at Johns Hopkins University in Baltimore, where I did a lot of experimental work for my first PhD in genetics and microbiology. One of my mentors during the early formative years of my career, Ted Maden, was the Johnston Professor of Biochemistry at the University of Liverpool. Following a short period of work in the UK with him and the late Jim Haslam, we applied for a Wellcome Trust grant and, when we got it a year later, I came back to Liverpool, not predicting I would stay here for much longer. It was at the University of Liverpool that I first got involved in eye-related research, looking at gene expression in the retinal pigment epithelium, and my career in eye and vision science began. In 2016, I became the Chair in Ocular Molecular Biology at the University of Liverpool. I never planned my career, but rather took advantage of opportunities that came along.

You recently became ISER's Vice-President for Europe – what does that mean to you?

The highest reward a scientist can receive is the recognition of their colleagues and to have their findings discussed and respected by their peers. With that come requests for involvement in professional organizations – the main ones in vision science being ARVO and ISER. Over the years, I have held different positions in both. Most recently, I served as Chair of the Biochemistry/Molecular Biology Section of the ARVO Annual Meeting Program Committee, which was a huge undertaking, and now I have been elected Vice-President for Europe at ISER. This appointment means a lot to me because it was voted for by colleagues around the world. It is humbling to think how many people must have voted for me based on what they knew about me, what I stand for – my research, and my career.

When I was appointed at the beginning of 2020, we were in the middle of preparing the biennial ISER Meeting to be held in Buenos Aires, Argentina. We continued to develop the program until the ISER Council made the decision to cancel the event due to COVID-19. It is a wise decision, but very disappointing – the meeting will now take place in 2024.

A position like mine brings with it the responsibility to promote the interests of the Society, increasing membership and supporting young researchers (focusing specifically on eye and vision scientists in Europe). I hope that, in three years' time, I will look back at my achievements in these areas with pride.

What are you working on at the moment?

My group has two main research areas in eye and vision science, both focusing on physiological processes and pathologies that develop at the back of the eye. The first relates to the molecular cell biology of the retinal pigment epithelium: how it functions, its health, what changes occur as a result of aging, and how they impact the development of AMD.

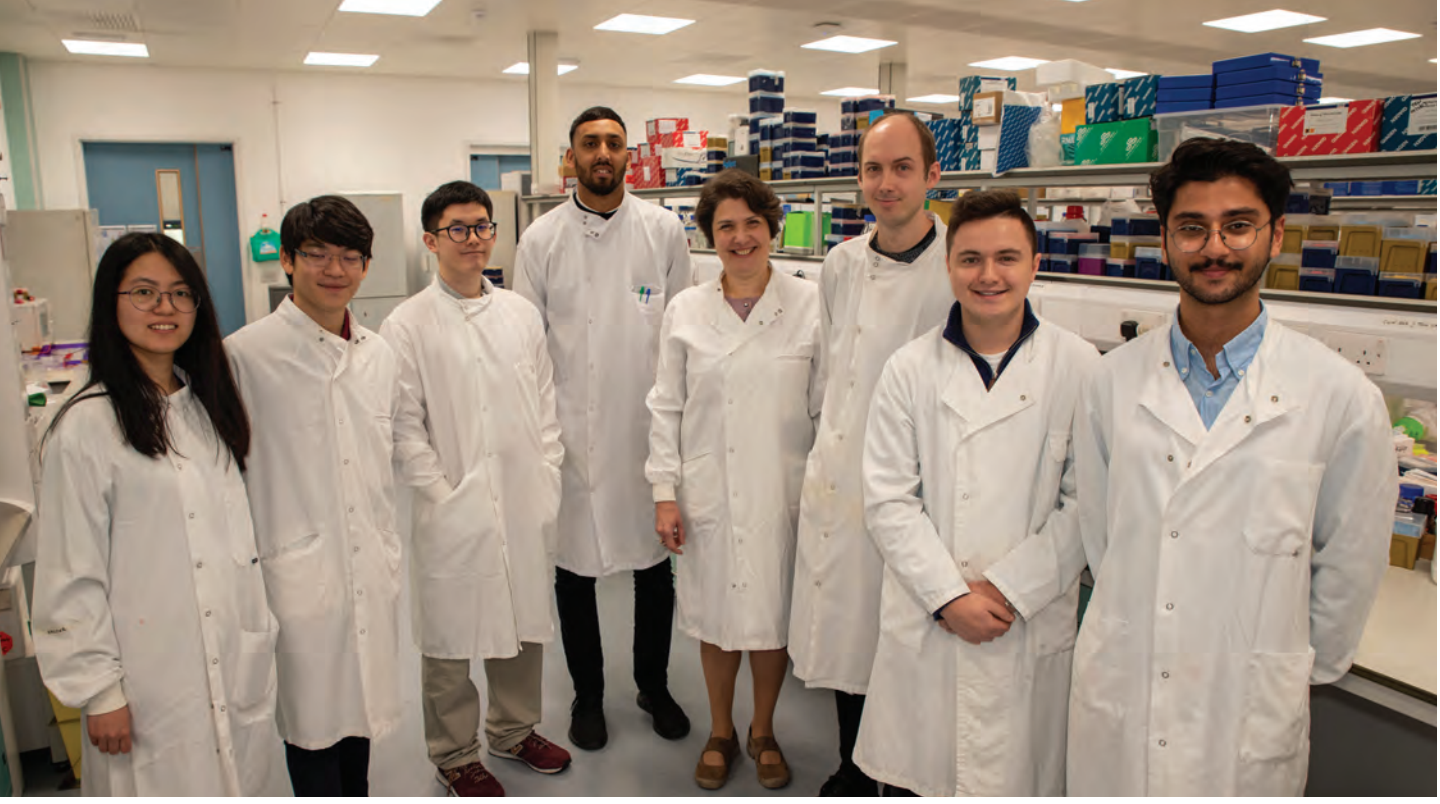
Our other area of research is the tissue immediately adjacent to the retinal pigment epithelium – the choroid, specifically in relation to the most common eye tumor, uveal melanoma. Over the years, we have contributed research on the controlled regulation of apoptosis – how cancerous cells become resistant to chemo- and radiotherapy.

