DECEMBER 2018 # 28

the Ophthalmologist™

Outside-In Innovation

How and why technological and scientific discoveries from diverse fields drive ophthalmology forward

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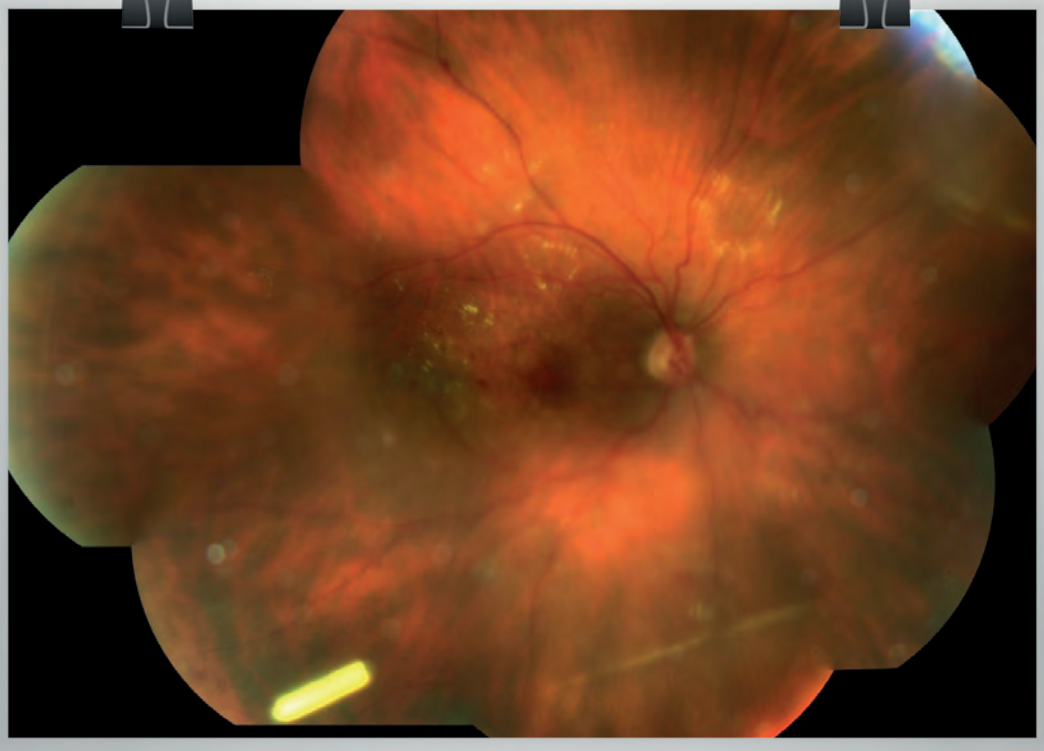

Micro-Sized Wonders

The powerful magnification in this fundus image montage highlights the Iluvien micro-implant like the bright yellow anther in a stargazer lily. Small enough to fit into a grain of rice 52 times, the intravitreal implant still packs enough power to provide a consistent and continuous therapeutic microdose of fluocinolone acetonide for up to 36 months. While its tiny size can make visualization challenging, this hidden gem is still working hard and providing treatment for the patient.

Credit: Joshua Mali, MD.

Do you have an image you'd like to see featured in The Ophthalmologist? Contact edit@theophthalmologist.com

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Constant improvement and innovation are at the heart of ophthalmology. We share some examples of technologies and discoveries "borrowed" from other fields.

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The Times They Are (Always) A-Changin'

One foot in the present, one foot in the past, and an eye on the future, ophthalmology is a profession caught between three worlds.

Ophthalmology is in a constant state of flux. Almost every day, a new technology is introduced, a new technique is perfected, a new voice heard. It is this constant change that makes ophthalmology so exciting – it never sits still. It seems fitting, then, that this issue focuses on innovation and change. Whether a change of thought, a change in practice, or a change in technology, ophthalmology must always move forward. In NextGen (page 32), Sneha Konda and Bala Ambati discuss which MIGS procedures are available today, while casting an eye on those still to come. In Sitting Down With…, John Berdahl talks about the future of healthcare – both here on earth and in outer space – but also reflects on his past. On page 42, John Sandford-Smith exalts the benefits of modern cataract surgery training – but explains why the old ways weren't all bad either.

Like all our contributors this month, we believe that change is good (often essential) and in that spirit, we are revamping our Power List for 2019. Yes, the list will still celebrate the most influential figures in the field, but instead of selecting the Top 100 ophthalmologists, we are looking for half that number in a more exclusive list; specifically, 50 of the best inventors, mentors, emerging leaders, surgical pioneers and champions of change... With our "Five Top Tens," we hope to showcase the best, the brightest, and the most forward-thinking that the world of ophthalmology has to offer.

You, The Ophthalmologist community, must decide who will appear on this literal "short list." If you know a doctor who's fighting for institutional change, a master surgeon who's always breaking new ground, or an educator generous enough to focus on shaping the next generation, please put them forward: http://top.txp.to/powerlist2019. Be fair, be kind, but most importantly, be honest. We look forward to seeing your nominations.

Phoebe Harkin
Associate Editor

Upfront

Reporting on the innovations in medicine and surgery, the research policies and personalities that shape the practice of ophthalmology.

We welcome suggestions on anything that's impactful on ophthalmology; please email edit@theophthalmologist.com

Restoration Project

Californian researchers have successfully restored sight to blind rats in a landmark study

The saying goes: "When it's gone, it's gone" – but what if that wasn't the case in sight loss caused by severe retinal degeneration? That's what a team at the University of California, Irvine School of Medicine, set out to prove in a breakthrough study (1). Following fetal retina sheet transplants, the researchers discovered that neurons in the vision centers of blind rats' brains functioned normally.

"It's been known that retinal sheet transplants can integrate into the degenerated eyes and allow the animals to detect light. But, beyond rudimentary light detection, it was not known how well the visual system in the brain functioned with the newly integrated retinal transplant," said David Lyon, Associate Professor of Anatomy and Neurobiology at the University of California, Irvine, in a statement to UCI.

"In this study, we found that neurons in the primary visual processing center perform as well as neurons in animals with normal healthy retinas," he said. The donor cells were sensitive to various attributes of visual stimuli – including size, orientation, and contrast – as early as three months following surgery. "These results show the great potential of retinal transplants to treat retinal degeneration in people," said Lyons. "Though more research is needed to determine effectiveness and acuity" (1).

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Bitesize Breakthroughs

The latest ophthalmology news – in brief

Ancient Roots

- Researchers at Johns Hopkins University School of Medicine appear to have uncovered an "ancient" light-sensing mechanism in modern mice (1) – and it is likely found in human retinas too. The team was researching the biochemical pathways of "non-image forming" photoreceptors (intrinsically photosensitive retinal ganglion cells or ipRGCs), when they discovered that one subtype (M4) didn't use the previously discovered phospholipase C pathway but something novel: HCN-channel-mediated phototransduction. And, perhaps more surprisingly, subtype (M2) appears to use both mechanisms. "Some evolutionary biologists have proposed that […], through evolution, these two mechanisms separated into different cell types. Our research seems to provide evidence that photoreceptors containing both light-sensing mechanisms may still exist in modern mammals," said King-Wai Yau, a professor of neuroscience, who led the study.

High and Dry

- Does dry eye affect visual function? According to a team at Wilmer Eye Institute, the answer is yes. In a study of 186 participants, those with clinically significant dry eye read fewer words per minute than those with dry eye symptoms only. It was found that chronic dry eye slowed reading rate by as much as 10 percent, making it difficult for participants to concentrate for longer than half an hour. Researchers collected small vials of tears from each participant for future studies in the hope of understanding the exact mechanisms behind the condition (2).

End to AMD injections?

- A Phase II clinical study has trialed an implantable, refillable drug delivery system for wet AMD. The device – no bigger than a grain of rice – contains a refillable reservoir of Lucentis and is implanted under the eyelid. In the study, led by Wills Eye Hospital in Philadelphia, some patients were able to go 15 months between treatments. Researchers hope the device will provide an alternative to the current standard of care for AMD – monthly injections – and result in better visual outcomes. "Fewer injections and office visits is exciting," said Carl Regillo, Chief of Retina Service and Professor of Ophthalmology. "If you're a week or two late for a visit from time to time, you may have a decline in vision, and you can't always recover from that. It's a relentlessly progressive disease (3)."

Picture Perfect

- For the first time, researchers have been able to view the retina in unprecedented detail by combining two imaging modalities – adaptive optics and angiography. The project, led by a team at the National Eye Institute, used deformable mirrors and computer-driven algorithms to compensate for light distortions, allowing researchers to see live neurons, epithelial cells and blood vessels in the outermost region of the retina. The team hope the multimodal approach will help in the development of targeted treatments for diseases like AMD and Alzheimer's (4).

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Sight Unseen

Are traditional glaucoma tests failing to detect central vision damage?

Glaucoma is a leading cause of irreversible blindness. It has no symptoms and causes no pain, but can lead to complete vision loss if left untreated. Visual field tests are the current standard of care for detecting glaucoma – but they may not be for much longer. According to a study by Columbia University's Irving Medical Center, the test significantly underestimates the severity of the condition by failing to identify macular damage (1).

"When looking for signs of early glaucoma, clinicians tend to focus on loss of peripheral vision and seldom on the macula," said Donald C. Hood, Professor of Ophthalmic Science at Columbia University, who co-authored the study. "Our work has shown that damage can and does occur in this area, and the most commonly used field test can fail to detect most of the damage."

To find out just how much damage is missed, researchers examined 57 eyes from patients diagnosed with early-stage of glaucoma using two different visual field measures – the 24-2 and 10-2 tests. The results were significant. "We found that in using the 10-2 visual field over 75 percent of patients diagnosed with early glaucoma had central vision loss," said Hood.

As a result, he recommends clinicians test all patients suspected to have glaucoma using the finer grid 10-2 test, supplemented by macular spectral-domain optical coherence tomography, within their first two visits. According to Hood, the alternative method comes at no extra cost and adds just 10 minutes to diagnosis time – yet significantly increases the accuracy of glaucoma diagnosis.

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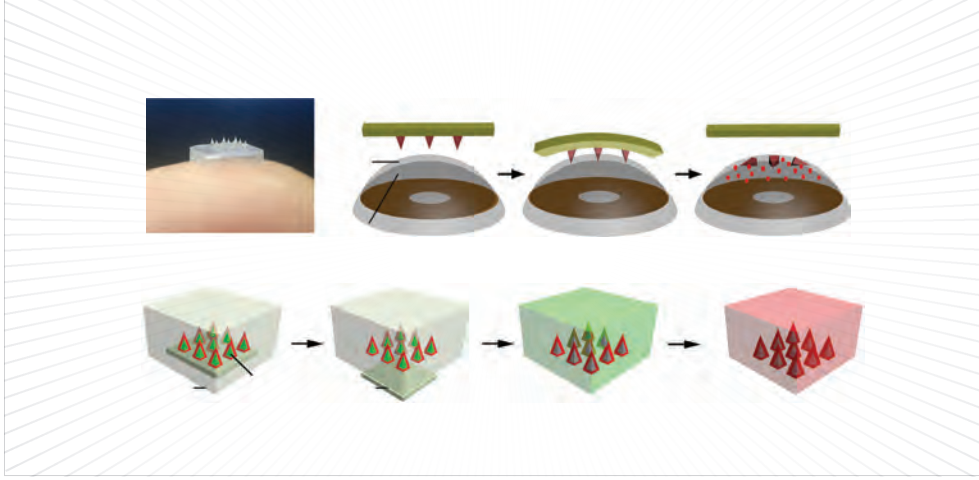

Credit: A Than et al., Nanyang Technological University

Through the Eye of a Needle

Could a double-layered eye patch answer common drug delivery problems?

Ocular drug delivery has its challenges; namely, that it requires high systemic doses, frequent topical doses (poor bioavailability and increased likelihood of side effects) or somewhat invasive intravitreal injections (not exactly welcomed by patients, so a non-compliance burden). Now, researchers at Nanyang Technological University, Singapore, believe they have found the answer… But it does still look like a miniature medieval torture device (1).

What is it?

A flexible eye patch with an array of detachable methacrylated hyaluronic (meHA)-based microneedles that are capable of releasing two different drugs at two different rates.

How does it work?

The microneedles are fabricated with a double layer of meHA and standard HA – which can act as micro-reservoirs for one or two therapeutic compounds, allowing biphasic controlled release. The meHA shell retains its structural integrity as a sharp point, dissolving slowly, while the HA-drug contained within the shell allows more rapid release after the microneedles have penetrated the ocular barrier. In theory, two drugs could work in tandem to offer a potentially more effective treatment for a variety of ocular diseases.

How is it applied?

Much like a contact lens. The patch is placed on the eye, the microneedles detach from the substrate, which can then be peeled away – all within 60 seconds.

And the benefits?

According to Professor Peng Chen, who led the study, "high drug bioavailability compared with conventional topic administration, much better patient compliance and safety compared with conventional intraocular injection, high efficacy due to controlled drug release kinetics and, most importantly, the potential to use a combination of drugs."

What's next?

In the paper, Chen and his team assessed quick release of an anti-inflammatory compound (diclofenac) and sustained release of anti-VEGF to counter corneal neovascularization in an alkali burn-injury murine model – but the list of potential applications is long. "There are no apparent limitations to the type of drugs the patch can deliver. Our ultimate goal is to translate the technology to treat other ocular diseases," says Chen.

References

1. *A Than et al., "Self-implantable double-layered micro-drug-reservoirs for efficient and controlled ocular drug delivery", Nat Commun, 9, 1, 4433 (2018). PMID: 30401883.*

Up in Smoke

Small-particle pollution could increase glaucoma risk in older men

Researchers have found a link between long-term air pollution and intraocular pressure – but only in those susceptible to oxidative stress. In the innovative study, the team collected data from 419 older men, measured each participant's eye pressure – and collected a host of other health factors – and analyzed the data against a black carbon modeling program. Black carbon – a common air pollutant – is smaller than 2.5 microns in diameter and capable of penetrating deep into the lungs, and the bloodstream. They found that men with certain genetic variations – namely, those vulnerable to oxidative stress – experienced increased eye pressure.

"Oftentimes, when we think about glaucoma we think about risk factors such as age and genetic predisposition – and we don't think about the environment," said Jamaji Nwanaji-Enwerem, PhD candidate at Harvard Medical School and lead author of the study. "But one thing we're starting to appreciate more is how the environment impacts health outcomes (1)."

The findings highlight the potential impact of environmental factors on IOP-related disease, and so Nwanaji-Enwerem and his team hope the study will be useful in future policy or public health initiatives.

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In My View

In this opinion section, experts from across the world share a single strongly-held view or key idea.

Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of ophthalmology. They can be up to 600 words in length and written in the first person.

Contact the team at edit@theophthalmologist.com

The China Study

Accessibility and affordability of cataract surgery has improved in China – but there is still more to achieve

By Ningli Wang, Director of Beijing Tongren Eye Center, Beijing, China

Access to healthcare has improved dramatically in China over the last two decades. Before 2009, there were only three basic medical insurance systems. But thanks to persistent efforts from the government – and significant financial support – 95 percent of Chinese people are now covered by medical insurance. At present, this insurance covers between 70 and 80 percent of cataract surgical expenses. Not only that, the government initiated the "One Million Cataract Blindness Project" in 2009 to provide free cataract surgeries for poorer patients, with additional financial and medical support from NGOs. To speak from the perspective of ophthalmic resources in China, the number of ophthalmologists reached 37,000 in 2018 – 1.5 ophthalmologists per 50,000 people. 36 percent can perform cataract surgery independently, and of those, 34 percent can perform phacoemulsification. Currently, over 85 percent of hospitals have established ophthalmology departments, with 88 percent providing cataract surgery independently. These developments have all greatly increased access to affordable cataract surgery in China.

