JANUARY 2018 # 17

the Ophthalmologist™

Ophthalmologists and the Outside World

What eye surgeons get up to outside of the clinic...

The ICO-Allergan Research Fellowship

THE ICO-ALLERGAN RESEARCH FELLOWSHIP

The ICO-Allergan Research Fellowship is supporting research that recognises innovation and advances the scientific understanding and clinical management of ophthalmic diseases from across the globe. As part of this fellowship the ICO and Allergan are delighted to be able to support a one-year research fellowship, to the value of $50,000.

The fellowship is open to young ophthalmologists (those under 40 years of age at the time of application) from around the globe, offering the chance to continue their research at a chosen university; preferably in a foreign country to where they live. Applications will be accepted for research work in the following subspecialties:

- Neuro-ophthalmology
- Pediatric ophthalmology
- Glaucoma
- Retina
- Tumours
- Uveitis
- Dry eye
- Cornea

HOW TO APPLY

Applications will open on 1st October 2017. For more information about the fellowship criteria and how to apply, interested applicants should visit the ICO's Education page – www.icoph.org/fellowships
Applicants will need to submit the following items with their applications:

- Copy of specialist exam
- Detailed CV
- Description of previous work in the field of the application
- Endorsement of the current Program Director
- Detailed description of how research work should be continued during the fellowship
- Feasibility confirmation of chosen host university
- A sustainability statement

APPLICATION DEADLINE

Submissions must be received by 15 January 2018. The fellowship winner will be chosen and notified at the Association for Research in Vision and Ophthalmology (ARVO) meeting (29 April – 3 May) and will be officially announced at the World Ophthalmology Congress (WOC) meeting in June 2018.

FURTHER INFORMATION

For further information about the fellowship, please contact the ICO Fellowships office.

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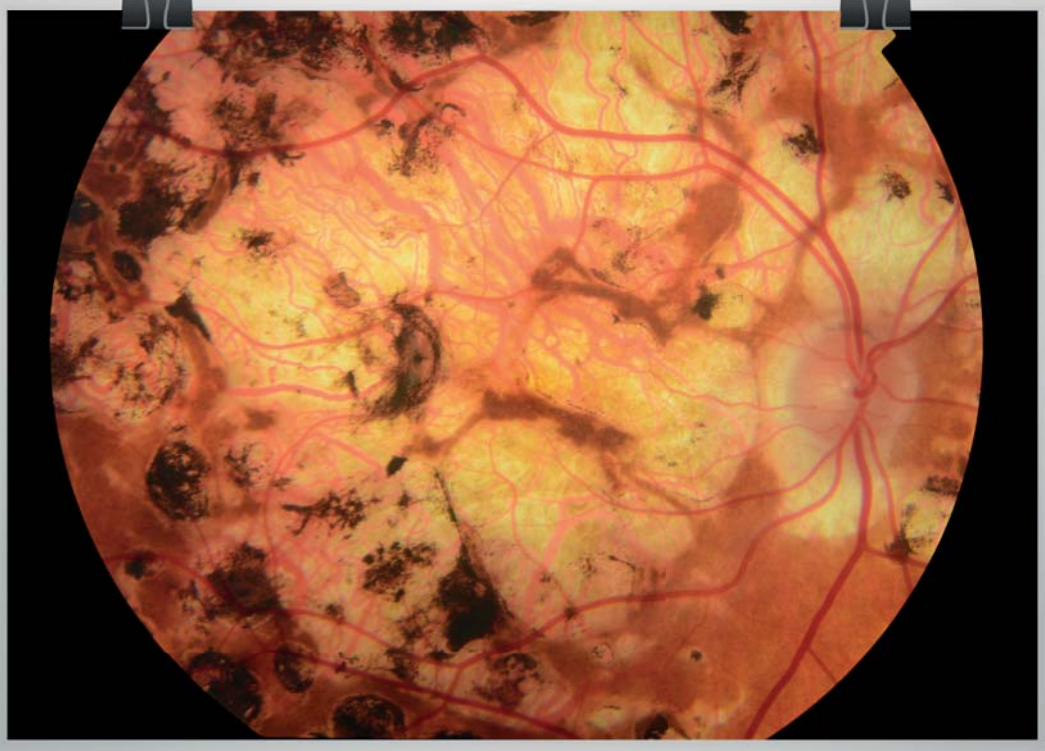
Image of the Month



Serpiginous Choroidopathy

This color fundus image was submitted by Jane Armitage, a Medical Illustration Manager from Calderdale & Huddersfield NHS Foundation Trust, Huddersfield, UK. Serpiginous choroidopathy – also known as white dot syndrome, geographic choroiditis or helicoid peripapillary choroidopathy – is an inflammatory disease characterized by chorioretinal lesions which can take on a serpentine or pseudopodial appearance.

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

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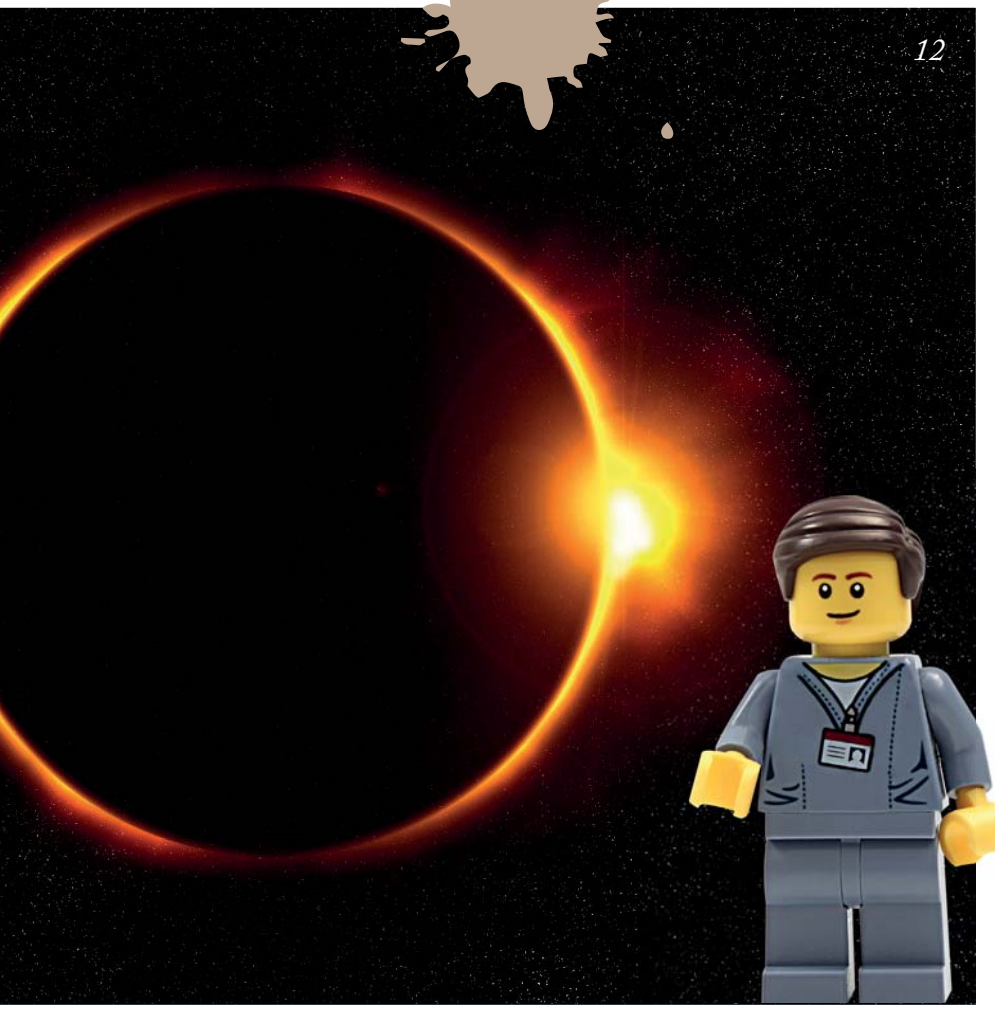

On The Cover

Tying in with the main feature's artwork theme, we turn to the world of Lego.

Upfront

the Ophthalmologist

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Corneal

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ASSESSMENT

Cynthia Matossian, MD
Matossian Eye Associates
Hopewell, New Jersey

"Ocular surface condition and dry eye is a critical assessment. I use the placido disc map of the OPD III to illustrate patients' level of dry eye: if the rings are not perfectly round, a little wobbly, irregular, broken up, or have dark spots on the corneal surface. I show my patients and let them know they have a pre-existing disease called dry eye syndrome that will not be affected by cataract surgery – that this disease process may indeed get worse over time so we can treat that separately. I distinctly want them to know that cataract surgery did not give them dry eye. Patients are able to understand for the first time the irregularities of their tear film and ocular surface condition."