What got you fascinated with the eye?

Retinal pigment epithelium is a fascinating tissue – and you have to be passionate about the tissue you work on! When we are born, this monolayer of cells at the back of the eye is formed and the same cells have to sustain our vision for our entire lives. Without them, the light sensitive cells – rods and cones – in our retina cannot survive and cannot function. Not surprisingly, it is the place where age-related vision changes occur, and gaining an understanding of those changes is behind everything I and the people working with me do. Developing interventions to slow down these aging processes will undoubtedly have implications for other types of cells, so I find this work extremely rewarding.

How does your research translate into clinical practice?

Even though we carry out fundamental research, we work quite closely with clinicians and pharmaceutical and R&D partners to develop ideas for novel therapeutic strategies – all our work forms



pieces of a bigger jigsaw puzzle that we solve bit by bit.

We also interact directly with patients. It's very important for researchers to see how the pathologies they work on affect people at different stages of vision decline. Both clinicians and patients have commented on how our findings have helped them in their daily routines – be it clinical practice or understanding of disease progression. What is most important is that we all learn from each other.

How do you help younger colleagues develop their careers?

I hugely value mutual relationships with people who are equally motivated, have a high work ethic, and enjoy overcoming challenges. I have been very fortunate to learn not only from senior colleagues, but also from talented younger people who get excited by science – it is a mutually beneficial association. It gives me great satisfaction to watch them develop as scientists and realize what they have learned and achieved. That moment when you watch their faces and see ideas click is fantastic! I have also mentored younger researchers as part of my roles at ARVO and ISER, including a special program for researchers from developing countries who make valuable contributions to eye vision research and ophthalmology practice in their countries.

How has COVID-19 affected research projects and academic teaching?

It has been a challenging time and we have had to adapt rapidly – both my research group and the wider community. It has only been a few months and yet it feels like a lifetime of learning new processes. We are constantly coming across new problems that require innovative solutions. Making things work in a new way gives me satisfaction, but it is extremely challenging and there is no end in sight.

Fortunately, at the start of the pandemic, my research group had already accumulated a lot of data, so we could focus on data analysis and writing – we had four major papers published in the last few months. Now, labs are open at around 50 percent capacity and running projects as efficiently as possible requires a lot more time and effort than I had imagined. We've had to be creative with working out what can be done from home and how individual researchers' roles can complement each other. I hadn't fully appreciated just how much time we would spend in virtual meetings and how demanding it would be to go through things that were so easy to communicate face-to-face just a few months ago. We have all had to adapt; fortunately, we have done it well, because there are still at least a few more months of this ahead of us.

In terms of online teaching, I opted for synchronous teaching and have insisted that students put their webcams on so that we can still have some interaction. It's great to see these young people eager to learn.

What aspect of your life are you most proud of?

My family life developed parallel to my career: my first two sons were born while I was doing my two PhDs and the birth of my third son coincided with a promotion at the University of Liverpool. Now, they are all very accomplished young men developing their own careers, and I feel immense pride seeing what they have achieved. My husband is a surgeon and it has been challenging to drive both our careers while creating the right home environment for our children, but they found inspiration in what we were both doing – just like I was inspired by my mother's work.

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE
Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

4 CONTRAINDICATIONS
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported *[see Contraindications (4)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

Data
Animal Data
Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation
Risk Summary
There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low *[see Clinical Pharmacology (12.3) in the full prescribing information]*. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

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

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*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).[3]

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. **Pivotal trial data:** The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study endpoints included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3]

A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease: ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

Indication

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information about XIIDRA®, please refer to the brief summary of Full Prescribing Information on adjacent page.

References: 1. US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed April 17, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020.

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