After the medical reform in 1998, an increased cataract surgical rate (CSR) saw the number of cataract operations performed per million population rise from 370 in 2000 to 2,205 in 2017. However, the CSR differs greatly in regions, being highest in Shanghai (4,251) and lowest in Hubei (763). Interestingly, in Shanghai, private hospitals completed more cataract surgeries than public hospitals, indicating that private hospitals are becoming an important force in preventing and treating cataract blindness. Furthermore, the cataract surgical coverage (CSC) in China among patients with severe cataract-related visual impairment and blindness has increased from 36 percent in 2006 to 63 percent in 2014, while good visual outcomes have increased from 47 percent to 62 percent in cataract-operated eyes.

But change is not happening as fast as some would like. Despite significant improvement, CSR in China it is still low compared with countries like the US (11,000) and India (6,000). Around 7.58 million patients with cataract-related visual impairment or blindness still await surgery in China. If we want to achieve a CSC of 95 percent, our CSR needs to reach 8,000. Not only that, even though the number of ophthalmologists has exceeded the standard defined by WHO in the "Vision 2020" initiative, most are in economically developed urban areas, with few working in rural zones, where the CSR and CSC are low. Of the 75 percent of county hospitals that can perform cataract surgery, most have only one or two cataract surgeons. Given the lack of experienced surgeons and qualified surgical treatment in county hospitals, some rural patients have to travel a long distance to seek surgical treatment in large cities – which can pose a problem; elderly patients who have difficulty traveling my not receive proper treatment. Though experienced ophthalmologists from provincial or municipal hospitals could come to county hospitals to operate on local patients, it would not substantially improve the surgical ability of local ophthalmologists or the eye care service the hospital provides.

A national training program called "Standardized Training to Elevate Eyecare in Rural China (China STEER)" has been established to improve the capability of county level hospitals to deliver high-quality eye care, including high-quality cataract surgery. Started in 2016, the strategy is set to redress existing CSR disparities between urban and rural areas. Given the expected rise in CSR – paired with a rapidly aging population – the financial burden of medical insurance system is expected to grow as well. Therefore, a multipronged strategy with new fundraising channels is needed to ensure patients receive the highest quality cataract care.

Easing the Pressure

It's time to change the way we think about premium lenses for glaucoma patients

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

The advances in surgical glaucoma technology have got doctors thinking about the possibility of premium lens implantation in a glaucoma patient – but the question is: why and when?

As in many areas of ophthalmology, there has also been an increased emphasis on improving quality of life and patient satisfaction in the glaucoma patient. With the introduction of microinvasive glaucoma surgery (MIGS) technology, we are now better able to reach that goal. Personally, I'm a big advocate of early intervention. If one of my patients has mild or moderate glaucoma, is on topical meds or has IOPs not at target, I will offer some type of MIGS procedure. The new glaucoma surgeries have allowed us to reduce the drop burden for our glaucoma patients, improve compliance, and, due to the high safety profiles, intervene earlier in the disease process. Another key characteristic of these MIGS procedures is the improved predictability of post-operative refractive outcomes compared with traditional glaucoma surgeries (such as trabeculectomy and tube surgeries). To me, it is no longer acceptable to "just bring the IOP down," but rather, we should strive to attain target IOP, while maintaining or even improving quality of life. Therefore, why shouldn't our glaucoma patients deserve premium options during cataract surgery?

Due to the unpredictable post-operative refractive outcomes of traditional glaucoma surgery, and the fact that we would wait to perform surgery until the patient had more advanced glaucoma, many of these patients were not good candidates for premium IOLs. Now that we are intervening earlier in the disease course (healthier fields and ONH), getting more and more patients off drops (decreasing the chance of ocular surface disease and noncompliance), premium IOL technology is often part of the IOL discussion. For me, toric IOLs are a great way to start incorporating premium lenses. There is really no downside to reducing post-op uncorrected astigmatism. On the whole, if a patient has corneal astigmatism – any more than 0.75 diopters – I feel it is worth addressing with a lens; studies have demonstrated improved contrast sensitivity in low light conditions when correcting this level of astigmatism. Even if a patient has advanced glaucoma, I use a monofocal toric lens or accommodating toric lens wherever possible. Sure, the patient may need additional surgery or even a standard trabeculectomy in the future, which could lead to wearing glasses or a change in prescription, but I always explain that to the patient ahead of time.

Historically, one would shy away from multifocal lenses in glaucoma patients because of the potential loss of contrast sensitivity inherent to these lenses, given that, as mentioned earlier, loss of contrast is one of the earliest manifestations of glaucomatous optic neuropathy. The newer lower add multifocal and EDOF lenses claim to offer less loss of contrast sensitivity than the previous higher add multifocal lenses, which has allowed us to re-evaluate the use of multifocal lenses, especially in the mild glaucoma patient. Another choice for me, the Crystalens accommodating IOL, has been a safe lens to implant in glaucoma patients as it is an aspheric monofocal optic that does not negatively affect quality of the image. I'm currently running my own study, looking into the mean deviation of glaucoma patients' visual field pre and post cataract surgery. By using ray tracing (iTrace, Tracey Technologies), we are also comparing HOA and MTF between Crystalens and various multifocal IOLs. Data should be available by ASCRS 2019.

I'm aware not everyone feels the way I do. As glaucoma surgeons, we are often primarily concerned with getting pressures down, and we sometimes don't think it is worth using a premium lens, such as toric lens – but I think that paradigm is starting to change.

We have already seen a huge shift here in the US, especially now, when there are so many options available. Don't dismiss the need for maximizing refractive outcomes in glaucoma patients – they deserve the same uncorrected quality of vision as everybody else.

Outside-In *Innovation*

HOW AND WHY TECHNOLOGICAL AND SCIENTIFIC DISCOVERIES FROM DIVERSE FIELDS DRIVE OPHTHALMOLOGY FORWARD

The ophthalmologists we speak with often point out that they chose ophthalmology because it is constantly changing and evolving, which, in turn, gives them great scope to continuously improve patient outcomes.

Few would argue that ophthalmology is one of the fastest moving areas of medicine; relentless improvement and innovation are its beating heart.

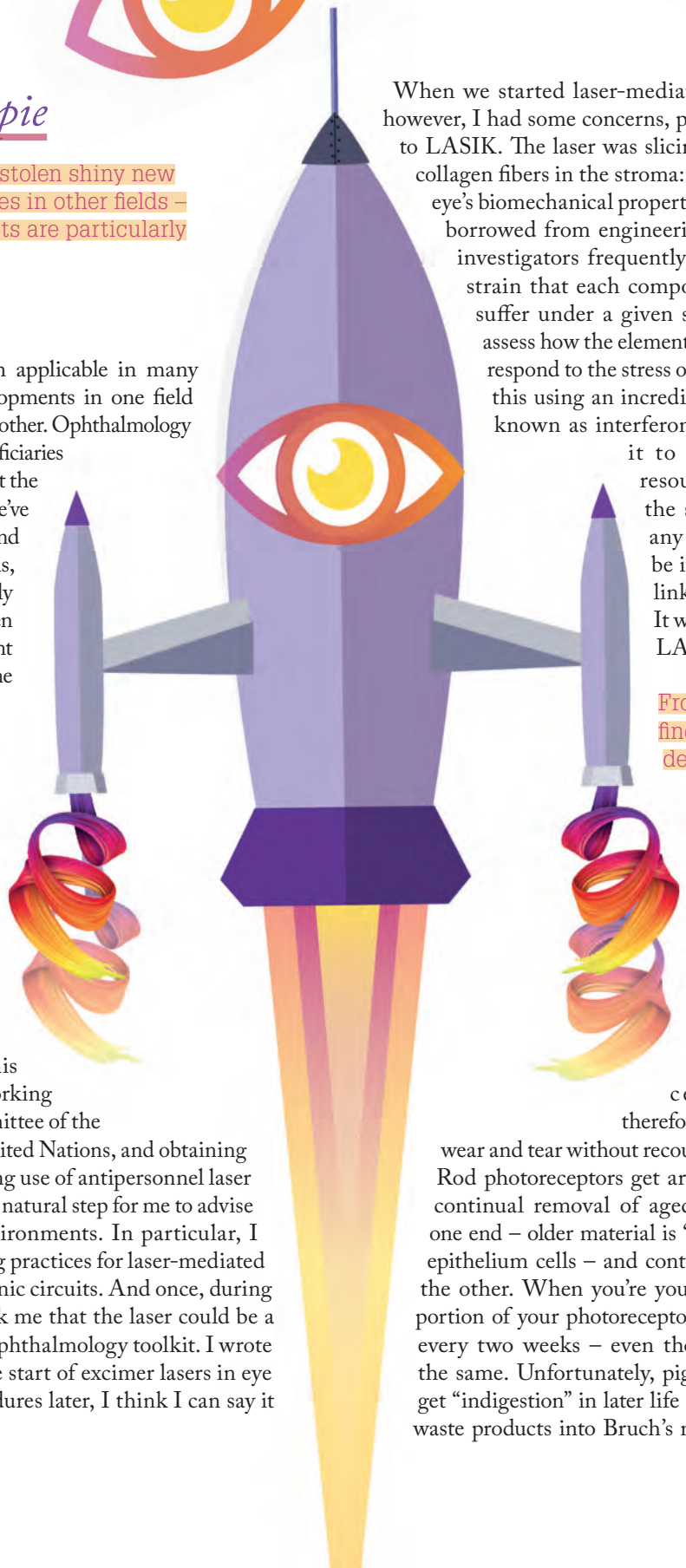
The careers of John Marshall and Bert Massie were driven by their ability to constantly seek inspiration for their ophthalmic inventions from other walks of life. Here, we tell their stories, and shed light on a handful of other "out of left field" ideas.

Eye of the Magpie

Researchers have always stolen shiny new techniques from colleagues in other fields – and some ophthalmologists are particularly effective thieves.

By John Marshall

Scientific methods are often applicable in many different areas: hence, developments in one field frequently enable progress in another. Ophthalmology has been one of the biggest beneficiaries of this process. Indeed, without the technologies and instruments we've taken from other disciplines and adapted for ocular applications, our specialty would be virtually unrecognizable. I've always been happy to acquire new treatment options for the eye; here are some of my favorite examples.



From silicon circuits to corneal surgery

Back in the 1960s, I did my PhD on laser damage to the retina, sponsored by the Royal Air Force (RAF). They were worried about the potential of laser weapons, so I spent a great deal of time developing safety data to protect air crew. This eventually resulted in me working with the International Committee of the Red Cross, addressing the United Nations, and obtaining a Geneva Convention banning use of antipersonnel laser weapons. From there, it was a natural step for me to advise on laser safety in other environments. In particular, I helped develop good working practices for laser-mediated manufacture of microelectronic circuits. And once, during a factory inspection, it struck me that the laser could be a very special addition to the ophthalmology toolkit. I wrote up a patent, and that was the start of excimer lasers in eye surgery. Fifty million procedures later, I think I can say it was a valuable patent!

When we started laser-mediated refractive surgery, however, I had some concerns, particularly with regard to LASIK. The laser was slicing through millions of collagen fibers in the stroma: would that disturb the eye's biomechanical properties? To answer that, we borrowed from engineering. In that discipline, investigators frequently have to calculate the strain that each component of a system will suffer under a given stress: for example, to assess how the elements of aircraft wheels will respond to the stress of landing. Engineers do this using an incredibly sensitive technique known as interferometry; and we applied it to the eye. With that resource, we could assess the strain associated with any kind of intervention, be it PRK, LASIK, cross-linking or cataract surgery. It was key to validating the LASIK approach.

From military range-finders to macular degeneration

More recently, I helped develop a new laser therapy concept for age-related macular degeneration (AMD). The advance had its genesis in a thorough understanding of retinal maintenance. Remember, retinal cells don't divide, therefore, they must cope with wear and tear without recourse to cell replacement. Rod photoreceptors get around this through the continual removal of aged pigment material at one end – older material is "bitten off" by pigment epithelium cells – and continual replenishment at the other. When you're young, the light sensitive portion of your photoreceptors is in effect, replaced every two weeks – even though the cells remain the same. Unfortunately, pigment epithelium cells get "indigestion" in later life and pass semi-digested waste products into Bruch's membrane: the Bruch's

membrane gets clogged up, interfering with transport processes and contributing to further waste product accumulation and sequelae, such as accelerated ageing, a risk factor for AMD.

My idea was to clean up Bruch's membrane and thereby rejuvenate the retina. But how? Conventional lasers for treating retinal conditions were all thermal systems and heat flow would destroy the photoreceptors. Short pulsed lasers were designed for posterior capsulotomies, and have their effect by producing cavitation – a kind of micro-explosion. You can't have that in the retina – it would result in hemorrhage. We had to design a new laser energy delivery system, using concepts derived from military range-finder technology – which I can't tell you about! Our new laser has a large spot size and an incredibly short (nanoseconds) pulse duration and a pixelated beam. This permits photodisruption of selected regions of the pigment epithelium without the thermal conduction to overlying photoreceptors that you would get with conventional lasers, and without destroying large areas of pigment epithelium (which would starve the overlying photoreceptors). Photodisruption activates pigment epithelium cells to release matrix metalloproteinase, which unblocks Bruch's membrane and thus modulates associated pathology.

LEAD gives weight to AMD laser therapy

- Trial: Laser Intervention in Early Age-related Macular Degeneration (LEAD)
- Investigational product: Retinal Rejuvenation Therapy (2RT; Ellex's nanosecond laser treatment for slowing progression from intermediate to late AMD)
- Double-masked, randomized, sham-controlled trial in Australia (five sites) and Northern Ireland (one site)
- Inclusion criteria: Age>= 50 years; diagnosed with AMD; at least one large drusen in each eye; no evidence of atrophy per multimodal imaging
- Recruitment: n=292
- Treatment: 12 laser spots applied to macular region each six months for 36 months
- In patients without pseudodrusen, 2RT was associated with a 77 percent reduction in rate of progression from intermediate to late AMD

"With CRISPR it is theoretically possible to treat autosomal dominant inherited disorders by cutting out the dominant negative mutation."

Ellex has recently adopted and developed this concept into the Retinal Rejuvenation Therapy (2RT) product. Data from a three-year, randomized, multicentre clinical trial (1) in intermediate AMD are very promising (Sidebar), and I believe that our hypothesis is proven and this approach will have a significant impact and potentially massive savings on the use of drugs to treat neovascularization.

CRISPR, cleaner cornea

Ophthalmology also commandeers molecular techniques where appropriate: for example, CRISPR-mediated gene therapy. This approach, based on modifications of a naturally occurring antiviral defence system found in bacteria, permits precise excision of specific DNA sequences. With CRISPR, therefore, it is theoretically possible to treat autosomal dominant inherited disorders by cutting out the dominant negative mutation. Indeed, if several related defects are positioned closely enough in the gene, we can excise them all in a single step. Thus, as long as the patient has normal sequences on the complementary chromosome, the approach may modulate or even cure autosomal dominant disorders.