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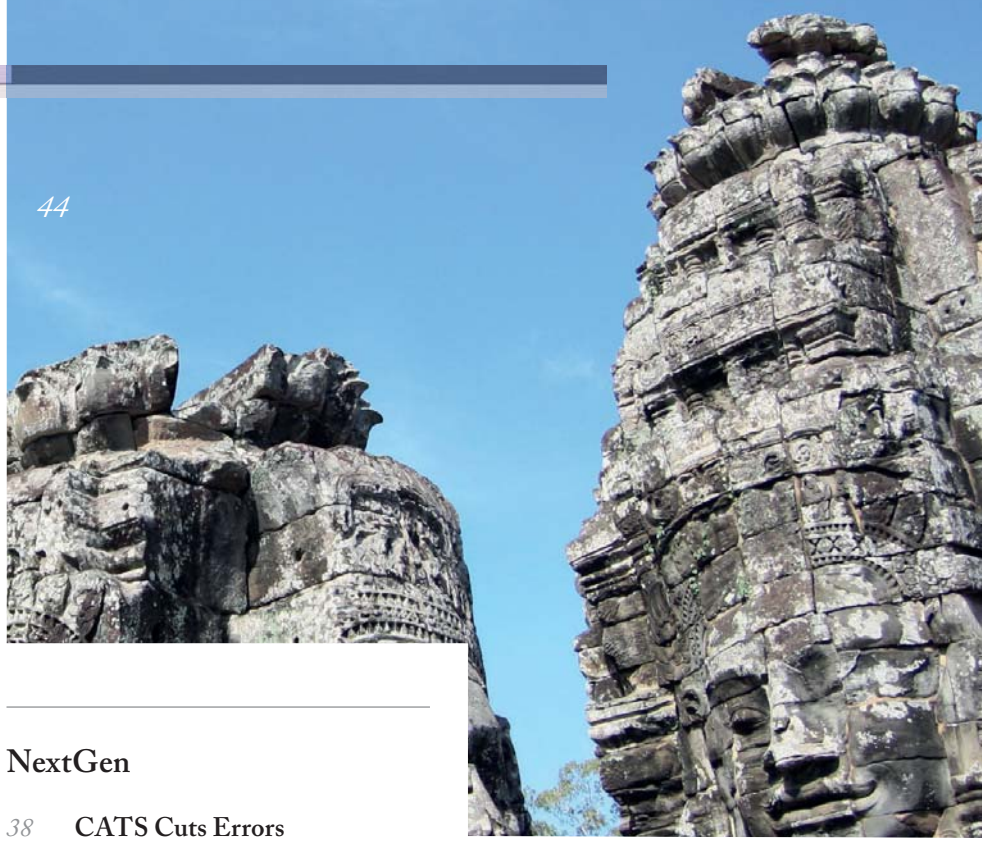

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Peerless

Can any other specialty match ophthalmology when it comes to pushing medicine forward?

I write a lot about how ophthalmology is at the forefront of medical advances; that rather than being a window to the soul, it's a window to not just the structures of the eye, but the vasculature and neural tissue too. We see exquisite engineering in instruments that can do incredible things – but surely innovation occurs in the rest of medicine too? Am I being blinkered, thoughtlessly repeating a mantra when the evidence to back it up in my mind is biased?

I don't think so. Spark Therapeutics' $850,000-a-dose Luxturna (voretigene neparvovec, which delivers copies of the functional *RPE65* gene for the treatment of retinitis pigmentosa) is one of the first gene therapies to be approved by the FDA – and the very first non-cancer therapy by them. We have the ophthalmic microsurgery robots being developed for use in the eye, which are pushing the boundaries of precision in robotic surgery, and which will almost certainly push the entire field of medical robotics forward – you can see clear applications elsewhere, particularly in neurosurgery.

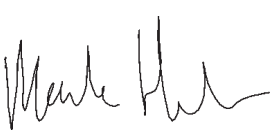
Only two issues prior, we had the story of Medisoft, an ophthalmology EMR that eschewed encoding billing information in all its forms for the data that's genuinely useful to clinicians who want to follow their patients and audit their outcomes. A large chunk of why ophthalmology is leading the way in artificial medical intelligence (AMI) – and, in particular, the use of machine learning to analyze medical images – is thanks to the quality information contained in that EMR system, which has helped train these AMI algorithms, and is bringing about (to use a Terminator reference) 'Judgement Day' far sooner than later – that point when computers, not humans, are reading the images and making diagnostic suggestions.

Even technology that's considered 'old news,' like the excimer laser, continues to improve – so much so that, in combination with (I want to say 'advanced', but it's actually 'routine') corneal biometry, suitable LASIK surgery candidates gain excellent outcomes virtually every single time. And I haven't even started examining the incredible diagnostic instruments that are now available.

So readers, I think you can start 2018 in the knowledge that you're part of an elite cadre, leading the way in medicine and medical science. And, without wanting to stir up age-old inter-specialty rivalries, could dermatologists say the same?

Happy New Year!

Mark Hillen
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

Artificial Win(telligence)

Can a deep-learning system really equal professional human graders in detecting retinal diseases?

With several groups and researchers developing artificial intelligence (AI) and deep learning systems for ophthalmic applications, diagnosis by machine is on the cards. Researchers at the Singapore National Eye Center and National University Singapore School of Computing have brought us one step closer with a deep-learning system that detects diabetic retinopathy and related eye diseases (glaucoma and AMD). But how does it compare with professional human graders? Using 494,661 retinal images from multiethnic (Chinese, Indian, Malay, Hispanic, African-American and White) patients with diabetes, the system demonstrated high sensitivity (≥90.5 percent) and specificity (≥87.2 percent) for identifying retinal diseases, comparable with the professional graders (≥88.5 percent and ≥99.3 percent, respectively). Daniel Ting, lead author on the corresponding paper (1), tells us more.

What impact will your AI system have on clinical practice?

It could potentially reduce total workload by 50–70 percent simply by removing non-referable images and allowing human graders to focus on the retinal images that need more attention. An established AI system could also be useful in conducting lifelong monitoring.

Any notable challenges in the course of your work?

Our team has come a long way. Together with another four co-inventors (Professor Tien Wong, Professor Wynne Hsu, Professor Mong Li Lee and Dr Gilbert Lim), we started developing and testing this AI system five years ago using retinal images that have been collected for over 10 years. Enormous financial and manpower resources have been poured into this AI project, and I am glad that our team has managed to overcome the initial obstacles and share our results.

What lies ahead for AI in medicine?

AI is the fourth industrial revolution in human history, and it will definitely revolutionize medicine in the next few decades. By having a robust AI algorithm, we also hope to deliver personalized medicine to the global population with diabetes, and we are certainly seeing similar trends in other medical specialties, such as dermatology, pathology and radiology. In ophthalmology, we certainly hope that that AI can help with repetitive workloads; for example, screening for diabetic retinopathy, glaucoma and AMD.

Pros and cons of using AI as a diagnostic tool?

Pros include cost- and time-savings, and zero intra-rater variability. Cons include the need for a large training dataset, technical expertise and supporting infrastructure.

Next steps?

We are currently in the midst of developing more algorithms for other retinal conditions, including retinal vein occlusions and retinal detachment.

Reference

1. *DSW Ting et al., "Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes", JAMA, 318, 2211–2223 (2017). PMID: 29234807.*

Redefining Navy Seal

Introducing the 'smart' polymer that could close ocular injuries on the battlefield

When a penetrating eye injury strikes, there is a need for speed. But what happens when the patient is in the middle of nowhere, with no access to emergency treatment? In such situations, repairing the damage with sutures isn't ideal: the procedure requires specialist training and risks infection...

Enter poly(N-isopropylacrylamide) – or PNIPAM – a biostable 'smart' polymer with thermoresponsive properties (see Figure 1a). The hydrophilic properties of its amide group (–CONH–) mean that PNIPAM is soluble at low temperatures. But when the polymer is heated to 32°C, the hydrophobic ($–CH(CH_3)_2$) groups interact, resulting in the formation of a gel-like aggregate as water is released from the structure. Cooling the polymer returns it to a soluble state.

PNIPAM's thermoresponsive and reversible solubility properties have made it a candidate for retinal implants (1). But in response to a plea from the US Department of Defense to provide a solution for sealing open globe injuries, researchers at the University of Southern California (USC) decided to fine-tune the polymer so that it could be used to seal ocular injuries (2). "Since the initial hydrogel's transition temperature was very close to the temperature of the human eye, we had to modify its properties to ensure that it would form a solid seal as soon as the gel was applied to the eye," said the paper's lead author, Niki Bayat (3). By co-polymerizing PNIPAM with N-tert-butylacrylamide or butylacrylate monomers, the team was able to optimize the formulation, as well as develop a custom injection tool that cools the sealant for application. The team demonstrated successful sealing of in vitro and in vivo models of ocular trauma (incision wounds in pig and rabbit, respectively): they found that the hydrogel was highly adhesive, could maintain pressures of up to 72 mmHg and prevent hypotony for 72 hours, and was biocompatible beyond the intended use period (3). Conveniently, the sealant can later be easily removed through application of cold water.

Beyond the battlefield, the team envisages that the system could also be useful for sealing eye injuries following mass casualty-related trauma. "First responders at a mass casualty incident could deploy the hydrogel while patients wait for their injuries to be completely repaired by an ocular surgeon in appropriate microsurgical facilities," said John Whalen III, corresponding author. "It could also be useful in ERs in rural areas where there isn't an eye center with such capabilities nearby" (2).