CRISPR gene therapy was originally envisaged for simple dominant negative diseases like haemophilia – but now we are applying it to more complex diseases, including ocular conditions, such as inherited retinal dystrophies. My opinion is that the cornea is a more attractive gene therapy target than the retina: rather than dealing with non-dividing neuronal tissue at the back of the eye, you only need to get to the DNA in the easily-accessible dividing cells on the front of the eye. That's

why we are targeting granular dystrophies, which are all caused by mutations in a small region of chromosome 5. As part of this effort, I'm assisting Avellino Labs, which is developing genetic screening for dystrophy, and also working with Tara Moore, our Head of Research at Ulster, to get our new therapy for corneal dystrophy into clinical trials. CRISPR for cornea really is the low-hanging fruit in ocular gene therapy, so watch this space!

Looking ahead

I expect ophthalmology to continue stealing from diverse fields. In particular, genetics will have a big impact on refractive surgery, and the development of rapid diagnostic systems will revolutionize healthcare in remote locations. For example, people are working on functionalized membranes that a patient could lick and insert into a smartphone to receive a rapid diagnosis anywhere. That could be a very important way of guiding critical therapeutic decisions in difficult environments, such as a space capsule. In the clinic, for example, in cases of red-eye, you really need to know if the condition is of bacterial, fungal or viral origin, so that you can appropriately treat it – get it wrong, and you could lose the eye. I look forward to seeing these kinds of advances appropriated for eye care, as others have been before them. Basically, as long as human ingenuity continues to produce attractive new innovations, the ophthalmology magpie will continue to feather its nest!

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From Star Wars to a New Hope

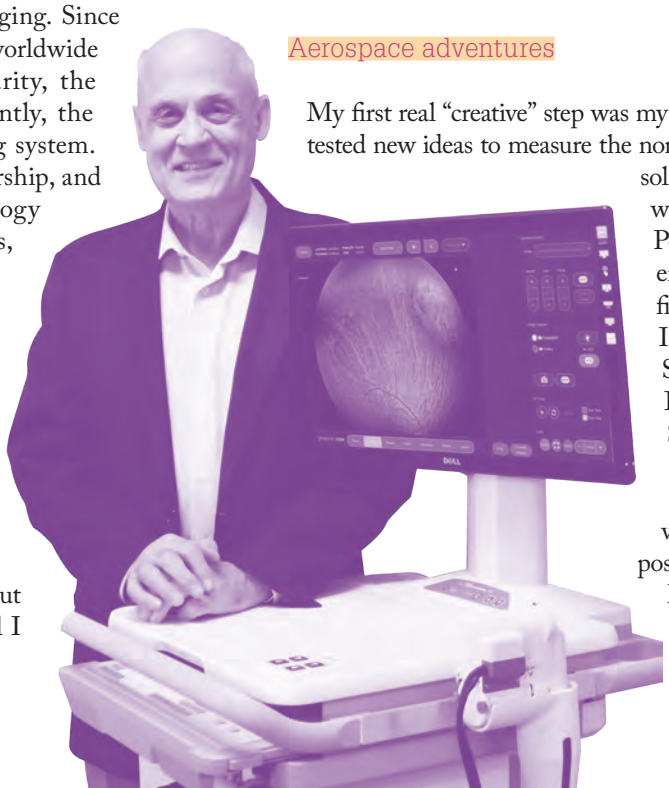
With Bert Massie

Bert Massie worked in the aerospace industry for many years, developing his knowledge and expertise in adaptive optics and interferometry. At the height of his career, he followed a calling: advancing the field of ophthalmology by responding to the most pressing needs for retinal imaging. Since then, he has developed the RetCam, used worldwide in screening for retinopathy of prematurity, the Micron for eye research, and, more recently, the ICON – an improved wide-angle imaging system. Here, he shares his passion for entrepreneurship, and describes how innovations in ophthalmology have been driven by the evolution of sensors, microprocessors and lasers.

A curious mind

I'm a scientist and an engineer but I tend to think of myself as an entrepreneur. I don't think that this is something you learn – it is a natural and intense personal drive. It is evident in everything I do; it gets me out of bed early in the morning.

As a young child I was very curious about how things worked. In early grade school I took my toy electric train engine apart because I really wanted to know what all those gears did. I developed an interest in astronomy, and for many nights lay outside on a blanket to watch the stars appear in the evening sky. I knew all the constellations. For an entrepreneur curiosity is foundational, but must be complemented by a creative mind, and a self-confidence and drive to develop the ideas that originate in your mind. For example, as a teenager I built a 12" telescope to explore an idea about how to obtain color images of galaxies.



Aerospace adventures

My first real "creative" step was my PhD thesis, where I tested new ideas to measure the non-linear properties of solids using ultrasound with laser probes. Post graduate school I entered the aerospace field, and for 11 years I was involved in the Strategic Defense Initiative, nicknamed Star Wars, and in my last aerospace role I spent five years working in a senior position at the Lawrence Livermore National Laboratory, which

is a federal research facility in California, US, focusing on finding solutions to security-related challenges. In my aerospace career I was awarded over 25 patents in optics, I published the same number of journal articles, and I edited a reference book on optical technology. I developed techniques for interferometry – classically, interferometers make accurate measurements of optical components – and my most interesting project was a high-performance two-wavelength interferometer. Optical Coherence Tomography uses multiple wavelengths, but at that time the required "low-coherence" sources did not exist, so I had to use two lasers, which required a high level of sophistication. Following this, I developed a novel adaptive mirror for correction of atmospheric aberrations on imaging of space objects.

In my last position with the national laboratory, together with my colleagues, I developed a technique to image space optics through the turbulent atmosphere without using adaptive optics. This technique was proven in experiments between an object on a mountain top and a lower altitude telescope.

I enjoyed working in the aerospace industry, but from the very beginning of my career – since my undergraduate years, in fact – I sought an opportunity where I could help people with vision impairment regain their sight. I sought a role where I could focus on more meaningful goals.

Problems and solutions

When I decided to make a career in ophthalmology, I found that much of my extensive optics knowledge and experience was applicable. I started working on various ophthalmic solutions, including a non-contact ultrasound-based tonometer, which worked, but was too expensive to merchandise. As it often happens, through a random series of events, I met a very prominent physician - A. Linn Murphree - who introduced me to the challenge of wide-field imaging in children. The device developed by Dr. Murphree and his team did not adequately perform, and I picked where they left off. I redesigned the instrument from the ground up, and this became the RetCam.

RetCam was originally developed to image retinoblastoma but was quickly adapted to image retinopathy of prematurity (ROP). This disorder potentially afflicts infants born before 31 weeks of gestation and weighing less than 1250 g. There is significant ocular morbidity associated with ROP, which usually develops in both eyes. It is among the most common causes of childhood vision loss and often leads to permanent vision impairment.

We were told that we would sell a dozen units, but the RetCam was widely adopted and there are now over 2,000 RetCam units in use around the world. It can be operated by non-ophthalmologists, who can send images to a central facility, where they are professionally evaluated. It greatly reduces the labor costs and the time it takes for the problematic cases to be picked up. A point that is especially vital in developing countries; there are very competent clinicians working there, but they don't always have the staff to screen every child. If diagnosis and treatment is timely, it is usually very effective and protects patients from lifelong blindness.

Answering the call

When I left the RetCam program, I focused on developing technology for eye and eye-brain research, using laboratory animals such as mice and rats, and introduced a retinal imaging microscope called the Phoenix Micron. Developing the mouse imaging system was quite difficult and there were times where I was certain that failure was just a day away. Nevertheless, the Phoenix Micron retinal imaging microscope became a reality. I was again told that I might be able to sell a dozen units – and we now have over 300 units in use in major institutions around the world.

At the age of 71, when I was about to retire, and with pressure from several sources, including several senior clinical leaders – I decided to return to clinical ophthalmology and develop a successor to the RetCam. The base technology for the RetCam had not changed since inception. Ophthalmologists had been complaining about issues with imaging patients from ethnic minority groups – those with darkly pigmented retinas – such as African Americans and Asians. The RetCam performed poorly with dark retinas and could not image adults. When the retina is dark, the light returned to the image sensor is lower than the scatter in the cornea. As a result, the image is lost in the haze.

In developing what became the Phoenix ICON my team and I accepted an absolute directive to develop high-contrast/high-resolution imaging even in darkly pigmented retinas, and in the process were able to also

Enabling Tech

Technological evolution of the last few decades has really influenced ophthalmology. When sensors, such as CCD or CMOS, entered the commercial market, the performance of instrumentation improved considerably. The sensor in the Phoenix ICON allows the provision of much lower light level onto the retina, enabling imaging of awake adult patients.

More powerful microprocessors have also had a major impact, and at first there wasn't a good way of handling digital data. Storage has also seen unbelievable gains in volume and affordability. The first RetCam had 600 MB of optical storage; now, we can store thousands of images. And we can transfer large data files easily and store images in the cloud – something that we had not considered previously.

Lasers are another example of seismic change. As a graduate student we built our own lasers, and now they are readily available to applications such as ophthalmology.

image adults – something RetCam had not been able to do. The Phoenix ICON design was a complete change from the RetCam and arose from a "blank sheet of white paper." Getting the light in and to the retina without the scatter is quite difficult – these difficulties were overcome, but only by ignoring a number of classic ophthalmic rules along the way!

The Phoenix ICON lived up to its objectives and is a wide-angle retinal imaging system with high-contrast imaging and ability to image adults as well. I believe Phoenix ICON's capability has the potential to contribute to new areas such as melanoma; all this is the subject of clinical trials for validation. We also have plans to provide the technology to countries requiring humanitarian assistance: we've been talking to The Queens Jubilee Trust in the UK, who can help us answer the needs for these systems in India.

Working backwards

I begin my projects by first being certain that the right question is identified. For example, many times RetCam users asked for more resolution, but they really needed improved visibility, meaning higher contrast. Innovations such as the Phoenix ICON and Phoenix Micron need to not only be a technological advancement, but also an advancement that makes a useful difference. Accordingly, as a final and acid test before I launch a project, I imagine myself standing in front of the physician and showing the device; if I do not see excitement from the user, I do not proceed.

Innovations must make a difference, not just be different, and that is one of the most important reasons for the decision on pursuing a project. This means of evaluation has served me well.

N.A.(Bert) Massie, Ph.D., has more than 40 years of experience as a lead entrepreneur of a variety of optical-based technologies. He is currently working for the Phoenix Technology Group.

Vision Restoration in 2D

Can graphene and molybdenum disulphide really find another application in artificial retinas?

After years of speculation about the exact properties and possible uses of graphene, the material was finally properly isolated and characterized in 2004 – an achievement that was recognized in 2010 with a Nobel Prize in Physics for the two University of Manchester physicists, Andre Geim and Konstantin Novoselov. Since then, its applications have included solar cells, dental discs, inks and bioadhesives.

Now, graphene – along with another two-dimensional material, molybdenum disulphide – is being used to fabricate artificial retinas. Nanshu Lu from University of Texas in Austin, who led the first demonstration of the flexible device, acknowledges that research is still at an early stage, but scientists believe the device could one day help restore sight in people affected with retinal diseases, such as macular degeneration or diabetic retinopathy, which affect millions of people around the world, causing vision impairment followed by complete vision loss. Outside of ophthalmologic applications, it is also believed that the device – based on a few thin layers of graphene and molybdenum disulphide, as well as layers of gold, alumina and silicon nitrate – could be used to track brain and heart activity through electronic tattoos on the skin's surface, possibly with the addition of transistors to

amplify the brain or heart signal.

Current implants used to help with restoring vision in affected individuals are silicon based. Unfortunately, the results are often unsatisfactory, with distorted or blurry vision, which in part down to the rigidity and a flat shape of the silicon-based implants; they simply cannot replicate the natural curved shape of the retina. The novel device appears to adapt to the shape of the eye and mimic its structural features. It includes an external circuit board, which is used to store the electronics used to digitally process light, stimulate the retina and receive signals from the visual cortex.

Reference

1. *American Chemical Industry, "A new generation of artificial retinas based on 2D materials" (2018). Available at: https://tinyurl.com/ychfajuk. Accessed November 20, 2018.*

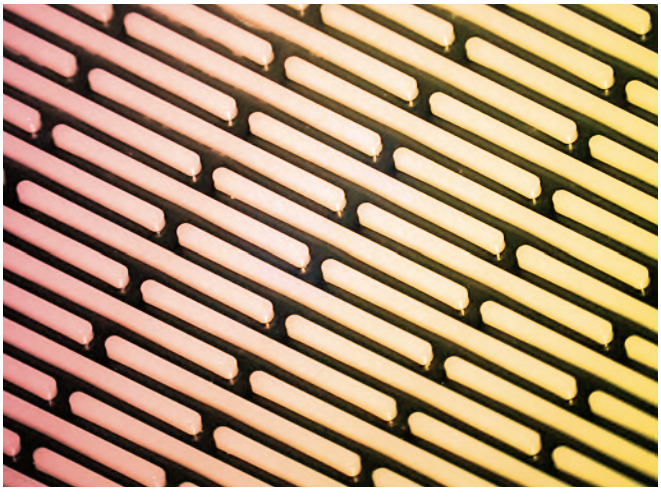
The Small Print

From semi-conductors to sight-saving therapies: introducing PRINT Technology

The need to produce smaller, more sophisticated drug or drug-delivery particles presents a challenge to pharmaceutical manufacturers. So, how do you guarantee high batch reproducibility and dose uniformity on a commercial scale? Simple – you look to the industries who do it best. Or at least, that's what Aerie Pharmaceuticals did when they acquired the rights from Envisia Therapeutics, Inc. to use Particle Replication in Non-wetting Templates – also known as PRINT® – technology in October 2017.

Integrating the precision of the semiconductor industry, with the efficiency and scalability of plastic films-based manufacturing, PRINT is capable of producing particles as small as a nanometer. It is compatible with a wide variety of drugs – including many classes of small molecules and biologics – and can be used to make combination products with multiple active ingredients.

Its versatility hasn't gone unnoticed. Aerie is using the PRINT platform to produce injectable intraocular implants, composed of a bio-erodible polymer that steadily releases drug over 4-6 months, for its two lead clinical development programs in retina – AR-1105 (dexamethasone) and AR-13503 (Rho kinase/Protein kinase C inhibitor) – for conditions such as diabetic macular edema and neovascular AMD. Aerie is also evaluating the use of PRINT-produced sustained-release therapies in glaucoma and ocular hypertension. Watch this space.



THE INNOVATORS 2018

The field of ophthalmology is constantly breaking new ground. As one of the most inventive fields in medicine, ophthalmology is often at the forefront of cutting-edge technologies and treatments. Here, some of the leading innovators from the ophthalmic space present their latest offerings: from imagers and diagnostics, to cutting edge refractive surgery and glaucoma care.

DELIVERING A NEW CONFIDENCE

A novel MIGS device, the Hydrus® Microstent, helps restore the eye's natural fluid flow

Glaucoma, the leading cause of blindness worldwide, unquestionably requires better treatment alternatives. Ivantis is a company focused on addressing this need. Recently, the Hydrus Microstent, a unique *ab interno* device, progressed from pivotal trial to FDA approval. Now, in addition to the US introduction, the company is making it commercially available in select international markets.

Roughly the size of an eyelash (8 mm in length), the Hydrus Microstent is a novel minimally invasive glaucoma surgery (MIGS) device that has been designed to reduce eye pressure by re-establishing aqueous flow through Schlemm's canal – the eye's natural outflow pathway. The Hydrus Microstent is constructed from nitinol, a highly biocompatible material commonly used in a wide range of medical device applications. Its flexibility allows the microstent to be inserted into the trabecular meshwork and placed in Schlemm's canal, where it acts to restore the eye's natural fluid flow in three key ways:

- *Bypass:* The Hydrus Microstent creates a direct connection between the anterior chamber and Schlemm's canal, thereby allowing aqueous flow to bypass the trabecular meshwork.
- *Scaffold:* Through dilation and support of Schlemm's canal, the Hydrus Microstent expands the canal's cross-sectional area without obstructing fluid access to collector channel ostia.
- *Span:* The unique reach of the Hydrus Microstent gives 90˚ coverage of Schlemm's canal, thereby extending over multiple collector channels; this eliminates the need for precise stent placement, and the need for implantation of multiple devices.