References

1. *M Tunc et al., "Reversible thermosensitive glue for retinal implants", Retina, 27, 938–942 (2007). PMID: 17891020.*
2. *Erica Rheinschild. "USC News: A new portable gel that could save an injured eye". Available at: http://bit.ly/EyeSeal. Accessed: January 2, 2018.*
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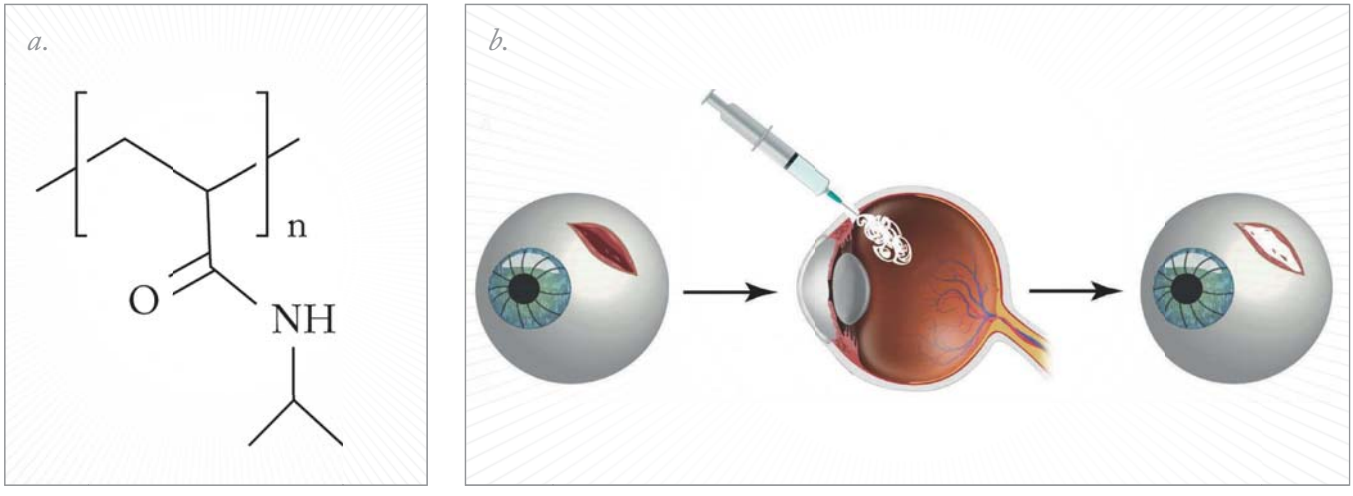
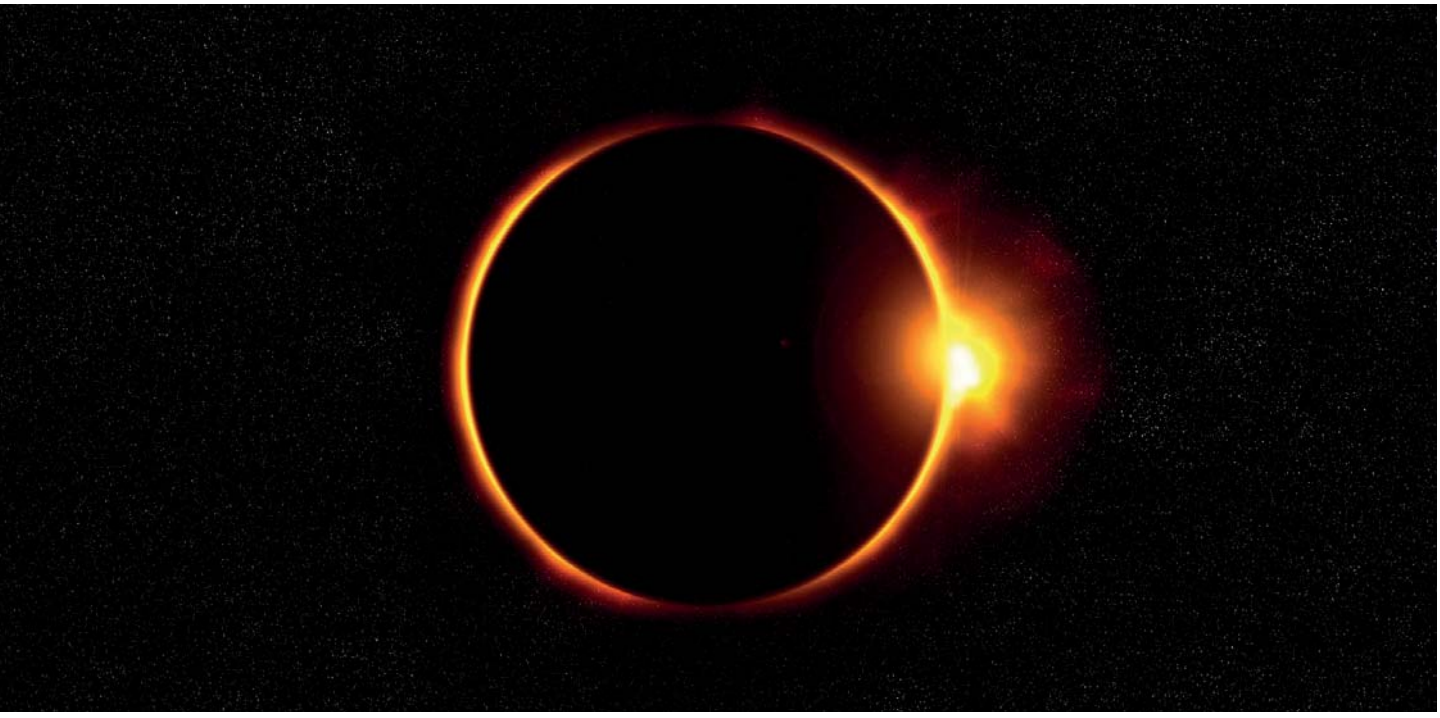


Credit: N. Bayat et al., (3).

Figure 1. The structure of PNIPAM (a), and how the modified PNIPAM gel is used to seal a globe rupture (b).



‘Un-eclipsing’ Solar Harm

AO-SLO imaging reveals the retinal damage caused by staring at the sun

August 21, 2017, marked the first total solar eclipse since February 26, 1979, to be visible anywhere in the US. But despite a comprehensive campaign advising people to take precautions to protect their eyes when viewing the eclipse, inevitably, some didn’t.

One such casualty presented to the New York Eye and Ear Infirmary of Mount Sinai three days after directly viewing the eclipse. The patient had viewed the solar rim for around six seconds on several occasions without using eclipse glasses. Realizing that the patient was exhibiting classic signs of solar retinopathy, the team involved in her care decided to find out more about the pathology of this rare condition, publishing what they found in JAMA Ophthalmology (1).

Avnish Deobhakta, the paper’s corresponding author, says, “It is well known that damage from an eclipse often leads to a persistent blind spot throughout life. We wanted to see how solar retinopathy manifested itself structurally and how it affected the photoreceptor layer.” Using adaptive optics (AO) scanning light ophthalmoscopy (SLO), the team made two key observations: disturbances in the cone photoreceptor mosaic at the fovea, and that the area of abnormal and nonwaveguiding photoreceptors was larger in the more seriously affected left eye. Although OCT angiography images appeared normal, en face OCT showed areas of hyperreflectivity at the fovea, and again, the left eye was more affected. The team also identified that the structural damage had a very specific shape. “We were surprised that the damage in the photoreceptor layer was extremely concordant with the shape of the exposed sun during the eclipse,” says Deobhakta. “Whilst this would have been our intuition going into the study, we did not expect it to be as concordant as it was.”

It is not yet clear whether the patient’s vision will recover, and the team are planning to re-image the patient upon follow-up. In response to their paper, Deobhakta reports that they have been contacted by more patients with a history of damage from previous eclipses who are offering to be imaged by AO. “Our hope is that we can better characterize the longitudinal damage of this condition, as well as determine if we can assess photoreceptor damage in other conditions with similar types of visual field defects.” With only six years to go until the next solar eclipse makes its way across the US sky in April 2024, let’s hope that a better understanding of the cellular damage caused by solar retinopathy will encourage all eclipse-viewers to wear appropriate protection.

References

1. *CY Wu et al., “Acute solar retinopathy imaged with adaptive optics, optical coherence tomography angiography, and en face optical coherence tomography”, JAMA Ophthalmol, [Epub ahead of print], (2017). PMID: 29222532.*

A Cup of Tea a Day...

Keeps the ophthalmologist away? Hot caffeinated tea appears to decrease glaucoma risk

For thousands of years, and in many different cultures around the world, hot tea has been considered a health-giving brew. The humble beverage has been linked to the treatment of many diseases, from cancer to cognitive decline – and now glaucoma, according to a recent study published in the British Journal of Ophthalmology (1). "Previous studies have suggested that caffeine consumption may be associated with glaucoma. We thought it would be interesting to take this one step further to see if there were differences between different types of caffeinated beverages," says co-author Anne Coleman, Fran and Ray Stark Foundation Professor of Ophthalmology, UCLA Stein Eye Institute, USA.

The US National Health and Nutrition Examination Survey (NHANES) of 1,678 participants, found that drinking hot tea daily conferred a 74 percent decreased risk of being diagnosed with glaucoma – but interestingly, no link was found between glaucoma risk and coffee, iced or decaffeinated tea, or soft drinks. According to Coleman, the protective effect could be related to the polyphenols in hot caffeinated tea, as they have been shown to be neuroprotective in animal models. But she also acknowledges that there could be beneficial lifestyle factors associated with drinking tea that were not covered by the study. The retrospective observational study also didn't look at factors such as cup size, brewing time or tea type.

"The next step is to look for this association in other large observational studies. The ultimate goal would be to randomize individuals to drinking hot caffeinated tea versus not, although this would be difficult to do as many people have a favorite beverage and do not want to change," says Coleman.

Time for tea?

References

1. *CM We et al., "Frequency of a diagnosis of glaucoma in individuals who consume coffee, tea and/or soft drinks", Br J Ophthalmol, [Epub ahead of print] (2017). PMID: 29242183.*
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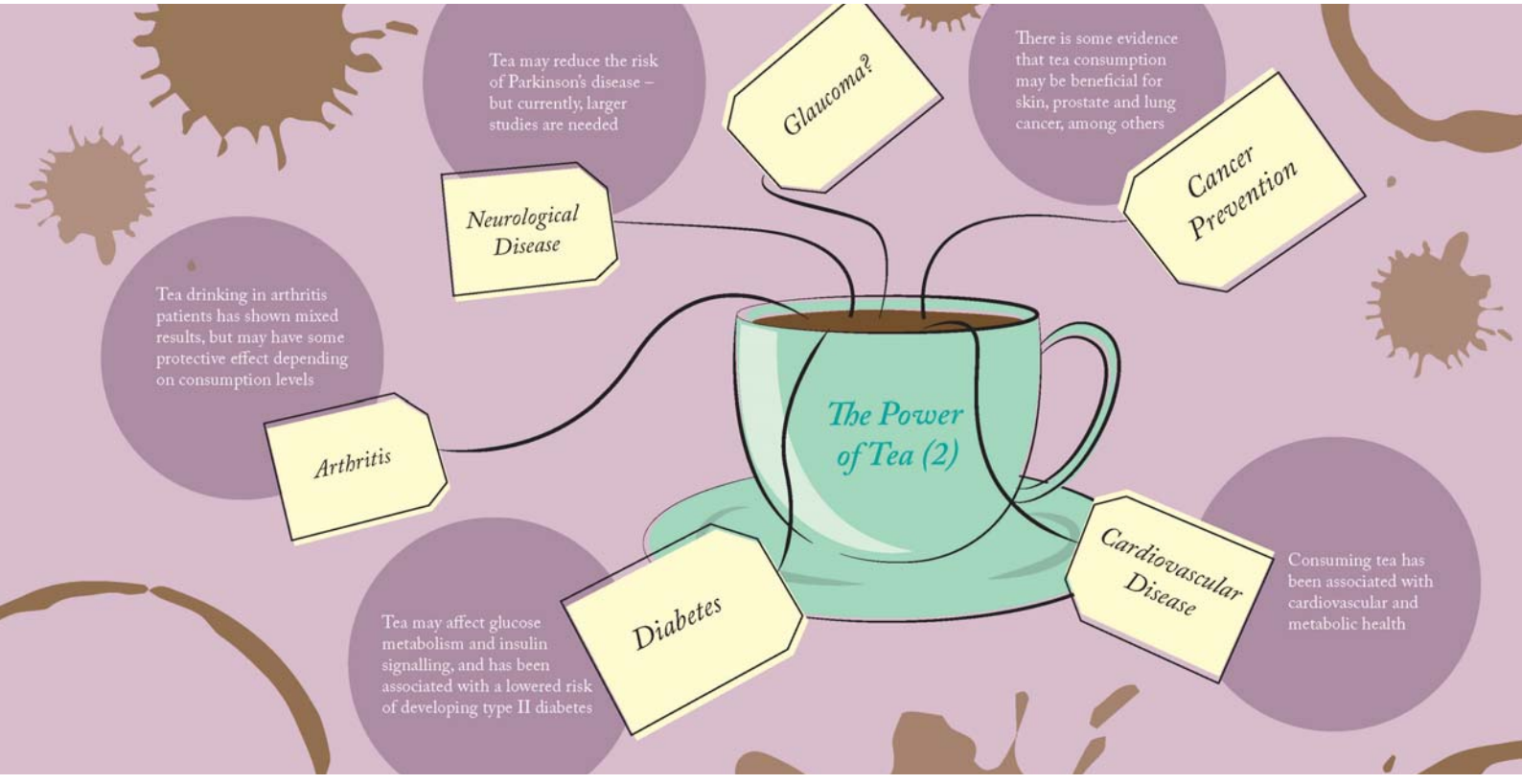

Drops of Silence!

Arresting AMD: topical siRNA therapy could be the future

There are currently no eyedrops to treat AMD or DME – mainly because the drugs on the market (or likely to arrive soon) treat these diseases with either recombinant fusion proteins (aflibercept), monoclonal antibodies (MAbs – bevacizumab), MAb fragments (ranibizumab), or humanized single chain antibody fragments (brolucizumab). Apart from inhibiting VEGF activity, they share another commonality; they are all far too large to be delivered topically and are, therefore, administered intravitreally. So the quest is on for a small molecule that: i) can inhibit retinal neovascularization (not necessarily through VEGF inhibition), ii) can be delivered in therapeutic concentrations to the retina by eyedrop, and iii) doesn't cause off-target issues on its journey from the ocular surface.

Small interfering RNA (siRNA) molecules are a tenth of the size of the existing crop of drugs, meaning they have the potential to penetrate from the ocular surface to the retina, where they act by silencing the expression of a target gene (Figure 1). The Spanish pharmaceutical firm, Sylentis, has developed a siRNA that silences the expression of *NRARP* – a gene that encodes a protein that stabilizes new endothelial connections during angiogenesis.

Efficacy studies in animal models (1) have shown that the siRNA-mediated reduction of retinal *NRARP* expression results in the regression of angiogenic retinal lesions to an extent equivalent to anti-VEGF therapy. Sylentis still have work to do; other topical AMD therapies are further down the road of clinical development. However, none are yet in late-phase clinical trial, so there's still lots to play for. Furthermore, in the intravitreal anti-VEGF world, we're seeing non-responders (particularly in DME) and people losing response over time. A different mechanism of action might help in these cases – and perhaps even in patients who have stopped responding to eyedrops of the future that employ a different mechanism of action.

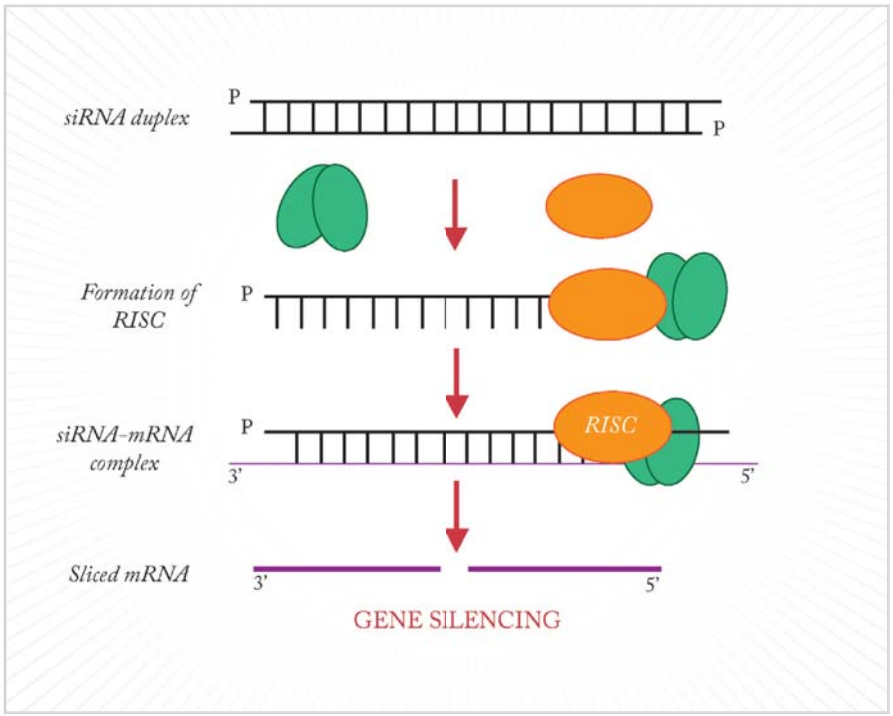

Figure 1. Gene transcription repression by siRNA. siRNA enters the cell, associates with other proteins forming the RNA-Induced Silencing Complex (RISC). Once in the RISC complex, the siRNA is unwound to form single-stranded siRNA. One strand remains part of the RISC complex, and is able to scan for, bind, and cleave its complimentary RNA. Once cut the cell recognizes the mRNA as abnormal, whereupon it gets degraded. No translation into amino acids occurs, and the gene is, in effect, silenced.

Reference

1. *C Pañeda et al., "Targeting NRARP with siRNA based compounds for the treatment of retinal neovascularization". Presented at the XIII Annual Meeting of the Oligonucleotide Therapeutics Society, Bordeaux, France, September 2017.*

Pain and Vision Gain

An analgesic is helping researchers explore new drug targets for sight-threatening diseases

Pentazocine is an opioid most commonly used to treat pain – but could it also be used to save sight? A team of researchers from Georgia, USA, previously found evidence that pentazocine can protect the cones of the retina – and have received a US$1.14 million grant from the National Eye Institute to explore the connection further. Ultimately, they hope to find new drug targets to treat causes of sight loss, including glaucoma and retinitis pigmentosa (1).

Pentazocine apparently binds to the sigma 1 receptor (S1R), activating a transcription factor – nuclear factor erythroid-derived 2-like 2 (NRF2) – which increases the expression of detoxifying and antioxidant genes. Last year, the team demonstrated that activation of S1R via administration of pentazocine could combat cone cell loss using a mouse model of retinal degeneration (2), and they suspect that its ability to modulate NRF2 levels is the reason for its protective effect. Building on this discovery, they conducted a study exploring how S1R activation and inhibition affects the survival of optic nerve head astrocytes, and found that S1R activation – again using pentazocine – protects cells from oxidative stress (3).

As oxidative stress is implicated in retinal degeneration, and has been previously linked with cone cell death (4), S1R becomes a promising drug target. Next, the team plan to further study how pentazocine affects NRF2 expression, and to see if the protective effects in the retina last over time.

References

1. *Jagwire News, "Scientists explore how a pain medicine also protects vision in blinding conditions like retinitis pigmentosa", (2017). Available at: http://bit.ly/2jYU5fk. Accessed December 15, 2017.*
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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

CXLUSA: Show Us Your Hand

Poorly managed epi-on CXL risks trashing the technique's reputation – and we're yet to be convinced of CXLUSA's effectiveness. A response to Roy Rubinfeld's "Time to Drop the Debate" (1).

By Theo Seiler, Founder of the Institute of Refractive and Ophthalmic Surgery (IROC), Zürich; Farhad Hafezi, Medical Director, The ELZA Institute, Zürich; Professor of Ophthalmology, Medical Faculty, University of Geneva and Clinical Professor of Ophthalmology, USC Gayle and Edward Roski Eye Institute, Keck School of Medicine, University of Southern California, Los Angeles; J. Bradley Randleman, Professor of Ophthalmology, Keck School of Medicine, University of Southern California, Director, Cornea, External Disease, and Refractive Surgery and Medical Director of Beverly Hills Clinic, USC Gayle and Edward Roski Eye Institute, Los Angeles; and Paolo Vinciguerra, Director of Ophthalmology Department Istituto Clinico Humanitas and Professor of Ophthalmology at Università degli Studi, Milan, Italy.