The landmark HORIZON Pivotal Trial was the largest MIGS controlled clinical study ever conducted – it assessed outcomes in 556 mild-to-moderate primary open angle glaucoma patients undergoing cataract surgery. Patients were randomized to receive either cataract surgery plus the Hydrus Microstent, or cataract surgery only (control). Key findings included:

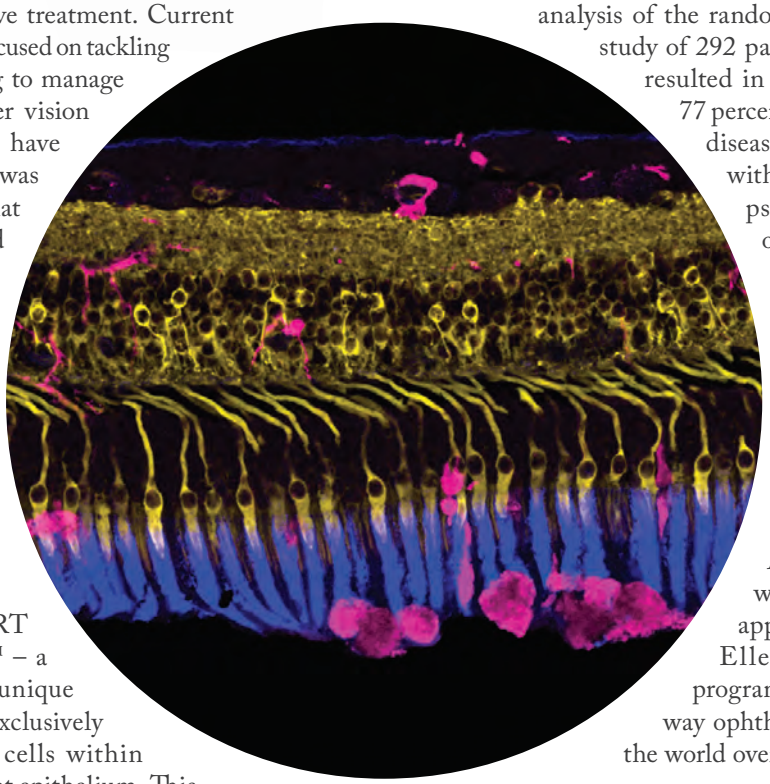
- Over 77 percent of treated patients exhibited IOP reduction of 20 percent or more (less than 58 percent of the control group achieved this level of reduction) – to date, the largest treatment effect reported for any MIGS pivotal trial at 24 months.
- The Hydrus Microstent group achieved more substantial IOP reduction than the control group (7.5 mmHg versus 5.3 mmHg – a 43 percent difference) – the largest difference in IOP reduction reported in a MIGS pivotal trial at 24 months.
- Follow-up showed that 78 percent of Hydrus Microstent patients remained medication-free at two years (as compared with 48 percent of controls) – again, the highest treatment versus control for medication elimination of any MIGS pivotal trial.

This data, together with its expanding history of use in patients – more than 4,000 cases, incorporating a wide range of disease severities – give both surgeons and patients confidence in this new MIGS procedure. At present, Ivantis is focused on marketing the Hydrus Microstent commercially in select markets; increasing levels of favorable real-world data associated with this device – and its unique risk/ benefit profile for treating mild to moderate glaucoma patients – will inevitably see demand grow outside those markets.

R IS FOR RETINA AND REJUVENATION

Meet the only clinically proven laser treatment to delay progression to late-stage AMD

AMD affects 11 million people in the United States alone. As patient populations age, the number will surely grow – and so too will the need for effective treatment. Current therapies are almost entirely focused on tackling late-stage AMD; attempting to manage patient symptoms only after vision loss and/or serious damage have occurred. But what if there was a way to intervene earlier? That was the question Ellex asked itself and then answered with 2RT® Retinal Rejuvenation Therapy – a new laser treatment that offers ophthalmologists the chance to delay the degeneration process in a significant proportion of patients with intermediate AMD – as highlighted in the LEAD trial (1).



So how does it work? 2RT uses Nanopix Technology™ – a nanosecond laser pulse in a unique pixelated beam profile – to exclusively target selected individual cells within compromised retinal pigment epithelium. This patented process stimulates a natural biological healing process in the retina – the rejuvenation – and improves the hydraulic conductivity of Bruch's Membrane. And because the process is gentle, it does so without collateral damage to the overlying photoreceptor rods and cones of the retina.

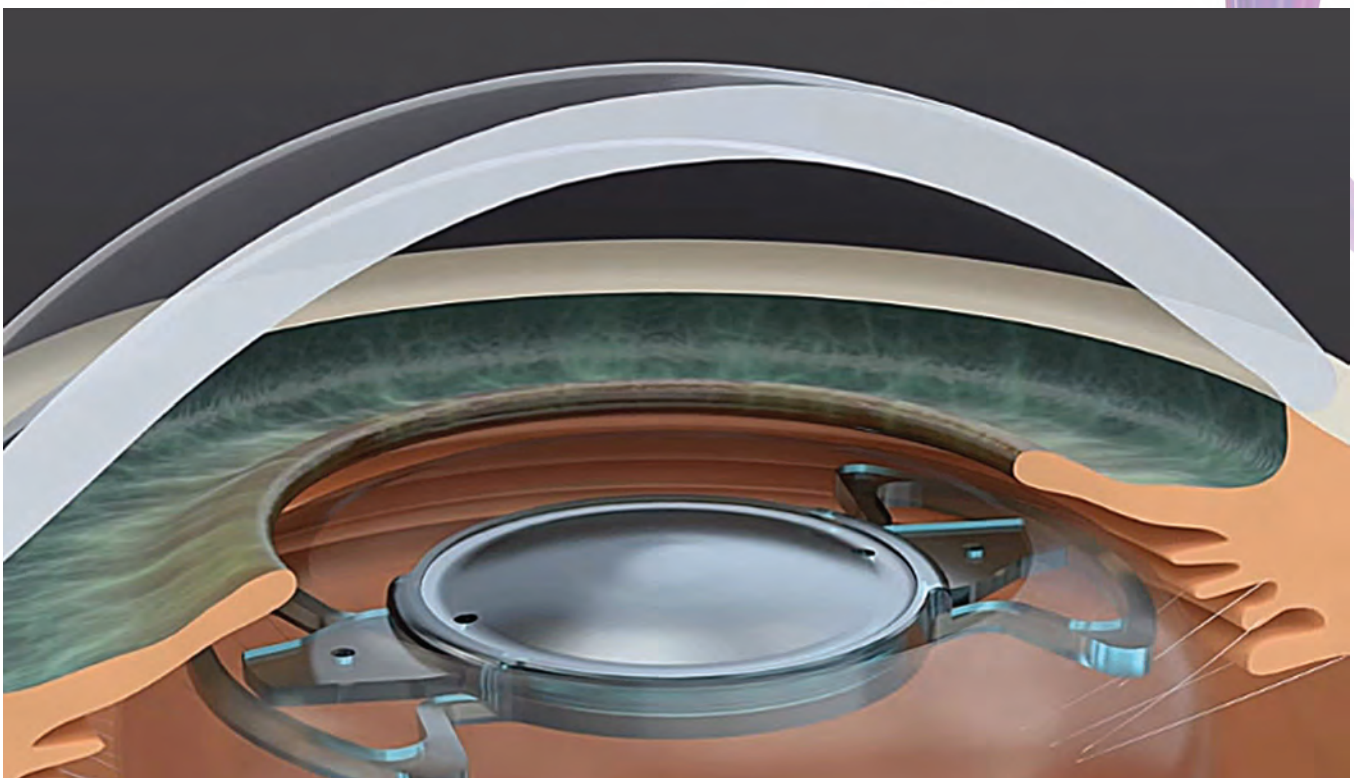
In the extensive, multi-center LEAD clinical trial over 36 months, it was shown that 2RT achieves a significant reduction in the rate of progression to late-stage AMD in just over three quarters of intermediate AMD patients. Specifically, post-hoc analysis of the randomized, sham-controlled study of 292 patients showed that 2RT resulted in a clinically meaningful 77 percent reduction in the rate of disease progression in patients without co-existent reticular pseudodrusen (76 percent of patients enrolled).

2RT Retinal Rejuvenation Therapy has already been approved for indications of clinically significant macular edema (CSME) in Europe and the United States – and for early AMD in Europe. And with its revolutionary approach to cell renewal, Ellex's unique treatment program looks set to change the way ophthalmologists treat AMD the world over.

2RT® is not approved for sale in the USA for the indication of early AMD.

Reference

1. *RH Guymer et al., "Sub-threshold nanosecond laser intervention in age-related macular degeneration: the LEAD randomized controlled clinical trial", Ophthalmology, (2018). PMID: 30244144*



THE INTELLIGENT IOL

How Precisight® IOL technology allows for lifelong adjustment

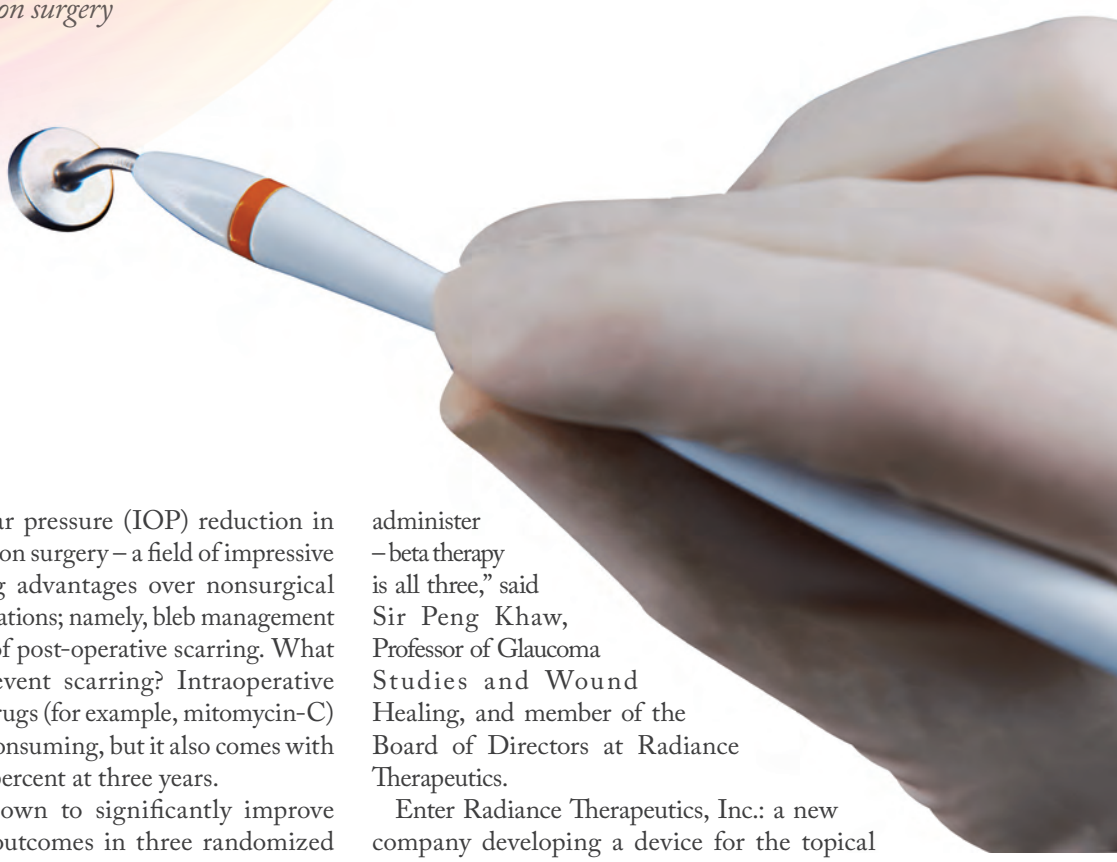
Premium lens patients have high expectations. But how can surgeons guarantee optimal outcomes with soon-to-be outdated technology? Enter the Precisight® IOL by InfiniteVision Optics. Unlike conventional IOLs, the Precisight® anticipates the potential for future enhancement to the patient's vision or the replacement of optical technology in the eye. The platform is composed of two optics, a base, which also functions as a docking station, and a front lens. In cases where a patient's vision needs to be enhanced, only the easily accessible front lens is exchanged, minimizing the dangers associated with full lens explantation. "Surgeons can be very cautious about which patients they recommend a multifocal lens to – and for a good reason: nobody wants dissatisfied patients," says Carsten Laue, President of InfiniteVision Optic. "But with the adjustable Precisight® platform, there is no need to worry. Both the surgeon and the patient know that there is a way to fix potential issues, and achieve the best possible vision – now and in the years to come."

The concept of an intelligent IOL can be traced back to Theodore Werblin, a surgeon from Princeton, who had the idea to separate spherical power from toricity and multifocality to reduce the inventory of lenses at a clinic. InfiniteVision took that concept to the next level by creating the adjustable Precisight® platform. "With the potential to make lifelong adjustments, patients no longer have to settle for sub-optimal visual outcome after cataract removal. Our personalized solutions have been designed to suit each patient's personal preferences and anatomical precondition, accommodating for the inevitable vision changes that happen over time," says Laue.

The Precisight® IOL is currently only available in Europe with a monofocal aspheric optic. Toric and multifocal optics are in development.

TACKLING SCARRING, IMPROVING OUTCOMES

Introducing Radiance Therapeutics: a new company focused on commercializing beta therapy for glaucoma filtration surgery



When it comes to intraocular pressure (IOP) reduction in glaucoma management, filtration surgery – a field of impressive innovation – has compelling advantages over nonsurgical treatments. But it also has limitations; namely, bleb management remains challenging because of post-operative scarring. What current options exist to prevent scarring? Intraoperative application of chemotherapy drugs (for example, mitomycin-C) is not only complex and time consuming, but it also comes with a failure rate approaching 50 percent at three years.

Beta therapy has been shown to significantly improve glaucoma filtration surgery outcomes in three randomized controlled clinical studies [1,2]. The most recent of these studies reported odds ratios indicating that beta irradiation therapy patients were five and a half times more likely to experience lower IOP at the end of one year than patients treated with antimetabolite mitomycin-C [3]. Beta therapy fits well into the surgical workflow and reduces scarring by using beta irradiation to down-regulate the fibroblasts at the heart of the scarring process – thus helping to maintain reduced IOP (notably, while minimizing stray dosing to non-target tissues). Beta therapy also avoids exposing medical staff to hazardous chemotherapy drugs, such as mitomycin-C – the current standard of care.

"For glaucoma surgery to be successful, anti-scarring therapies must be effective, consistent in dosage, and fast and easy to administer – beta therapy is all three," said Sir Peng Khaw, Professor of Glaucoma Studies and Wound Healing, and member of the Board of Directors at Radiance Therapeutics.

Enter Radiance Therapeutics, Inc.: a new company developing a device for the topical application of beta therapy for trabeculectomies or MIGS drainage device implantation sites.

Sir Peng Khaw has the final word: "In combination with new drainage devices, beta therapy could revolutionize the treatment of glaucoma."