When it comes to corneal cross-linking (CXL), every single one of us is currently in the "epi-off" camp. Why? Because corneal ectasias like keratoconus need to be dealt with effectively – and, if CXL is the right approach to take for an ectatic cornea, then performing epi-off (rather than epi-on) CXL is almost always the right choice. It's the collagen in the corneal stroma that needs to be cross-linked; riboflavin, UV-A light and oxygen need to reach the stroma to do that, but the corneal epithelial cells form a very effective barrier to riboflavin penetration and oxygen diffusion (2). That's why the original Dresden protocol required epithelial cell debridement (3). It's also why no epithelial-sparing – epi-on – method has come close to the effectiveness of epi-off CXL – even iontophoresis, where a small electric current is applied to enhance riboflavin penetration (4). We would all love to be able to perform an effective epi-on procedure for our patients – such an approach promises patients less pain, a reduced risk of infection and transient haze, faster recovery, easier post-procedural aftercare and more… But we don't, because we won't risk having to repeat the surgical procedure at a later date and having patients suffer progression from that delay. Epi-on CXL, despite all of the advances in riboflavin formulations and delivery methods, still isn't as effective as epi-off CXL in terms of cross-linking the cornea, adding biomechanical strength, and crucially, halting the progression of corneal ectasia. Nothing the CXLUSA group have presented to date has convinced us otherwise.

Our first concern comes down to the fundamentals of the scientific method. The CXLUSA investigators have presented one-year data (5) from 341 keratoconic eyes that suggest significant improvements in uncorrected visual and corrected distance visual acuity (UCVA and CDVA) of 0.5 and 1.0 lines, respectively, a -0.45 D improvement in Kmax, and data from 217 eyes suggesting an almost 30 percent reduction in higher order aberrations (HOA) and coma (5,6). But there was no control group – a huge concern – and these results do not come close to what can be achieved with epi-off CXL (7). And let's not forget that science is based on a simple principle: publish your methods and let others repeat your experiment and confirm your data. In the CXLUSA consortium's

case, the important missing factor is the nature of their bespoke riboflavin solution. The formulation remains a mystery, and other sites have not been supplied with the solution so that they may try and repeat the experiment. Until that happens, the validity of their results will remain in doubt.

Another concern relates to some of the outcome measures relied upon to show therapeutic effect: UCVA and CVDA. We've seen from the work of David O'Brart that even non-treated keratoconic eyes can improve in visual acuity, likely due to patients learning the chart during the trial. Therefore, in effect, the CXLUSA group cannot guarantee that their results are different to those of epi-off control populations. Worse, the consortium's reported outcomes failed to reach the FDA's therapeutic response endpoint of 1 D flattening of Kmax (5) – a standard that every other epi-off (standard and accelerated) protocol has reached.

Further, none of the eyes had documented keratoconus progression prior to CXLUSA cross-linking being performed. In general, about a third of patients that come to our clinics have progressive keratoconus, so the question is: how can you claim that the method works to halt keratoconus progression when you're treating many patients who are stable? The CXLUSA consortium has presented outcomes that showed 7 percent of eyes with increased Kmax of 1 D or more at 12 months (6). If one-third of the cohort were progressive pre-CXL, then the 7 percent is equivalent to a 21 percent failure rate, which matches the failure rates described in every major epi-on study in the literature. We'd also like to see some biomechanical proof of the CXLUSA cross-linking protocol's effectiveness soon, and more details about the demarcation line depth achieved, as a measure of how much tissue is involved in the cross-linking process.

There are regulatory concerns too. If the CXLUSA group have indeed found the "Holy Grail" of truly effective epi-on CXL, then in Europe, at least, it appears to be unlawful to have a monopoly over a medical treatment, per Article 53(c) of the Guidelines of Examination for the European Patent Office. Presumably the CXLUSA consortium wishes to commercialize its product so that it may be administered to as many patients who might benefit as possible. We asked Peter S. Hersh, the Professor of Clinical Ophthalmology at Rutgers Medical School – and the medical monitor of the clinical study that led to the FDA approval of CXL for the treatment of keratoconus – to explain what needs to be done to obtain FDA approval. His response: "The company needs to have an IND (investigational new drug) and IDE (investigational device exemption) for the FDA – the former for their riboflavin solution and the latter for the device". In terms of clinical data to get that approval, the FDA needs "A formal clinical trial, typically with a randomized control group, carried out to demonstrate safety and efficacy of the device and drug." So we find it strange that the epi-on functional data that consortium claims to have obtained does not appear to have been collected in an FDA-compliant manner – something that you would think renders the commercialization of the product somewhat in jeopardy. If their objective is not commercialization, what is their goal?

We all want a functioning epi-on CXL that's as effective as epi-off CXL. If CXLUSA cross-linking proves to be that, we will all gladly embrace it. It's not even that we don't believe the word of the superb ophthalmologists that form part of the CXLUSA consortium when they stand at the podium and present their data. There's a basic level of disclosure that's expected in science and medicine, and it isn't being met, which concerns many of us. Their justification for not doing so – commercial sensitivity – for us, is wearing thin. In our view, they should trust in their intellectual property portfolio and release the proprietary solution for validation and verification at external clinical sites. What is the point of having a wonder drug if nobody can benefit from it? On the other hand, what if CXLUSA cross-linking, when deployed in a wider patient population, isn't as successful as it is claimed to be? If it results in significant numbers of patients needing re-treated, then we risk trashing the reputation of CXL worldwide. A wider evaluation would help spot any such lack of efficacy signal. To date, epi-off CXL with riboflavin is the only intervention in keratoconus that's able to halt progression in many cases. If fewer patients were to receive it because of reputational damage, it would be a tragedy.

To use a poker analogy: we're done placing bets – it's time for the CXLUSA consortium to show their hand.

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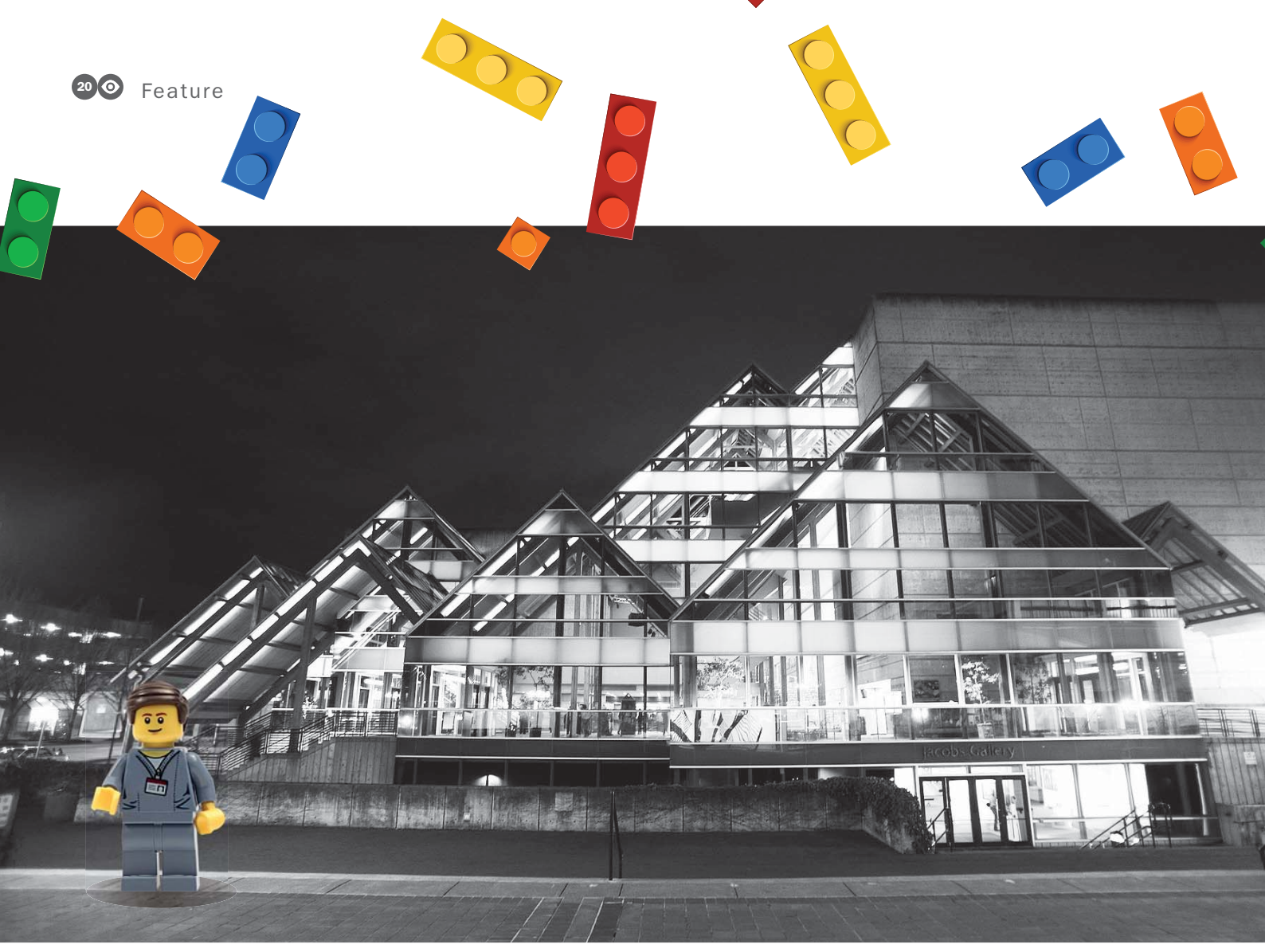
OPHTHALMOLOGISTS and the **OUTSIDE WORLD**

Howard Fine on how external influences shaped his practice of ophthalmology, and Günther Grabner on how a career in ophthalmology shaped what he did next: archaeology

By George Beiko

Eye surgeons don't operate in a vacuum – neither literally nor figuratively. They tend not to practice medicine when they leave their workplace at the end of the day. But what goes on in the rest of a surgeon's life still broadens knowledge, expands horizons, and provides new experiences – some of which filter into how they practice medicine. Howard Fine is a great exemplar of taking advantage of an outside influence; his love of orchestral music – and interest in how conductors martial their musicians – had a real impact on how he ran his operating theater.

Of course, the converse is also true: the process of becoming an ophthalmologist, then practicing it over a career, equips people with a whole gamut of skills that are applicable to many activities outside of the clinic. A case in point is Günther Grabner, who in retirement transitioned from practicing medicine to practicing archaeology. Here, he shares how knowledge and experience gained in the lecture theater, wetlabs, and years in the clinic have positively affected his new pastime.



CREATING YOUR OWN MASTERPIECE, WITH HOWARD FINE

Howard Fine's reputation precedes him. Whether you've seen him riding a motorbike around Hawaii or Alpine mountain ranges with Richard Lindstrom, or know him as one of the most influential and renowned ophthalmologists of the last half-century, he has shaped cataract and refractive surgery more than most. He has not only been a clinical investigator for nearly 50 ophthalmic products, but has also personally designed (or redesigned) nearly 40 ophthalmic instruments, and introduced almost 40 surgical techniques. His first degree – Engineering, from MIT – has certainly helped inform how he's practiced and innovated in ophthalmology over the years. But there has been another external influence that has profoundly changed how he practiced ophthalmology: orchestra conducting.

How did you get involved with orchestras?

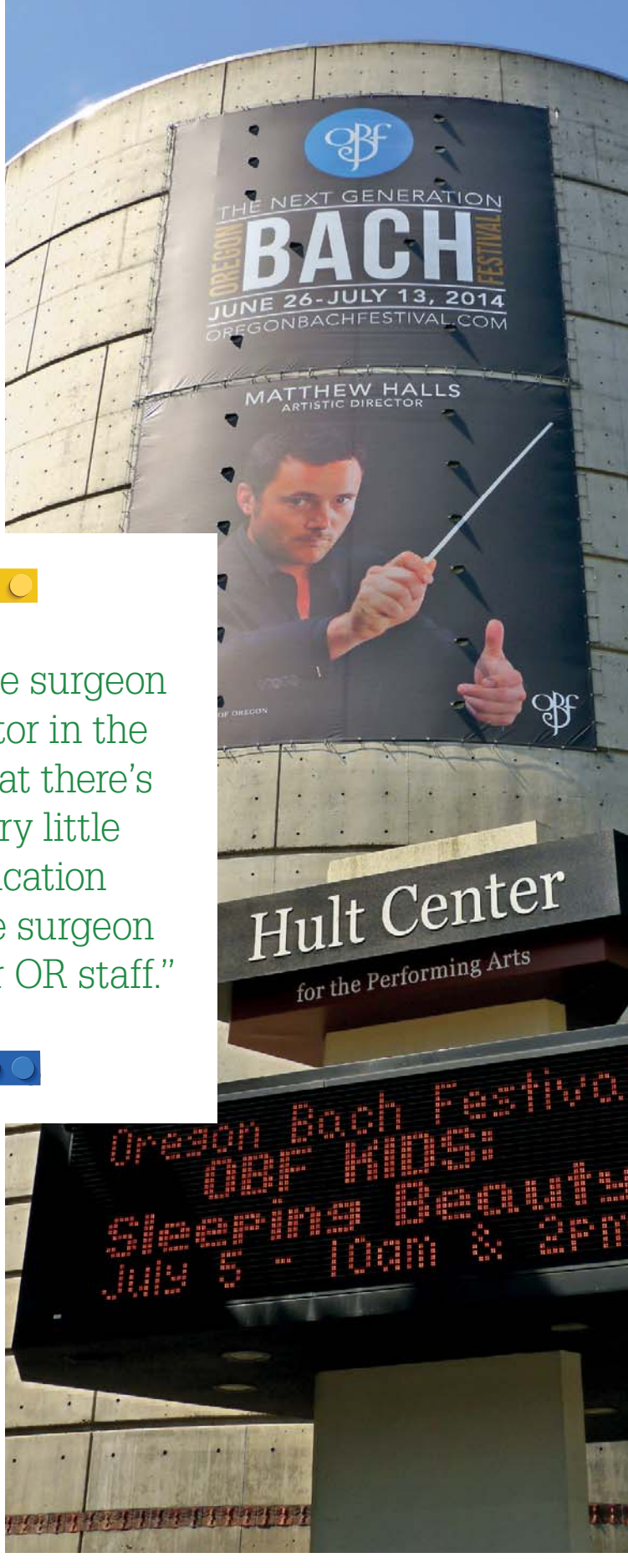
I've always been interested in classical music, but I was especially drawn to the conductor because he seemed to be bringing the music out of the orchestra and the vocalists. I always told my wife that I'd give everything else up, if I had that ability.

When I arrived in Eugene, Oregon, in 1970 to start my practice, it was the year of the city's first Oregon Bach Festival. It started out as a symposium for conductors who were interested in learning from a world-renowned master conductor, Helmuth Rilling, who was representing the International Bach Academy from Stuttgart, Germany, and is viewed as one of the leading interpreters of Bach – he has memorized everything that Bach has written, and conducts without a score!

My wife and I have attended every Bach Festival (bar one) since 1971. Each year, in addition to concerts, there are classes, with the biggest being the master conducting class. Accomplished conductors from all over the world attend, and

all are there to spend time with Helmuth Rilling. As a surprise birthday present, my wife arranged for me to become an auditor in that year's Oregon Bach Festival master conducting class – no small undertaking: the class takes place over 14 days and each session lasts 9 hours.

The morning consists of a three-hour session where conductors and soloists are instructed pretty extensively by Helmuth Rilling. In the afternoon, there's a full orchestra and chorus rehearsal, and in the evening there's a concert, at which time Helmuth Rilling explains what Bach was trying to achieve, some of the interesting aspects of the music, what's different about the music. A segment of the conducting class directs a portion of that evening's concert – and the students in the master conducting class sit up on the stage during the rehearsal and the performance. So we get to look at the conductor, and we can understand what he's trying to do and see how he works.



> "I realized the surgeon is a conductor in the OR – and that there's usually very little communication between the surgeon and his or her OR staff."

What really struck me as amazing was Helmuth. He was a superb teacher and communicator, never critical, and he always explained what was going on. The areas that he covered were all important; he always emphasized precision, control and clarity. He taught the mechanical aspects of conducting, which is an aesthetic as well as an athletic event: the left hand is used mainly for rhythm, the right hand for entrances and exits and emotion and other directions like higher, lower, softer, louder, faster, slower, longer, shorter. He doesn't command or tell people what to do, so as much as he gives them an invitation to participate. And this is something that you really feel as he's doing it. When he gets everyone on the same page – highly focused and intensely engaged – a musical masterpiece is the likely result.

How does this have parallels with your professional career?

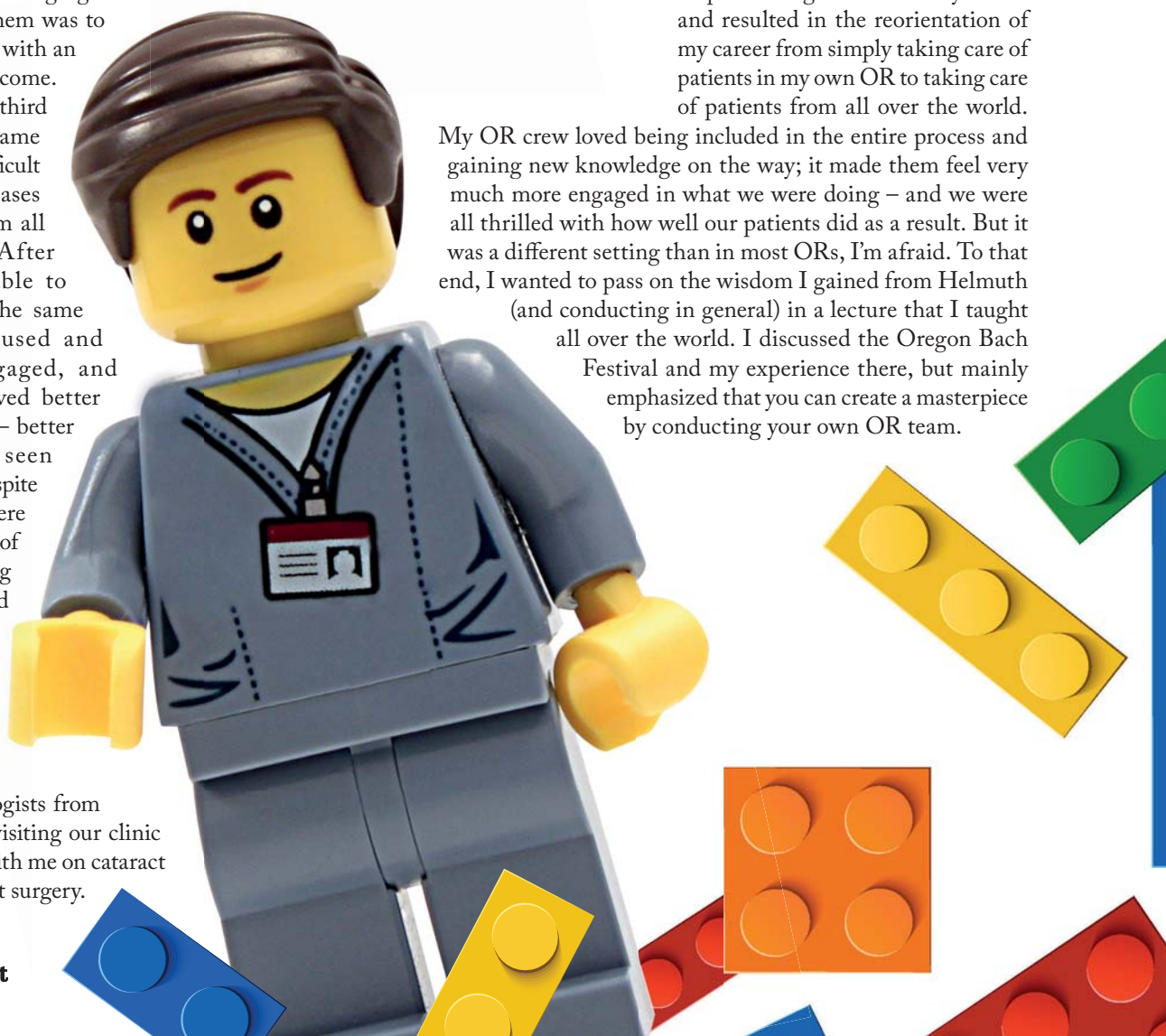
My interest in conducting, and learning about it, had no relevance to my practice when I started – but I came to understand that it gave my practice a horrendously advantageous boost. I realized the surgeon is a conductor in the OR – and that there's usually very little communication between the surgeon and his or her OR staff. It's a strange thing, but

surgeons really don't spend enough time with their OR staff, who are akin to the musicians and the vocalists. I realized I wanted to be like Helmuth; to lead by education and explanation, and I wanted to invite my OR crew to participate in something that I thought was very worthwhile doing.