1. *Kirwan, JF et al. Effect of Beta radiation on success of glaucoma drainage surgery in South Africa: randomised controlled trial. BMJ, doi:10.1136/bmj.38971.395301.7C (published 5 October 2006)*
2. *Dhalia, K et al. Is Beta Radiation Better than 5 Flurouracil as an Adjunct for Trabeculectomy Surgery When Combined with Cataract Surgery? A Randomized Controlled Trial. PloS ONE 11(9).*
3. *Cook, C., et al. Trial Registry DOH-27-0117-4030. Pending Publication.*

A PERSONAL SOLUTION TO A GLOBAL PROBLEM

From outer space to the inner eye, iDESIGN Refractive Studio is revolutionizing laser vision correction

Johnson & Johnson Vision has been at the cutting-edge of laser vision correction for 30 years. It developed the first femtosecond laser for LASIK flaps and corneal transplants, pioneered the use of 3D active tracking in LASIK procedures, and played an instrumental role in the approval of LASIK for NASA and US military personnel – and the company is about to make history again with the iDESIGN Refractive Studio: the first and only system to use topography-integrated, wavefront-guided technology for laser vision correction.

The platform, which received FDA approval in June 2018, is currently available worldwide. It is the only available LASIK platform approved by the FDA for monovision LASIK in presbyopic myopic patients; a procedure that corrects vision in patients over 40 years old who are nearsighted, but who also have trouble seeing up close. The development of the sensor within the iDESIGN System was the result of an earlier discovery by Johnson & Johnson Surgical Vision Scientists, which NASA also used to accurately measure and shape the mirrors in the James Webb Space Telescope and transmit the high resolution images of deep space back to earth. The same sensor technology in the iDESIGN Refractive Studio now allows surgeons to take a number of precise measurements prior to LASIK treatments. Using an "inside-out" approach, the system performs a wavefront analysis of the inside of the eye, detailing any imperfections in the patient's vision. The system then turns to corneal topography, scanning the outside surface of the eye to measure and analyze tiny variations in curvature and elevation – all in just three seconds. The resulting combination of measurements allows the iDESIGN Refractive Studio to deliver a one-of-a-kind personalized treatment plan for patients – and a number of benefits for surgeons:

- Improved planning to optimize outcomes
- Improved diagnostic capabilities to ensure an informed view of the patient's refractive error
- Improved workflow for better practice and patient efficiency

"Personalized treatments rely on accurate measurements – and that's exactly what you get with the iDESIGN Refractive Studio," says Griffith Altmann, Head of R&D for Surgical Instrumentation at Johnson & Johnson Vision. "Our technology helps surgeons deliver outstanding patient outcomes and grow their practice. It's simple – when you measure better, you treat better."

The iDESIGN Refractive Studio is just one example of Johnson & Johnson Vision's commitment to the eye care community. It will join a suite of innovations working to restore sight to the 250 million people worldwide struggling with visual impairment – but it won't be the last. With the company's global footprint and strong relationships with key thought leaders in ophthalmology and optometry, Johnson & Johnson Vision will no doubt continue adding to its legacy of innovation for years to come.


iDesign
Refractive Studio
Johnson & Johnson VISION
iDesign
Refractive Studio

the Ophthalmologist™

Advanced Glaucoma Technologies North American Forum

Now Available On Demand: Watch Here: bit.ly/AGTondemand

Join Ike Ahmed and a panel of world-leading experts in the field of glaucoma surgery for a live discussion, now available on demand. The program provides ophthalmologists with an impartial and authentic body of content that addresses many of the questions, concerns or barriers to adoption of MIGS and other technologies.

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Mighty MIGS

Minimally invasive glaucoma surgery looks set to transform IOP management – but which interventions are currently available, and when, how and on whom should they be used?

By Sneha Konda and Bala Ambati

MIGS is a growing area of interest for glaucoma specialists and general ophthalmologists alike – and there are four reasons why. The first is the growing population and longevity of glaucoma patients; second, the financial burden, cost-ineffectiveness, and subsequent noncompliance to routinely prescribed/first line standard of care: pressure lowering eye drops; third, the reported toxicity and exposure to preservatives that these daily drops impose on the ocular surface; and fourth, the complications of filtering surgery, such as a trabeculectomy or tube

At a Glance

- *MIGS represents a world of possibility in interventional glaucoma management because of their excellent safety and efficacy profile, as well as patient convenience*
- *To optimize surgical success, surgeons should assess several factors prior to attempting MIGS by conducting a thorough, pre-operative clinical examination*
- *While there are many approved and pending options available, a lack of data makes it difficult to come to definitive conclusions*
- *Glaucoma specialists and general ophthalmologists alike should collaborate to develop a framework that details when MIGS approaches are suitable – and for whom.*

Confounding factors	*Examples*
Conditions that may obscure the angle	(a) corneal opacities (b) conjunctival disease/scarring (c) ocular surface disease (d) significant anterior synechiae (e) certain facial anatomy – small palpebral fissures
Conditions that impair proper positioning/maneuvering	(a) cervical spine instability (b) inability to follow commands, necessitating increased anesthesia
Presence of conditions that carry a higher failure rate	(a) aphakia (b) neovascular glaucoma (c) diabetes

Table 1. Surgeons should assess several factors prior to attempting MIGS.

shunts. But which MIGS procedure is right for your patient? To help you decide, here's a concise overview of approved and emerging surgical interventions to decrease patient dependence on glaucomatous drops.

Surgical technique

Angle surgery frequently involves intraoperative use of the gonioprism. Manipulation of this device has a steep learning curve, involving coordination and maneuvering of the position of the patient, lens and microscope, while visualizing the tissues and structures of the angle. The Volk gonio lens (Volk, Tuscon, AZ) combines the prism with a fine-ring type stabilization system, which facilitates visualization without compression of the cornea. Prior to using the prism in conjunction with glaucoma surgery, surgeons should familiarize themselves with the lens intraoperatively alongside routine cataract cases, as adequate visualization seems to be the rate-limiting step in angle surgery.

Anatomic underpinnings

While visualizing the tissues and structures of the angle, it is important to orient with certain anatomical landmarks and know the normal/abnormal variants of each – and it is especially critical for eyes with preexisting pathologies, such as diabetic eyes, where the anatomy can be extremely delicate. If the first attempt at manipulating the tissues and placing the device or performing the procedure is unsuccessful, a second attempt in the same location is often impossible. A thorough, pre-operative clinical examination is vital to optimize surgical success (Table 1).

Getting on top of IOP

There are several different mechanisms by which each device/procedure exerts its desired effect on reduction of intraocular pressure (Table 2).

With respect to risks, the physician and the patient should be aware of the following:

i. Schlemm's Canal: this reservoir is similar to the physiological pathway of aqueous humor, and literature touts a higher safety profile. Reflux from collector channels can lead to hyphema. As with any glaucoma procedure, hypotony can occur. Devices like iStent and Hydrus can dislocate.
ii. Suprachoroidal space: this reservoir is dissimilar to physiological pathway, allowing for risks, such as cyclodialysis cleft with hypotony, late closure of the cleft with rapid rise in pressure due to atrophy of natural outflow structures, hemorrhage, inflammation, and hyphema.
iii. Sub-conjunctival space: similar to (2), this reservoir is not physiologic, and carries similar risks as above. Devices like the Xen or InnFocus can dislocate. In addition, though potentially as efficacious as trabeculectomies – a similar mechanism to filtration – it carries similar risks due to bleb-related complications, such as infection and fibrosis.

IOP Reduction Mechanism	*Specifics*	*Example*
Increase in outflow of aqueous humor…	i) through trabecular meshwork to Schlemm's canal via penetration/perforations ii) through suprachoroidal space via shunts and drainage devices	i) iStent, Hydrus, Goniotomy, Canaloplasty ii) CyPass, Solx
Decrease in production of aqueous humor…	through ablation of ciliary body epithelium	Endoscopic Cyclophotocoagulation
Increase in subconjunctival filtration…	through creation of a new opening/formation of a bleb through which aqueous humor can flow	XEN-gel stent, InnFocus

Table 1. Mechanisms of IOP reduction and surgery/technology on offer

"The possible additive effect of inserting two or three stents instead of one is currently being investigated."

Approved MIGS

Xen (Allergan, Dublin, Ireland)

Placed through a clear corneal incision, the Xen device opens up a subconjunctival filtration pathway creating a fistula and resultant bleb. The bleb may cause conjunctival scarring, so an antimetabolite is often used. Formation of posterior blebs is preferable to anterior blebs, because of the decreased likelihood of bleb dysesthesia. This conjunctival procedure is relatively contraindicated in patients with aphakia, intraocular silicone oil or prior failed filtering/conjunctival surgery. Patients on multiple drops pre-operatively are typically told to substitute with oral acetazolamide at least one month prior, to optimize ocular surface. This device is only approved by the FDA in cases of refractory glaucoma unresponsive to drops and failure of initial surgery.

Limited studies exist that speak to the safety and efficacy of this device. In a clinical study of 30 eyes, mean IOP reduction was 6.2 mmHg at 12 month follow-up. Literature speculates that filtration bleb formation, as occurs in trabeculectomy, may result in complications such as encapsulation and subsequent scarring (1-3). In the study cited above, encapsulation of the filtration bleb was reported in one case (3.3 percent), which typically requires close postoperative follow-up with needling, revision procedures or prolonged course of topical steroids to reduce inflammation.

iStent (Glaukos, San Clemente, CA)

The iStent is a trabecular bypass device that is placed with a 25-gauge MST micro-canal, bypassing the trabecular meshwork. This device is ideally placed in the area of Schlemm's canal with the highest density of collector channels, targeting drainage into large aqueous veins. Some investigators speculate the future use of imaging, such as optical coherence tomography (OCT), to accurately localize high-concentration areas of collector channels/aqueous veins pre- and perioperatively. The possible additive effect of inserting two or three stents instead of one is currently being investigated. The iStent inject, consisting of two stents placed at two different areas of Schlemm's canal, is still in the process of FDA approval.

In one retrospective study of 134 eyes in 100 patients undergoing combined cataract extraction and implantation of iStent, mean IOP reduction was 3.6 mmHg at one year follow-up, with 94 percent of patients achieving their preoperative IOP goals (1,4). Several head-to-head comparisons of iStent and phacoemulsification versus phacoemulsification alone have been shared in the literature. In a systematic review of 37 studies, iStent implantation was reported to have a 9 percent IOP reduction rate at 12 months follow-up, compared with 4 percent with phacoemulsification alone (5). The safety profile of iStent and cataract surgery was reported to be similar to phacoemulsification alone.

The most common complication reported with iStent implantation is transient hyphema (up to 19 percent). Other reported complications include stent obstruction/malposition (up to 10 percent), but reported cases typically did not require additional corrective intervention (4).

"Endoscopic cyclophotocoagulation uses laser technology to ablate the ciliary body epithelium to decrease aqueous body production."

Goniotomy

A surgical procedure typically performed with a trabectome (NeoMedix, Tustin, CA), goniotome (Neomedix) or a Kahook Dual Blade (KDB; New World Medical), goniotomy removes a portion of the trabecular meshwork, increasing aqueous humor outflow. It does not penetrate the sclera, and is not associated with blebs. The most common reported complication is blood reflux; occasionally, cyclodialysis clefts with associated hypotony can occur.

Historically, this procedure was used mainly in the context of congenital glaucoma, where the procedure was incisional. There is a wealth of scientific studies that evaluate the efficacy of this procedure in the pediatric population, but more literature is needed to address its increasing use in the adult population.

In the adult version, dual blade systems are used to excise a portion of trabecular meshwork. In a recent retrospective study of 71 adult eyes, there was a mean decrease of 4.6 mmHg IOP 6 months post-operatively (6).

ABiC

Ab interno canaloplasty (ABiC) uses a flexible microcatheter inserted through a clear corneal incision viscodilating and catheterizing Schlemm's canal, the trabecular meshwork and the distal collector channels circumferentially. It is a modified version of the traditional canaloplasty, but does not require a suture to create tension and maintain aqueous outflow. An attractive feature of this procedure is that it restores the natural anatomical outflow system of the eye with no implantation of artificial devices. In a case series of 228 eyes reported by Ellex iScience, an IOP reduction of 8.1 mmHg was reported at 12 months follow-up. However, this procedure is technically complex and relatively long to perform. It can rupture Schlemm's canal or travel into false channels with potential complications.

Cypass (Alcon, Fort Worth, TX)

Approved in the US in July 2016, Cypass has been used in Europe for over a decade. It creates a passage of flow from the anterior chamber to the suprachoroidal space. Supraciliary devices, such as Cypass, are associated with a higher degree of complications – such as hypotony and IOP elevation – than trabecular bypass devices, limiting their use to milder forms of glaucoma. In a study involving 167 eyes of 142 patients, mean IOP decreased by 4.3 mmHg at 12 months follow-up, with the most common complication being early hypotony (up to 23 percent) (4,7). Reports of late closure of the cleft with rapid spikes in IOP are emerging.

Endoscopic Cyclophotocoagulation

Endoscopic cyclophotocoagulation uses laser technology to ablate the ciliary body epithelium to decrease aqueous body production. Its precise delivery of laser beams allows direct visualization of the ciliary processes without damage to the surrounding structures. In a randomized control trial of 636 patients, ECP and phacoemulsification was compared with phacoemulsification only; combined treatment resulted in an IOP reduction of 3.3 mmHg, with no significant reduction in IOP (8). As its efficacy has not been clearly demonstrated, it has not become popular.

MIGS pending approval

Solx (Solx Inc, Waltham, MA)

This gold microshunt, similar to CyPass, increases outflow from the anterior chamber into suprachoroidal collector channels. However, it does so ab externo, via trans-scleral dissection versus corneal incision. It is under FDA investigation undergoing phase III clinical trials, with preliminary clinical data showing about 9.3 mmHg mean IOP reduction at 12 months follow-up. Complications reported include anterior chamber inflammation and hypotony.

Hydrus (Ivantis, Irvine, CA)

Hydrus is an intracanalicular scaffold that is inserted into the nasal quadrant of Schlemm's Canal, promoting flow directly into distal collector channels, bypassing the trabecular meshwork. It is currently in phase IV clinical trials for FDA approval, but has already been approved in Europe. In a randomized controlled trial of 100 patients, mean IOP reduction was 9.4 mmHg. Reported complications include transient IOP elevation (up to 20 percent), transient hyphema (up to 10 percent), and iris adhesion/synechiae (up to 20 percent) (1,4,9).

InnFocus (InnFocus Inc, Miami, FL)

Currently in the final phases of FDA approval, InnFocus is a small microscopic tube inserted through a surgically created scleral flap, shunting aqueous fluid from the anterior chamber to the subconjunctival space. It is implanted via conjunctival and Tenon dissection (ab externo), with formation of a diffuse bleb that extends posteriorly. Preliminary data discussed by several investigators show a mean IOP reduction

"Glaucoma specialists and general ophthalmologists alike should collaborate to develop a framework that details when MIGS approaches are suitable – and for whom."

of approximately 10 mmHg from preoperative baseline, half of which occurred in the initial postoperative period (3). There are risks of bleb-related infection, leaks, and fibrosis, and – as with any glaucoma surgery – hypotony is a potential complication.

Mighty MIGS?

The options for MIGS have increased exponentially over the years because of their numerous potential benefits over conservative treatment (eye drops) and more aggressive surgical options, such as trabeculectomy or tube shunts. MIGS procedures, along with advances in laser technology – for example, SLT, micropulse cyclophotocoagulation – could conceivably move to the forefront in glaucoma management because of their excellent safety and efficacy profile, as well as patient convenience. They provide a viable venue for earlier, long-term intervention for glaucoma with less need for strict patient adherence, and can be done concurrently with cataract surgery, reducing patient costs and operative/anesthesia risks.

There is no shortage of options in this growing sector of glaucoma treatment. Although comparisons between several MIGS devices and trabeculectomy do appear in the literature, more comparative head-to-head clinical studies between different MIGS devices need to be performed. Such comparison will better address the pros and cons of each option to better guide surgical management and patient selection. Though clinical trials are underway, the data points and investigation methods are not uniform, making definitive conclusions about the utility of each difficult. Standardized, universal evaluation of each of these devices and procedures needs to be devised and implemented, including the following criteria:

- Safety endpoint
  - frequency of complications
  - types of adverse events
- Efficacy end points
  - complexity of surgical technique
  - scope of tissue manipulation
  - reduction in IOP
  - reduction in medications
- Guidelines for patient eligibility and contraindications
  - preoperative clinical examination
  - severity and type of glaucoma
  - number of preoperative glaucomatous drops
  - prior failure of surgical/ medical treatment

Glaucoma specialists and general ophthalmologists alike should collaborate to develop a framework that details when MIGS approaches are suitable – and for whom. Nevertheless, the growing myriad of options is promising; together, they represent a whole new world of possibility in interventional glaucoma.

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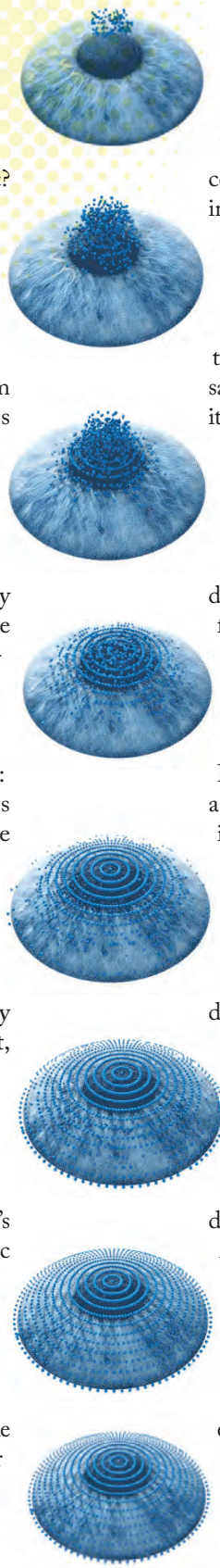
It's All in the Small Print

Eye drops rely on "Grandma technology," says Sean Ianchulev, and patients deserve better. His solution? Use inkjet instrumentation to print drugs onto the cornea: smaller doses, smarter delivery, safer therapy.

With Sean Ianchulev and Louis Pascale

Patients dislike glaucoma eye drops; the delivery mode is inconvenient and imprecise – in fact, unlike no other medical field, in ophthalmology we deliver the wrong dose more often than we do the prescribed one – with many studies now demonstrating that only one third to a half of all patients are able to successfully deliver the indicated topical dose to their eye (1). Most of the time they miss the eye altogether or deliver 200-500 percent overdose causing side effects, waste and missed compliance. Ophthalmic formulations cause a range of unwanted side effects from discoloration to periorbital dermatitis. Hence the famously high non-adherence levels associated with topically-applied glaucoma medication. But given that the standard eye-dropper method dates from before the 20th century, should we really be surprised that it's problematic? Ianchulev certainly takes this view, and is indignant that the subject isn't more broadly discussed. "Physicians are using a 150-year-old device to deliver 50 microlitres of drug into a seven microlitre tear film volume – no wonder eye drops are poorly tolerated!" But now Ianchulev's company, Eyenovia, is bringing 21st century engineering to ocular drug delivery. "By marrying piezo-printing technology with smart drug delivery, we're completely disrupting the eye-drop technology," he says. In fact, the implications of the Eyenovia technology go far beyond issues of drug tolerability: some of the off-target effects associated with eye drops are life-threatening, and include cardiotoxicity symptoms, such as arrhythmia and bradycardia. So, by reducing off-target tissue exposure, Ianchulev's microdosing approach may improve not just patient comfort, but patient safety – good news for patients, physicians and healthcare systems alike.



What's new about the Eyenovia approach? Discarding the ancient eyedropper, Ianchulev's team has turned to piezo-electric ink delivery systems – well known for precise delivery of suitable amounts of ink onto paper – by modifying such technology to administer 6–8 µL drug doses that are more compatible with natural physiology; in other words, the volume delivered does not overload the eye with fluid in the same way as an eyedropper. Louis Pasquale, Ianchulev's clinical collaborator, makes another important point: "Keeping the administration volume to 8 µL or less is important; larger quantities cause a lachrymal reflex that washes much of the dose out of the eye," he says. "When you think about it, it's amazing that glaucoma eye drops work at all – much of the administrated dose is washed out by the lachrymal reflex." Avoiding this wash-out is not only more efficient in terms of drug use, but also more pleasant for the patient.

When and where

But it's not just about how much drug is delivered. Piezo-electric technology is also precise (imagine if your inkjet printer was not!). Eyenovia's device aims to accurately and uniformly coat the small volume of drug onto the corneal surface (where intraocular drug penetration occurs) (2). Could such efficient drug delivery also lead to less frequent administration? Time will tell.

In any case, microdosing intuitively indicates less drug-associated toxicity. And if the side effects are reduced, patients should hopefully be less reluctant to adhere to treatment regimens; hence, one of the first indications being explored by Eyenovia is glaucoma medication (Box 1), where satisfactory regime compliance is a long

At a Glance

- *Sean Ianchulev's company, Eyenovia, is using piezo-printing technology to change the eye-drop delivery process*
- *The new piezo-electric delivery system is capable of delivering small doses of 6–8 microlitres – volumes compatible with natural physiology*
- *The microdosing system will reduce side effects associated with the eye drop toxicity*

Small doses, big target: microdosed latanoprost for chronic angle closure glaucoma.

We spoke to Louis Pasquale, a glaucoma specialist at Mount Sinai who is working with Eyenovia on the chronic angle closure glaucoma (CACG) trial.

Until recently, I was at the Massachusetts Eye and Ear Infirmary; now that I've moved to Mount Sinai, it's easier to be actively involved in the Eyenovia CACG-latanoprost microdose trial. The Eyenovia collaboration has grown from work that Sean and I did on telemedicine and microdosing a few years ago. At that time, we were investigating the efficacy of microdosed phenylephrine for mydriasis. As an eye drop, phenylephrine can cause problematic side effects, not least elevated blood pressure. However, we showed that the microdose formulation has no such effect (1).

Now, we are following up the phenylephrine work with an investigation of microdosed latanoprost for CACG; current efforts are aimed at extending our recent proof-of-principle study on latanoprost microdosing. In the present trial, we have tested the product in 30 healthy volunteers, and demonstrated that latanoprost microdosing mediates IOP reduction equivalent to latanoprost eye drops at 80 percent lower total dose exposure, at least in the short term. And now that we have shown short-term efficacy, I'm helping to design a bigger trial, hopefully a six-month study. This will, inter alia, answer questions about topical and ocular side effects, which of course we would expect to be much lower for the microdose product than for eye drop latanoprost. The plan is for a large multi-center trial in 2019; New York might be one of the centers, because it has a huge volume of CACG patients and a wonderful clinical research centre. Overall, the aim is to have an FDA-approved device in patients' hands within two years.

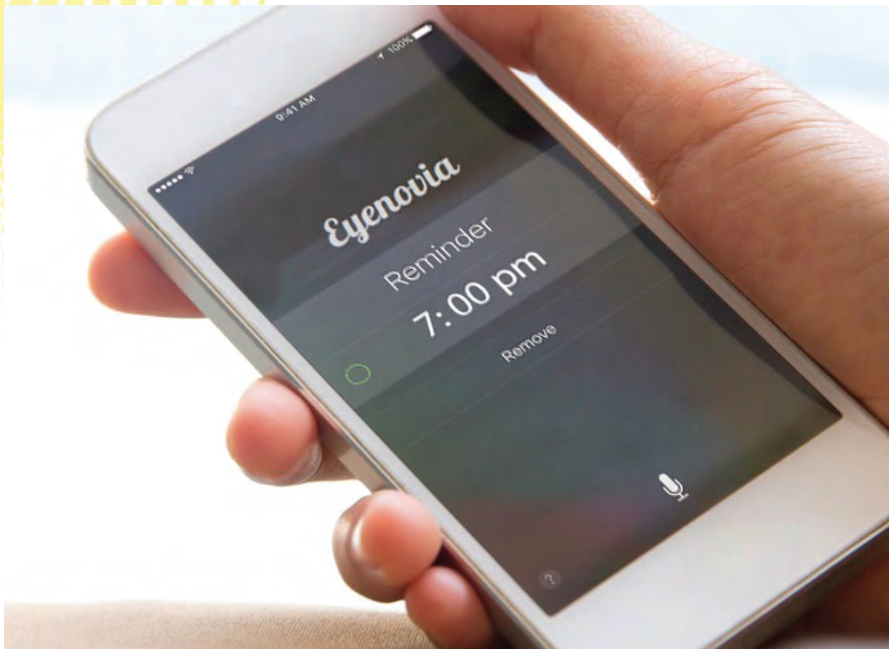
We also intend to look at the feasibility of self-administration by patients. That's what the device is designed for: glaucoma is a chronic 24/7 disease, and ultimately we need a device that patients can operate themselves, so that they can manage their glaucoma independently. We'll have to teach patients how to work the device, but we don't anticipate many problems – it's very straightforward. The device has an LED light; the patient looks at the light, and actuates the device; one spray, and eight microlitres of drug get printed onto the cornea. It couldn't be simpler. And since the spray speed is faster than the patient's blink speed, it will be very difficult to get that step wrong.

Looking ahead, this trial will hopefully kill two birds with one stone: it will give US physicians an effective product for CACG, and at the same time it will get the microdose device into the mainstream of glaucoma treatment. This is important – there is a real need for a product that significantly helps CACG management, and my view is that the time has come for us to consider alternative methods of drug delivery in this field. Eyenovia technology should also be a game-changer in the pediatric setting: dilating children's eyes can be a little traumatic, and our system should be a better way of doing it. And there are many other opportunities for our system: for example, future products might include newly approved drugs and fixed combinations of older drugs. Microdosed atropine for slowing myopic progression in children is also very promising.

I have worked with Sean for some years now, and I'm very fortunate that he keeps involving me in his innovative ideas. The Eyenovia approach is a particularly exciting step forward, and I believe it represents a fundamental paradigm shift in terms of treating glaucoma patients. It is a long-overdue advance: even when I was a resident, back in 1987, I knew that the eye-dropper approach was problematic. When used correctly, they work, but we can do better. So that's what the Eyenovia approach is about, and it's great to be involved.

way off. In this context, it's interesting that Eyenovia has taken compliance one step further by coupling an app that reminds patients when their dose should be taken with Bluetooth-enabled monitoring of device actuation. According to the Eyenovia website, its "intelligent electronic system is one of the first smart technologies to enter FDA clinical trials for ophthalmic use."

Finally, as well as assuring physicians that their patients will be safer and more compliant when taking existing drugs, Eyenovia's approach could open the door to products that – because of toxicity issues – are currently not approved in eyedrop form. "There is Level 1 evidence for atropine slowing the progression of myopia in children by 60 percent (3). However, we haven't been able to prescribe atropine eye drops because of their side effects. The option of accurate microdosing completely changes this situation," says Ianchulev. "Small, precise doses may eliminate eye-drop toxicities and turn an unacceptable drug into a tolerable product."



Room to grow

However innovative the technology, for a company to survive, the objective must also make commercial sense – a point not lost on Eyenovia. Potential markets for the technology are large, and include not only adult glaucoma and pediatric myopia patients, but also the 80 million patients in the US alone per year who undergo dilation in the doctor's office – and suffer stinging or burning eyes from the preservative and the dual overdose, since doctors often use two agents simultaneously to dilate the pupil (tropicamide and phenylephrine) (4). "Eyenovia microdosing delivers the same therapeutic benefit as eye drops, but much more mildly – in a high-precision single microdose of a fixed co-formulation of the two drugs," says Ianchulev. He adds that the improved safety associated with controlled microdoses suggests that GPs could start administering drugs that previously were only provided by specialist ophthalmologists, making patient management more straightforward and cost-effective. Ultimately, however, Ianchulev sees the technology as far more than just a means of enabling delivery of third-party drugs; the company is building a pipeline of proprietary formulations, including three products in Phase III – for mydriasis, myopia and chronic angle closure glaucoma – and one in Phase I for dry eye.

And the longer-term aim? Ianchulev has set his sights high: nothing short of resolving the world's myopia problem… In the meantime, he'll settle for lower side effects and a transformation in adherence monitoring. If Eyenovia's tech does end up being disruptive, what of the loser? Well, when compared with piezo-electric Bluetooth-enabled microdose delivery, the humble eyedropper starts to look like something not just from a previous century, but from the dark ages!

Font of wisdom: piezo-printing drugs

- Piezo-print technology in a handheld device allows ocular drug delivery in precise 6-8 microlitre volumes
- Exposure to formulation-related irritants is decreased by 80 percent – while retaining a biological effect equivalent to that mediated by eye-dropper delivery
- The technology is applicable to monotherapy products and to drug combinations, and is anticipated to reduce side effects and improve compliance
- Indications include large markets: adult glaucoma, office-based dilation, and pediatric patients, such as premature infants and children with myopia (prevalence: 5 million)
- The device is in Phase III trials in three indications: microdosed latanoprost for chronic angle-closure glaucoma, microdosed atropine for prevention of myopia progression in children, and microdosed phenylephrine/tropicamide for eye dilation.