And so I educated them; I spent a lot of time teaching them about new techniques, new technologies, and why it was worth the effort to abandon some aspects of what we were doing in favor of something better. I spent a lot of time explaining what was difficult about upcoming challenging cases. My invitation to them was to provide the patient with an unusually good outcome.

Later, about one-third of my practice became "train wrecks" – difficult and challenging cases referred to me from all over the world. After a while, I was able to get everyone on the same page, highly focused and intentionally engaged, and we actually achieved better surgical outcomes – better than any I had seen published – and despite the fact that we were dealing with some of the most challenging cases from around the world. In fact, almost all of those sent to us were visually rehabilitated, and we had many young ophthalmologists from all over the world visiting our clinic to do fellowships with me on cataract surgery and implant surgery.

"My invitation to them was to provide the patient with an unusually good outcome."



What overall impact has it had on your life and work?

I honestly believe my interest in conducting had an impact that no one could have anticipated. Helmuth Rilling has been a friend to me for many years now – and, in many ways, he changed my life. I certainly have favorite conductors, but what so impressed me about Helmuth was his emphasis on precision, control and clarity – all essential aspects of cataract surgery as well.

I am very much aware that the fine arts can have benefits to society that are unforeseen and unrelated to their original goals. Conducting certainly helped me a great deal in my career and resulted in the reorientation of my career from simply taking care of patients in my own OR to taking care of patients from all over the world. My OR crew loved being included in the entire process and gaining new knowledge on the way; it made them feel very much more engaged in what we were doing – and we were all thrilled with how well our patients did as a result. But it was a different setting than in most ORs, I'm afraid. To that end, I wanted to pass on the wisdom I gained from Helmuth (and conducting in general) in a lecture that I taught all over the world. I discussed the Oregon Bach Festival and my experience there, but mainly emphasized that you can create a masterpiece by conducting your own OR team.

RETIREMENT DONE RIGHT

Are you still practicing ophthalmology in retirement?

I see patients for half a day per week, and these are almost all patients that I have operated on in the past. You know, one of the things that makes ophthalmology unique is that we don't disrobe anyone, and so our life in the clinic with them is much more relaxed and social. I've got patients that have been with me so long they're more like friends; last month, I saw a woman in whom I did retinal detachment surgery when she was a young woman, she was a high myope, and much later I did cataract and IOL surgery on her. When she was in for a routine exam about a month ago she said, "You know Doctor Fine, when you first told me I had to go to the hospital to have my retina fixed, my biggest concern was where I was going to get a babysitter for my two-year-old son – he just celebrated his 44th birthday!" Such contact and continuity with people over a period of decades leads to a different relationship than the average doctor-patient relationship. When our surgery is highly successful, our patients absolutely love what we do – and we love being able to provide a wonderful enhancement of their lives.

How did you wind down to half a day's work per week – and what has helped fill the void?

I absolutely loved what I did and I never looked at work as work. And that's why I could work so hard and long. And was I ever busy?! I invented 40 different instruments, I innovated 35 or 40 different surgical techniques, I published over 800 journal articles, I was a referee for most of the ophthalmic magazines, and I spent a great deal of time teaching and demonstrating surgery at congresses. I conducted over 40 FDA-monitored studies and worked with industry almost all of that time. But I also knew that I wanted some time in my life when I was in control of my own schedule – when I could decide, "Yes! Next Wednesday I'm going to go to our beach house."

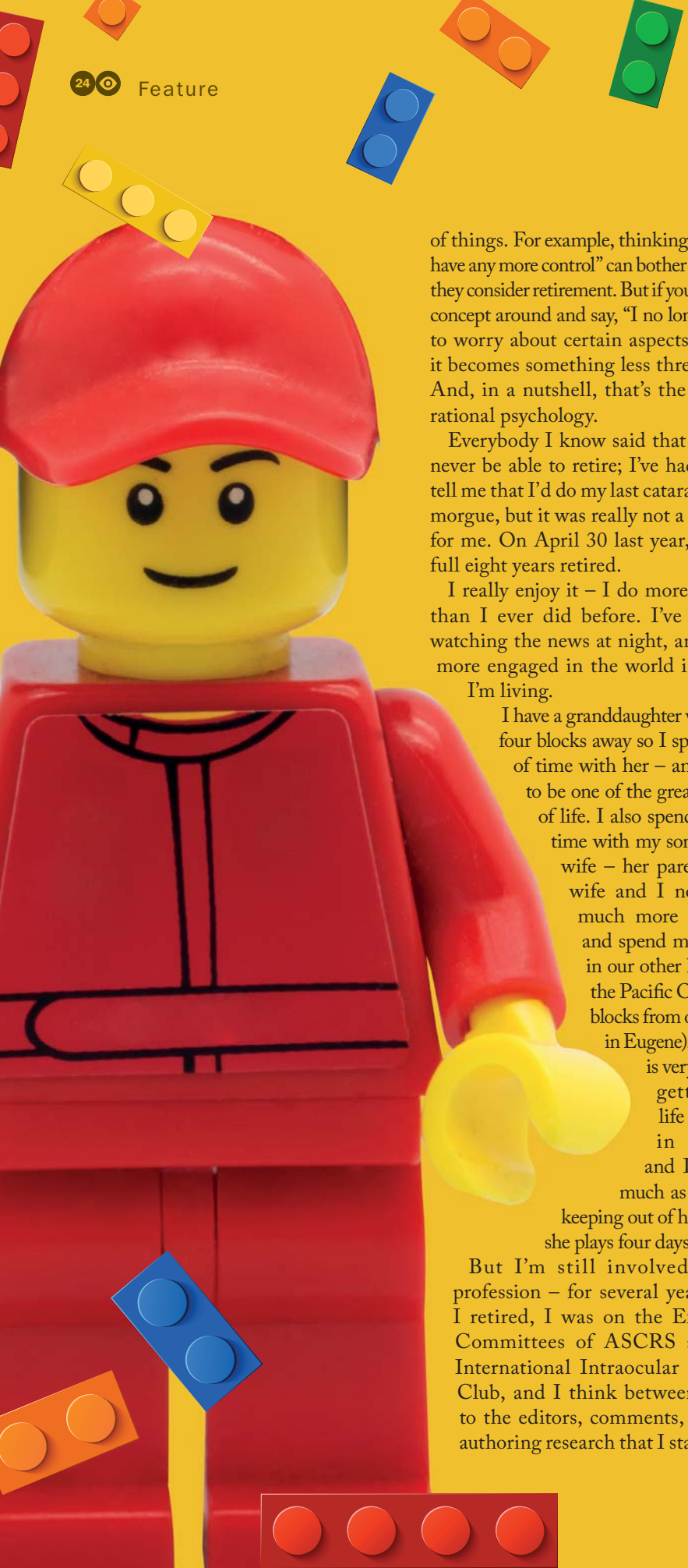
I started my search for the perfect retirement at the age of 55, believe it or not – but finally achieved it at 73. I talked to a lot of people, I looked at good examples, bad examples, successes and failures. But the thing that helped me most was a psychologist who worked for our clinic.

The 150 employees at our clinic are all self-insured for mental health and can have three appointments with a mental health specialist, a psychiatrist or psychologist each year at no cost. I decided that I would like to speak to a psychologist about retirement. Tom Fauria specialized in life's transitions, so I made an appointment to see him four or five years before I retired. He asked me to send him a CV before he saw me the first time. My CV is long... 53 or 54 pages long with downsized type! In our first appointment, Tom told me point-blank that there was no way someone like me could retire without a loss of self-esteem and feelings of guilt. Why? Because my many activities nourished me. But he also had a solution.

I saw him three or four times a year for the two or three years prior to my retirement, and he helped me enormously. Through working with Tom, my practice administrator and my wife, I was able to retire in an entirely smooth way. I began about three years before retirement, taking one day off a week, then two days off, and in the last year I was working just three days a week. On my 73rd birthday, I did 20 cataract surgeries, and that was the end of my active career. And I had no trouble with it, no trouble at all, as we were prepared.

What advice were you given to help you prepare for retirement?

Basically, the psychologist emphasized 'rational psychology,' which differs greatly from the psychoanalytical approach of 'uncovering' – going back into the past and seeing what key events in your life have impacted your behavior, your thinking and your mental health. One example of rational psychology is looking at alternate ways of the meaning



of things. For example, thinking, "I won't have any more control" can bother people as they consider retirement. But if you turn the concept around and say, "I no longer have to worry about certain aspects of life," it becomes something less threatening. And, in a nutshell, that's the basis of rational psychology.

Everybody I know said that I would never be able to retire; I've had people tell me that I'd do my last cataract at the morgue, but it was really not a problem for me. On April 30 last year, I was a full eight years retired.

I really enjoy it – I do more reading than I ever did before. I've enjoyed watching the news at night, and being more engaged in the world in which I'm living.

I have a granddaughter who lives four blocks away so I spend a lot of time with her – and find it to be one of the greatest gifts of life. I also spend a lot of time with my son and his wife – her parents. My wife and I now have much more freedom and spend more time in our other house on the Pacific Ocean (60 blocks from our home in Eugene). My wife is very close to getting her life Master's in Bridge, and I help as much as I can by keeping out of her way as she plays four days a week!

But I'm still involved in my profession – for several years after I retired, I was on the Executive Committees of ASCRS and the International Intraocular Implant Club, and I think between letters to the editors, comments, and co-authoring research that I started but that has been finished by my partners, I've ended up with about 50 publications since I retired eight years ago!