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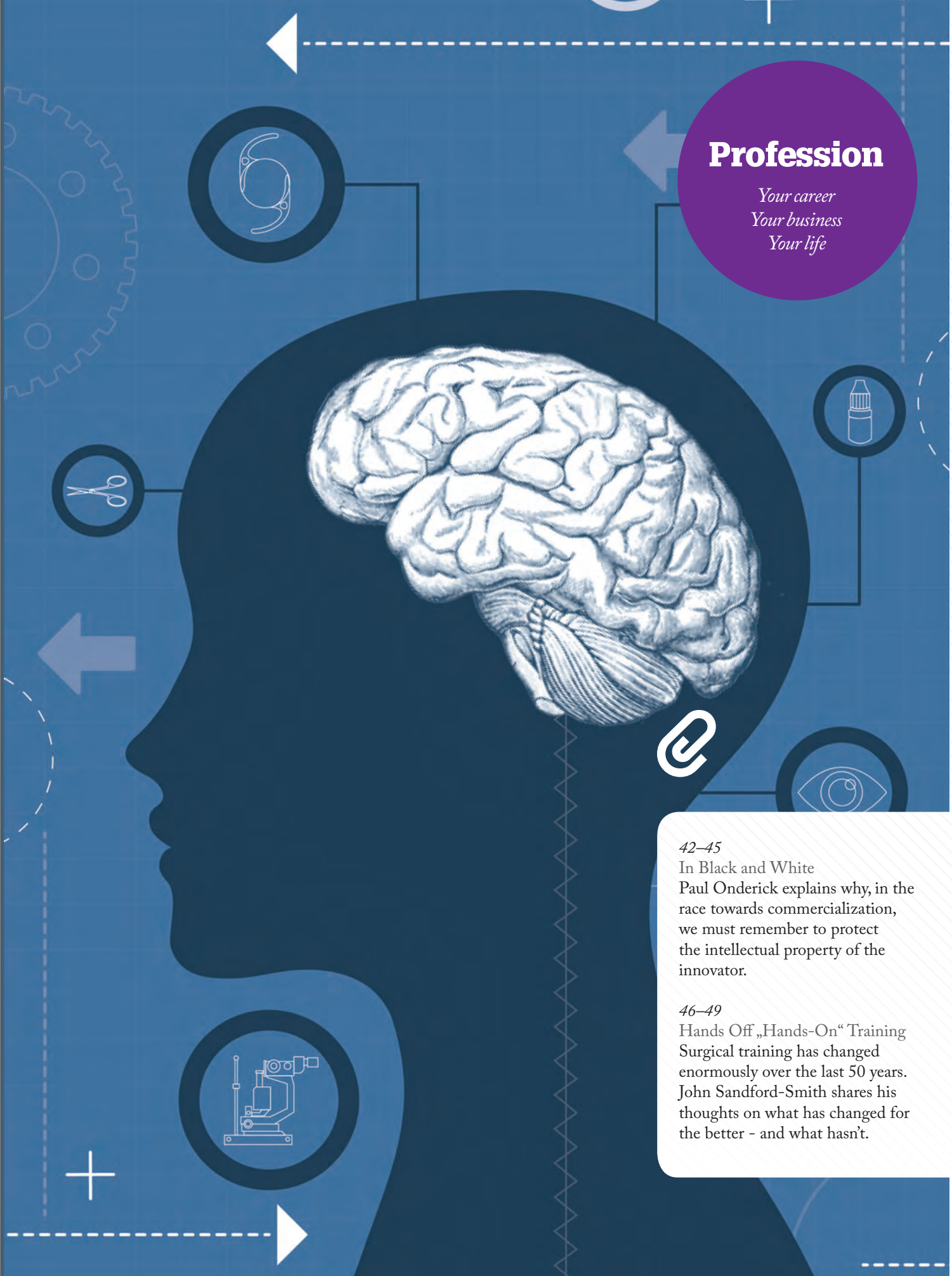

Profession

Your career
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In Black and White

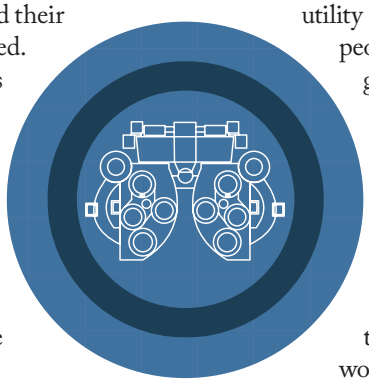
Modern ophthalmology relies on novel ideas being explored and developed. In the race towards commercialization, let's not forget to protect the intellectual property of the innovator.

By Paul Onderick

A radiologist at Hennepin County Medical Center in Minneapolis, Minnesota, and the Head of the hospital's innovation arm recently launched a software venture that coordinates rides for patients who struggle to find transportation to appointments. Thanks to a partnership with rideshare giant, Lyft, a pilot program produced a 20 percent reduction in no-shows. An orthopedic surgeon in Rockford, Illinois, invented a surgical undergarment to allow patients more privacy than traditional hospital gowns. Modicine PatientWear is now used in a number of hospitals across the United States. A Canadian cardiologist developed a software platform that allows ultrasound images to be shared in real time via smartphones and tablets. Philips has already integrated it into its portable ultrasound system. A British ophthalmologist made the mental leap from laser-inflicted injury to laser-assisted surgery – 50 million procedures have since been performed (see page 16).

These are just a few examples of the innovations that are happening in hospitals, clinics and other medical institutions around the world. These technological advancements all created new business – in some cases, huge amounts of business. They also created intellectual property (IP). The laws surrounding IP are complex, but a general understanding can go a long way to avoiding costly disputes, assigning property rights appropriately, and ensuring that relationships between medical professionals and their employers are not damaged. The following scenarios represent situations that often arise when innovation becomes rooted in the culture of an institution. They are also situations where consulting with an IP attorney can be extremely helpful.

"The laws surrounding IP are complex, but a general understanding can go a long way to avoiding costly disputes."



When you have an idea that you are developing into something novel, useful and non-obvious.

Everyone has ideas, and no one owns an idea as such. Ideas are passed around, discussed and written about all the time. IP law provides a way to establish a property right in an idea or at least in the useful application of an idea. Patents are government-granted property rights that can be obtained by filing an application with United States Patent and Trademark Office (USPTO). The basic requirements for a patentable invention are that it be novel, useful and non-obvious. Novelty means that the invention is new, that is, not previously known. Usefulness or utility is nearly intuitive to most people and is a requirement generally easily met. Non-obviousness is a less clear and much more complex concept, but generally can be thought of as when a person having ordinary skill in the art to which the invention pertains would have been somewhat surprised at the invention.

Patent rights can be obtained only by filing a patent application with the USPTO or in patent offices in other countries. The jurisdiction of patent rights is limited to the country in which the patent application is granted. While any inventor can file their own patent application, patent law is complex and filled with pitfalls for the unwary. Accordingly, if you think you have a patentable invention you should consult with a registered patent attorney as soon as possible. Patent rights can be lost by public disclosure of an invention prior to the filing of a patent application, under certain circumstances.

At a Glance

- *Innovations that create new commercial opportunities constitute intellectual property and need to be protected appropriately*
- *Patents can be used to protect novel, useful and non-obvious ideas, and are important to have in place before publication*
- *Legally-binding agreements are an essential part of creating new partnerships or joint ventures*

"Researchers and doctors can be so eager to share their discoveries that assessment of potential business value is often overlooked."

When you are about to publish or present your latest findings or ideas, but suspect or wonder whether the content may contain something of business value.

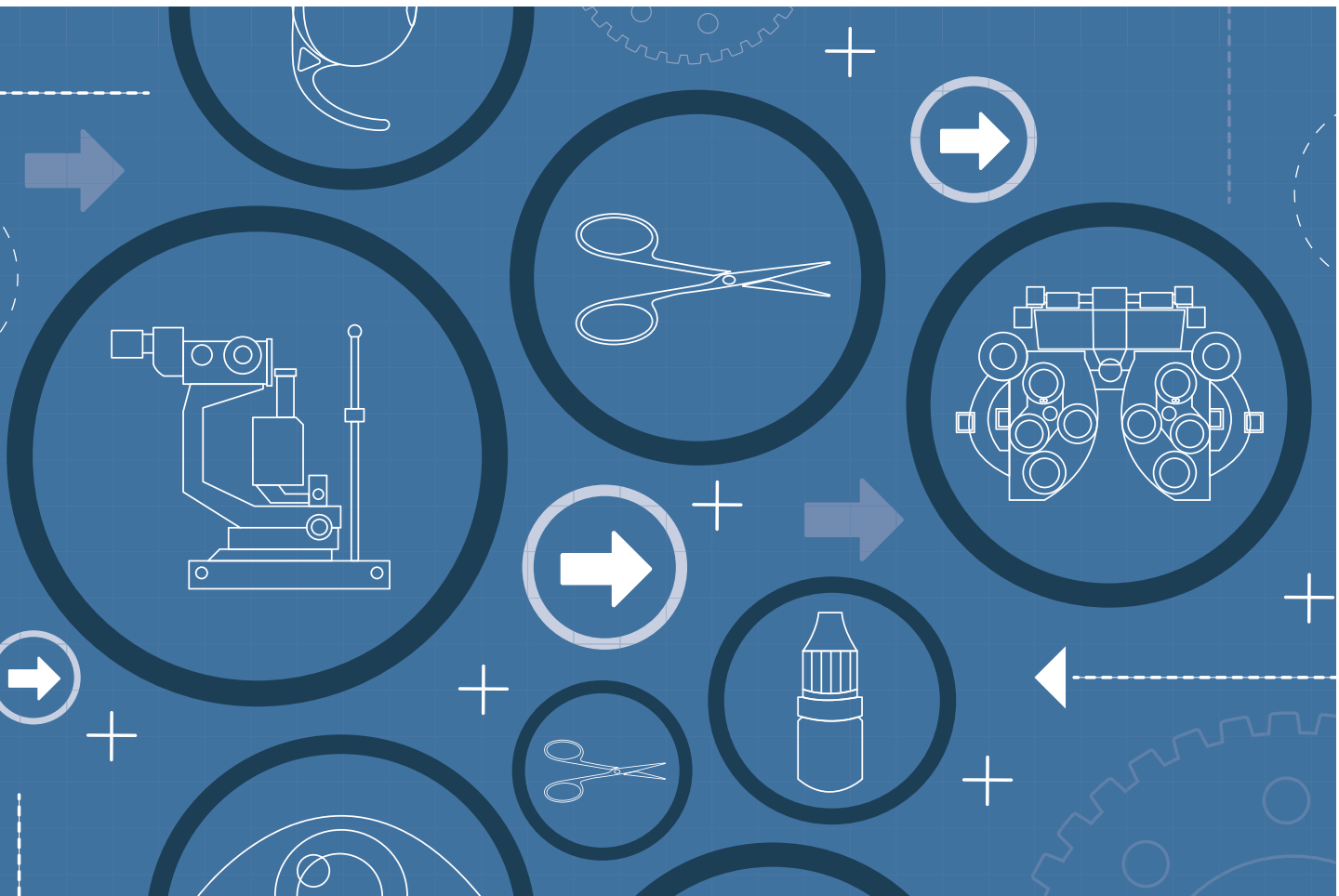
Researchers and doctors can be so eager to share their discoveries that assessment of potential business value is often overlooked. As mentioned above, patent rights can be lost by public disclosure or publication of information. In addition, under current law, others may take your idea and run with it and, while they cannot patent your idea as it was not invented by them, they may be able to seek patent protection on further developments that build upon your idea, which can potentially limit your opportunities to use your own idea commercially. Consultation with a registered patent attorney prior to your publication or presentation can help preserve your IP rights.

When you may have said too much at a conference or meeting or to a colleague researching in the same field.

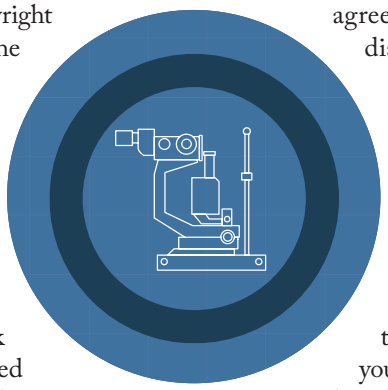
If you are already at the point of having published or presented your work publicly there may be ways to preserve at least some of your IP rights with prompt action. Patent law provides a "grace period" during which you can still seek patent protection if you have made a public disclosure. The grace period is for one year and the contours of the grace period are somewhat unclear because of amendments made to US patent law in 2013. Nonetheless, if you have spilled the beans, there may be ways to recover by filing a patent application as soon as possible.

When you plan to use an image, illustration, or writing in your publications or marketing materials that you don't own.

It's extremely easy to search for and download images online for use in presentations, to better illustrate innovations or to enhance marketing



materials. However, using an image or other published material without proper authorization from the copyright holder can, potentially, cost you thousands or tens of thousands of dollars. Consultation with an IP lawyer can help you navigate the complexities of copyright law, saving you from the hassle and potential legal costs involved if you infringe the copyright of others. By the way, contrary to popular belief, whether you made any money from the use of a copyrighted image or a derivative work based on a copyrighted image is not especially relevant to your liability. You can still be held liable for copyright infringement even if you've not made any money from your use of copyrighted material.



When you are considering adding flair to your presentation by incorporating a music or video clip.

Just like text and online images, audio and video recordings are protected by copyright law. Making use of them in a presentation may create liability. In general, if you are not certain that an audio or video clip is licensed for use it is safer not to use it. There are often ways that you can make use of audio or video clips either by paying a licensing fee, subscribing to a paid service, or by making use of materials that are in the public domain. An IP lawyer can assist you here and help set up internal policies to avoid copyright infringement by other employees.

When you are about to get involved in a joint venture or with a corporate partner.

Joint ventures and cooperative agreements with corporate partners can rapidly become very complicated and involve one or more legally binding agreements. Consultation with an IP lawyer can help you protect your rights and understand what you are trading for the benefits you receive. It is critical to outline and document who will own the various IP assets that come out of the joint venture or cooperative agreement to avoid future disputes. Due diligence in advance can assist in establishing a clear understanding as to who will own what. Further, it can be helpful to research what relevant prior art is owned by others to determine whether you will be free to practice the inventions that arise out of a joint venture.

When you are considering the use of public domain software as a basis for a product or service.

J Copyleft and GNU are alternatives to copyright that are sometimes used by software developers to produce and promote software they wish to make available in the public domain. However, that does not mean that you can use the software in any way you want. These approaches place limitations on what you can do with the software, how you can modify it and what attribution is required in anything that you produce by using it.

When you want to name your breakthrough product or service.

Trademarks identify the source of a product or service. Trademarks grant certain rights to the trademark holder. One of those rights allows the trademark holder to prevent others from using a confusingly similar trademark for a similar product or service. Before you commit significant resources to establishing a name for a product or service, a trademark search should be conducted to provide assurance that the name you wish to use is available, or to help you find out early on that it is not, before you make a significant investment in branding, packaging, advertising, and other marketing collateral.

When you want to know who owns the copyright to materials such as text, photographs, video, and audio recordings that you have produced.

Generally, the ownership of copyrighted materials automatically vests in the author. However, this can be changed by written agreements such as the agreement you may have made with a research institution, a university or your employer. Employment agreements, research agreements, fellowships, internships, and residencies may all involve agreements that proactively change the ownership of IP or transfer your rights to someone else. You may not be able to change these agreements, but understanding what they are and how they affect you lets you know where you stand as to the ownership of the IP you develop.

Intellectual property is complex and can be high-stakes. From helping a hospital resident/researcher understand and resolve IP ownership issues with an employer to taking breach of contract issues to Federal Court, my colleagues and I have seen how contentious these issues can become. The lesson we continually pass on to clients is that proactive planning is always easier and less expensive than resolving issues after a dispute arises.

Paul Onderick is a patent attorney and licensed optometrist whose practice focuses on assisting clients in seeking patent protection and developing and managing patent portfolios.

Hands Off "Hands-On" Training

Over the last 50 years, eye surgery and surgical training have altered beyond all recognition. But dedicated trainers and graded hands-on training remain the two foundations

By John Sandford-Smith, Emeritus Consultant Ophthalmologist at Leicester Royal Infirmary, UK

"The past is a foreign country; they do things differently there." That certainly goes for cataract surgery and training – but the old ways of learning weren't all bad, and maybe we can still learn from those far-off times today. Conversely, we shouldn't be shy of sharing our experience with those countries who have fewer resources than we do, and who might benefit from assistance with skills acquisition.

Yesterday

My own training has been somewhat haphazard – that's simply the way it was 50 years ago. Consider how I began: in January 1964, soon after qualifying, I turned up at a very busy "eye camp" in a rural area of Pakistan after driving across Europe and Asia in a Land Rover. I brought enthusiasm, but precious little experience. And that could have been a problem, because at that time – and in that part of Pakistan – specialist medical care was virtually non-existent outside Karachi or Lahore, so the hospital was obliged to tackle everything other than neurosurgery or thoracic surgery. But my mentor, Ronnie Holland – a legend who had been running the hospital for 25 years – wasn't worried; he just gave me some basic instruction, and set me to work on hernias, scrotal swellings, piles and bladder stones. And within weeks of that, Ronnie decided I should also learn

cataract surgery! This was after all an "eye camp," but over the years it had also tackled other chronic surgical problems.

My cataract training procedure went like this: Monday – watch Ronnie perform intra-capsular extractions; Tuesday – start hands-on training for each step of the cataract procedure; Wednesday – do complete procedures independently (but under Ronnie's supervision); Thursday – do everything other than complicated cases and "only eyes" while Ronnie goes off to deal with the outpatients! Remember, there were no operating microscopes or videos to review your work in those days, so my ability to observe Ronnie's technique was relatively limited – it really was a case of learning by doing.

Even in the UK, I tended to learn my surgery in a hands-on, serendipitous way. For example, in 1972, I had to stand in for the consultant who was training me after he fell ill. Before his absence, he'd started using the new iris clip intraocular lenses, which could be inserted following intracapsular cataract extraction, and had become very enthusiastic about them. After consulting my colleagues, I decided this was a reasonable approach for uni-ocular cataract patients. I proceeded with this new technique, using loupes, without any supervision (there wasn't anybody available to supervise me). When the consultant had fully recovered, I reverted to being his trainee, and eventually we jointly published one of the earliest reports on intraocular lens implants (1).

This experience in somewhat "off-the-cuff" adoption of new techniques was immensely helpful towards the end of the 1970s, when ophthalmic surgery changed rapidly. Operating microscopes were supplanting binocular loupes for intraocular surgery; intraocular lens implants were increasingly common; and extra-capsular extraction was beginning to take over from intra-capsular as the standard procedure. Again, like most other young consultants at the time, I had to more or less teach myself these new procedures. But it also became clear that the "teach-yourself" approach had limits. For example, in the 1990s, I tried to pick up phacoemulsification through attending courses, studying videos and observing procedures undertaken by one of my skilled ex-trainees. That wasn't quite enough to guarantee good results when I started using the technique, and I had a couple of dreadful outcomes as a result of my inadequate phaco experience. Similarly, in 1999, having seen a marvelous video of small-incision sutureless cataract surgery (SICS), I was convinced that I could quickly teach myself this technique. In fact, I consistently failed to deliver the nucleus properly until a more experienced African surgeon kindly showed me where I was going wrong.

Today

Nowadays things are – or should be – totally different. Access to "wet lab" facilities gives trainees the chance to develop their skills before being exposed to real patients, and the development of teaching attachments for operating microscopes allows the trainer and the trainee to see exactly what each one is doing. This permits efficient, low-risk training, which is good for everyone, the surgeons and especially the patients. It also has a "fast-to-fail" advantage, in that early exposure to the demands of the various techniques enables trainees who lack the required dexterity to change career early on.

Nevertheless, the modern system is by no means perfect, and over the years I have observed that in some countries it is possible for trainees to finish formal training without being ready to perform cataract surgery. One key weakness of the current system, in my opinion, is our failure to assess the vision and the manual dexterity of potential trainees. I have had two postgraduate trainees who I am sure had no stereopsis: they constantly failed to appreciate how deep their instruments had penetrated into the eye. Consequently, I counseled them both to concentrate on medical ophthalmology. One took my advice, but the other did not and continued to struggle – and, unfortunately, also continued to produce sub-optimal outcomes. On another occasion, I noticed that a trainee of mine seemed to have great difficulty discerning the finer details of his procedures. On investigation, I discovered that he was highly myopic – his best corrected visual acuity was 6/12. I had been unaware of this, because he had been using extended-

"Some wealthier countries may take the view that practical surgery is not an essential part of the postgraduate training program."

wear soft contact lenses. Fortunately, he soon realized that his surgical ambitions needed to be reconsidered.

As a result of these kinds of experience, I suggested at a committee meeting that all potential trainees should have their stereopsis and corrected visual acuity measured. Much to my surprise, I was told by a very senior colleague that this would be discriminatory! It is an unfortunate attitude – I believe it's far better to counsel struggling trainees at the beginning of their career, rather than to watch them go through years of training only to have their ambitions frustrated.

Another weakness of our current system is evident at the other end of the experience spectrum: namely, the issue of elderly surgeons who stubbornly refuse to give up surgery despite having developed a condition, such as a tremor, that could put their patients at risk. This phenomenon – together with evidence that patients treated by younger doctors may have better outcomes than those treated by older doctors (2) – strongly suggests that we need a way of monitoring surgeons towards the end of their careers.

More generally, I believe that we also sometimes fail to give trainees proper "hands-on," graduated and supervised training. Some wealthier countries may take the view that practical surgery is not an essential part of the postgraduate training program, and is only relevant to a minority of those who complete their formal training. Such a view is understandable in rich countries with an abundance of post-graduates – but in countries with perhaps only one ophthalmologist per million people, all ophthalmology trainees should learn how to do surgery, especially cataract surgery. It's also worth pointing out that while a postgraduate trainee from a developing country may be delighted to get a scholarship to study in a Western country, the reality is that they are much more likely to get useful and valuable skills if they attend one of the excellent postgraduate training institutes – for example, in India – which are focused on giving "hands-on" SICS training.

Tomorrow

In the developing world, where one might find barely one ophthalmologist per million people, most eye surgery is inevitably cataract surgery. But it's still not enough to eradicate cataract blindness. What should we do? The obvious solution is to train non-doctors in standard techniques, and the increasing acceptance of this strategy – in Africa, for example – suggests that it will be the future. Indeed, in those countries where there is still a huge backlog of cataract blindness, taking that route is a "no-brainer," for the following reasons. Firstly, both undergraduate and postgraduate training are much shorter and therefore less costly. Secondly, non-doctors trained in this way are much more likely to remain in rural areas, where they are more needed. Thirdly, being less trained and less qualified, nurse surgeons are more likely to be content with a lower salary scale, and are very much less likely to emigrate. And finally, because their training has been more focused and intensive, their surgical outcomes tend to be as good as, if not better than, those of "fully" trained ophthalmic surgeons. Many African countries accept the role of non-doctors to do lid rotations for trichiasis, but very few actively promote and train nurse cataract surgeons.

Changing the situation in the developing world, however, may also require wealthier countries to deliver assistance with training programs; local training programs are not always adequate because of the special circumstances of the countries in question. These circumstances include poor salaries for teaching staff, and difficulties in putting aside time for training because of heavy surgical workloads in these countries. Furthermore, in countries where few can afford private fees, the need to supplement salaries through private practice disincentivizes surgeons to train others who will then compete with them in the small private practice market. Hence, outside support aimed at training programs may be essential for some countries.

Unfortunately, not everybody welcomes the advent of nurse surgeons, even in countries where the need is greatest. I have personally been involved in training "nurse cataract surgeons" in Africa, and could see little difference between their skills and those of fully-trained ophthalmologists. Nevertheless, local ophthalmologists were often very unsupportive, and in one case, plainly obstructive. I don't think that this stems from a wish to maintain high standards – after all, numerous audits have shown that a properly trained nurse cataract surgeon delivers outcomes as good as those of an ophthalmologist. Rather, I think it is more about professional rivalries and preservation of

one's privileged position (and income) after many years of training. One sometimes saw the same friction between ophthalmologists and optometrists in Britain about 30 years ago; today, fortunately, there is much more co-operation. Hopefully, we will see a similar change in attitude in those countries where ophthalmologists are in critically short supply; there is more than enough work for everybody in the developing world, so ophthalmologists have nothing to fear from nurse cataract surgeons.

Not all parts of the developing world have adequate regulation, and, sadly, poor cataract surgery remains a significant cause of blindness in some places. Conversely, in the same countries, we can find hospitals that deliver outstanding work. I suspect that these particularly effective units often owe their success to the qualities of a single individual: charisma and dedication, for example. Such qualities hopefully attract colleagues who either have the same vision or soon acquire it. I remember two particular examples: a Burmese lady who was working single-handedly in a provincial town in Myanmar, and one of my ex-trainees who was working for an NGO in central Africa, also single-handed. Each could do 5,000 cataract operations a year and audit their results. If everyone working in the developing world had the same vision and ethic as these people, the problem of unnecessary cataract blindness would disappear almost overnight. Unfortunately, the norm is to just manage as best as one can in often difficult conditions; it is hard to maintain high levels of concern about the needs of a poor community when your own salary is low and your hospital poorly equipped. But hopefully this situation will change, perhaps via the impact of non-profit organizations; in Pakistan, for example, the Pakistan Institute of Community Ophthalmology, the Leyton Rahmatullah Benevolent Trust and the Al Shifa trust are having a remarkable influence on cataract blindness throughout the country. I believe that particular individuals and groups, by changing local attitudes and training practices, could entirely change tomorrow's ophthalmology environment in the developing world. Hopefully, one day they will look back on some of today's practices as if looking at a foreign land!

Reference

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Time Well Spent

Sitting Down With… John Berdahl, Partner at Vance Thompson Vision, Founder and CEO of Equinox, Sioux Falls, South Dakota, USA.

How did you come to work at Vance Thompson Vision?

My grandma is my hero. So when Vance was recruiting me from fellowship, he took a selfie with her and said: "Your grandma wants you to do her cataract surgery and she's not willing to travel more than 75 miles for it. Looks like you're joining me." That sealed the deal.

What's the best thing about being an ophthalmologist?

Delivering on the trust that my patients put in me in their moments of vulnerability. In a professional capacity, I try to inspire students, fellows and colleagues the same way my heroes inspired me. We've only got one swing at life, so we need to go for it!

You're a member of the Vision for Mars team – what's it like working with NASA?

I feel like a kid in a candy store… To grow up in a town of 500 people and be able to assist the professionals who are dedicated to getting the first humans to Mars – it's not the typical story. I think it will be the single, most unifying moment in human history. If I can play even a tiny role in that monumental feat, my kids will think I'm cool. It's especially gratifying that the principle of intraocular with intracranial pressure to treat glaucoma could help long term space flight. So terrestrially Equinox is using negative pressure goggles to treat glaucoma, while in space perhaps positive pressure goggles could treat papilledema.

You also co-created the MKO Melt – what was the idea behind it?

The most painful part of cataract surgery is starting the IV, and we weren't convinced we needed it. We tried sublingual administration in liquid form and thought it worked well, but it didn't have everything that we needed – the same with IV ketamine and midazolam. So I approached Imprimis and said, "I've come up with something a little different. I think we have a real opportunity to help patients." Historically, there has been very little innovation in anaesthesia for eye surgery, but the MKO Melt is getting adopted quite rapidly.

You seem to have an innovative streak…

If I have an idea and it won't go away, I've got to act on it. I don't feel like I have some special ability – my mind just doesn't rest until I come to a conclusion.

Can you tell us more about your current project – Expert Opinion?

It's an online second opinion service that basically gives people access to world class care from anywhere. For example, if someone was diagnosed with Fuchs dystrophy and their ophthalmologist wasn't great at explaining the procedure, they could go to ExpertOpinion.md. There is a list of ophthalmologists with prices by their names: the doctors choose the price they charge and patients choose their doctor. World experts may command a higher price, where other fantastic doctors may choose a lower price. The patient can see a video of us, along with our online ratings, how many surgeries we perform, and our publications. The doctor you pick reviews your records, writes a report and sends you an audio file telling you what your treatment options are and recommendations.

What are the benefits?

Patients can choose a doctor without having to take a day off work, and doctors don't have to be in the clinic. It's good for everyone. Ten years ago it would have been crazy to say: "I'm going to pick somebody up and take them to the airport for $20." Now Uber is a $52 billion company. Airbnb is the same story. All they do is connect people who have a service with someone who needs a service, and make that as frictionless as possible. In my mind, there is no more precious and valuable service than what doctors provide to patients, but it is one of the hardest to access. We're trying to make that as easy as possible.

"I try to inspire my students, fellows and colleagues the same way my heroes inspired me."

What's the future of ophthalmology?

Of course, I think noninvasively dialing in IOP will be important for normal tension and severe glaucoma patients. I believe changeability/upgradability versus adjustability is going to be the story of IOLs 10 years from now. I also think drug delivery is going to be a big deal and, as a burgeoning presbyope, I really hope we get a consistent solution in the next three to four years – whether that means better IOLs or an eye drop we can use on demand.

What drew you to ophthalmology?

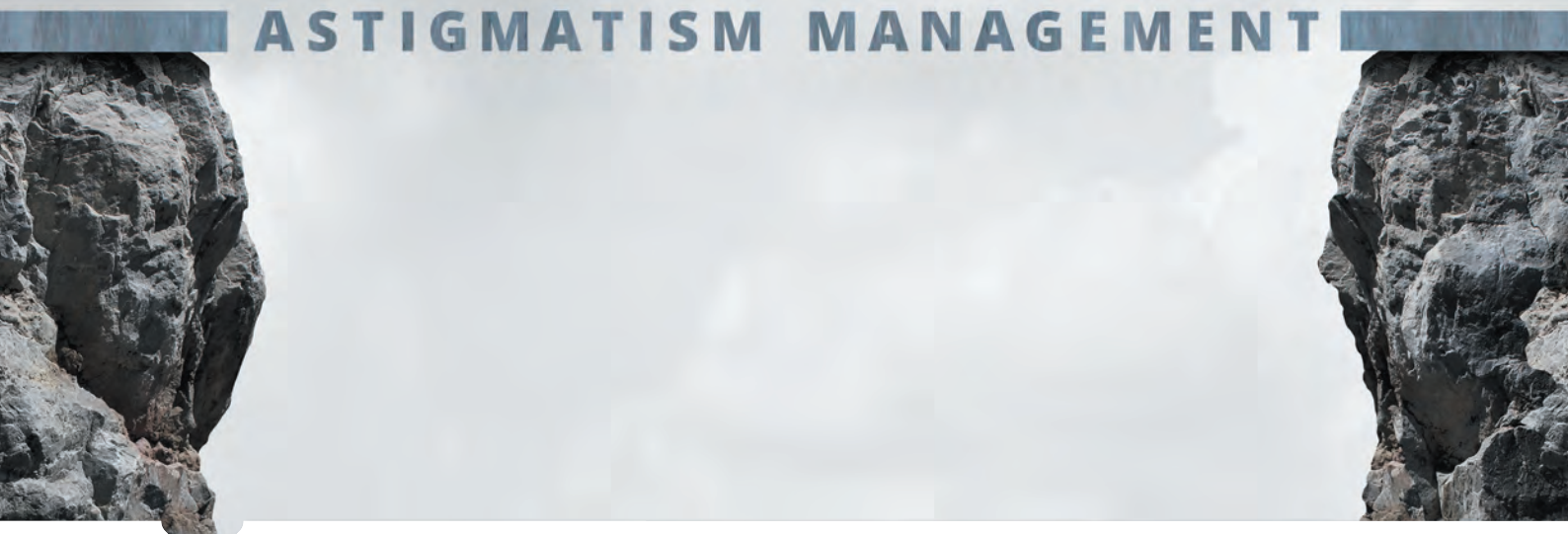
I originally wanted to be an optometrist; it was actually my family optometrist who suggested I should become an ophthalmologist instead. He gave me the single most actionable piece of advice I have ever received: "A few years of work on the front end of your life to do what you're meant to do for the rest of your life is always time well spent." He said: "Humor me and do the MCAT," so I did, and it's been like a hand in a glove from the moment I started my residency.

Any final comments?

If I had been given a blank piece of paper 25 years ago, I would not have had the courage to write my story as well as it has turned out. I'm just really grateful for our profession.

1,386,254.5 Diopters

of astigmatism went unmanaged in U.S. cataract ORs in 2017.*[,1]



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