And the half day a week that I see my patients from so long ago is a pleasure rather than a burden. I consider my life as being full; I do occasionally dwell a little (in a good way) on the past, thinking about how much fun I've had, how much I've enjoyed what I've done – and, to be honest, how much I've helped people. My mother was very religious, and she was perhaps disappointed that I could never be religious like she was, but I think she took a lot of pleasure in the fact that I wanted to help people, so I was able to contribute through my career.

Do you have any advice to people earlier in their careers?

Well, I think the advice that I give most young people is: do the things that you like to do during your career. If you start working in an area that looks like an opportunity because fewer people are working on it, but it's not something you like, it's a mistake. You're going to get busier and busier, and pretty soon you'll get stuck with it. I would also advise people to consider retirement early on. Many people tell themselves they'll never retire or think that they don't want to retire. But, as we age, our physical abilities leave us, and we're less energetic. And, as we all know, we may not see as well as we once did, which could limit surgery or other activities.

By honestly considering retirement, you can see a path to it, which helps significantly. I can honestly say it was seamless for me; not one day went by when I thought, "This is a bad deal." I simply went from loving surgery the last day I worked, to being relieved in the new peace and freedom that retirement gave me. It's also important for people to realize that retirement need not be heavily goal-directed.

OPHTHALMOLOGY'S INDIANA JONES,

WITH GÜNTHER GRABNER

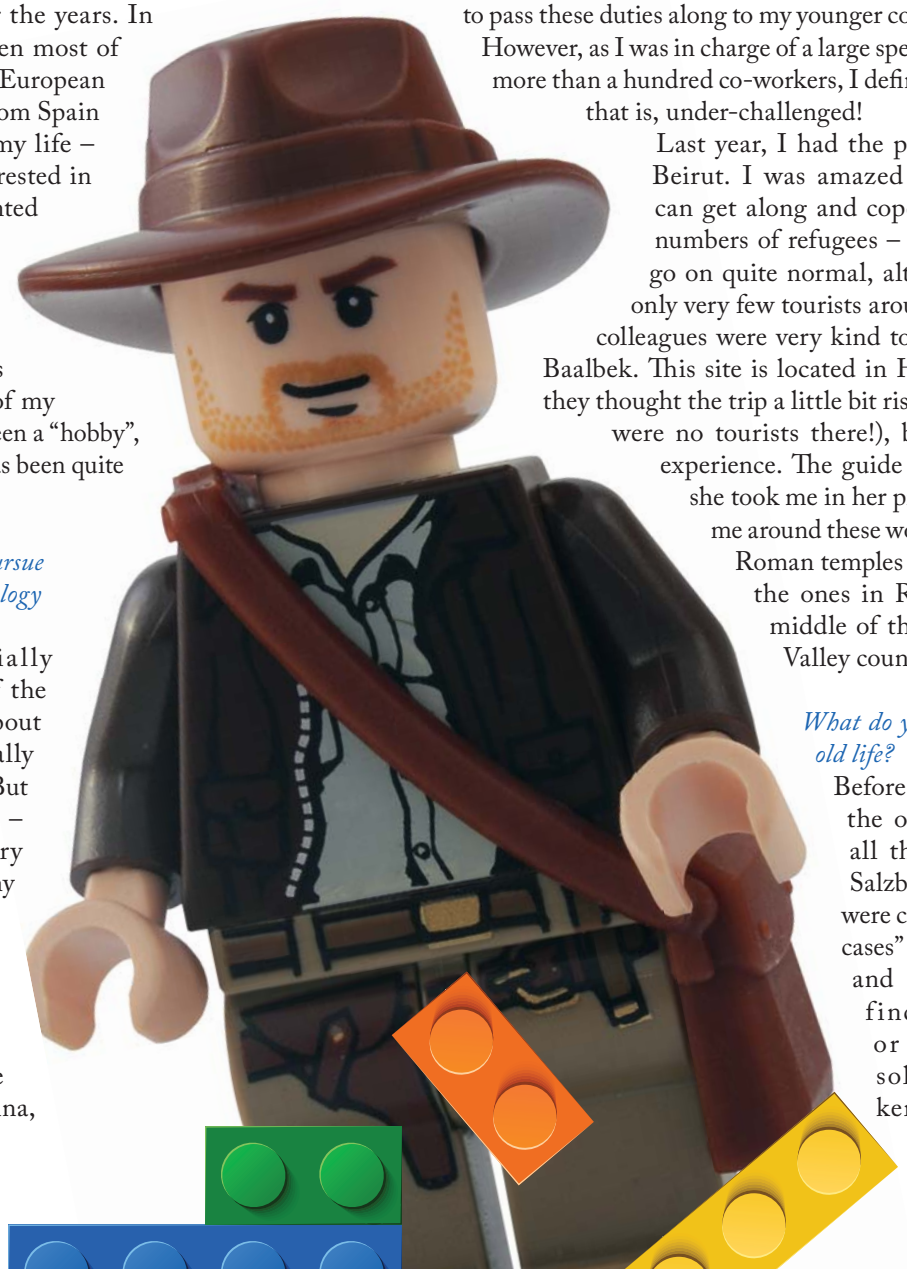
Günther Grabner had a stellar career in ophthalmology. He founded Austria's first Eye Bank in 1977 in Vienna and was a pioneer in corneal refractive surgery from the early 1980s. His work has spanned uveitis, presbyopia treatments with lasers, inlays and intraocular lenses, kerato-prosthesis surgery, glaucoma surgery and large epidemiological studies. If you've ever heard of the Salzburg Reading Desk – a system that precisely measures near visual acuity performance, that's his too. He's sat on many industry advisory panels, journal editorial advisory boards, and has held high office in many international ophthalmological organizations.

Today, you're still likely to find him in an academic setting – but not necessarily at the Eye Clinic of the Paracelsus Medical University in Salzburg. In his retirement, you're more likely to find him in a lecture theater with his fellow Archaeology

undergraduate students – or perhaps performing field work at an archaeological dig.

How did you transition from ophthalmology to archaeology?

That was easy: my father-in-law was a very prominent Austrian prehistorian for over half a century. He was Chairman of the Institute of Prehistory, and for many years, Dean of the University of Vienna. He started in the 1920s and retired in the late 1970s, but worked daily in the field until his death in 1985. Back in 1975, when I was engaged to his daughter (we married in 1976 and now have great fun with our first grandchild, Maria) I went to his lectures and truly enjoyed them. I had always been interested in archaeology (and later, in prehistory), and I've visited many sites in Greece, Turkey, Italy and Egypt over the years. In fact, I've probably seen most of the relevant southern European archaeological sites from Spain to Lebanon during my life – and I became so interested in the subject that I wanted to study it properly and just followed my interest… Second to eye surgery (which was the greatest passion of my life), this has always been a "hobby", never "work", and it has been quite a blessing…



Did you find time to pursue your interest in archaeology alongside work?

No. Until I officially retired as a Chair of the University Clinic about two years ago, I really didn't have the time. But my senior co-workers – they have become very dear friends over many years – gave me a wonderful farewell gift: two weeks' "digging" vacation with the Salzburg archaeologists on the Greek Island of Aegina, near Athens. There, I spent time at an excavation site that had been going on for about half a century – always run by the Salzburg academics. I enjoyed it a lot. In September 2016, I decided to study prehistory in earnest and started to go to the University of Vienna to take classes and pass exams; in fact, I go to the lectures at the very Institute that my father-in-law had chaired.

It was quite a change – but it feels easy because I'm still seeing patients in my two offices – in Vienna and Salzburg – once a week in each, and still doing surgery at both locations in private hospitals, so I haven't completely left ophthalmology; it's rather a smooth transition. I'm still going to some of the large international (and some local) meetings and giving some instructional courses, so I keep busy – but I'm hoping to pass these duties along to my younger colleagues very soon! However, as I was in charge of a large specialized clinic with more than a hundred co-workers, I definitely feel "retired", that is, under-challenged!

Last year, I had the pleasure of visiting Beirut. I was amazed how the country can get along and cope with these huge numbers of refugees – but life seemed to go on quite normal, although there were only very few tourists around! The Lebanese colleagues were very kind to arrange a visit to Baalbek. This site is located in Hamas country, so they thought the trip a little bit risky (basically, there were no tourists there!), but it was a great experience. The guide was a lawyer, and she took me in her private car, showing me around these wonderful, enormous Roman temples – even bigger than the ones in Rome – set in the middle of the beautiful Beqaa Valley countryside.

What do you miss about your old life?

Before retirement, I had the opportunity to see all the patients in the Salzburg Eye Clinic that were considered "difficult cases" with my colleagues and then we tried to find good surgical or "conservative" solutions, such as keratoprostheses of

different types (we were the referral center in Austria).

I really miss these "challenging" cases. Each day, patients with severe traumata to the eye, very young children with congenital cataracts, challenging cataract cases, acid burns (of which I saw a lot), and sometimes even patients requiring keratoprostheses (KPro) would come in. This can take a lot of your time (up to four hours, a minimum of twice or sometimes even three times to restore vision in one eye) e.g. for osteo-odonto-KPro which I learned to perform from my dear teacher Giancarlo Falcinelli in Rome. In Austria, you usually do not see such patients after retirement in a government-funded position, because you require a specialized clinic with some rarely used equipment to do the procedure. Routine cataract surgery, in general, is not really a surgical challenge for me, but "rebuilding" severely injured corneas? That was a privilege and I still miss it greatly. Now I mostly see patients that I've known for quite some years and with whom I have built up a relationship. They like to chat with me and they still come in for surgery, but it's not the great daily challenge that I was used to and loved.

Are you filling that challenge gap with your pursuit of archaeology?

Well, it's a completely different challenge! The first challenge is that I'm three times older than the 19–21-year old students on my first course – I'm old enough to be their grandfather! In fact, most of the professors at the Institute knew my father-in-law, because he was their teacher. Indeed, I'm also older than all of the teachers, which is another "mental" challenge...

I've read a lot about archaeology over the years and keep asking questions in the lectures. In geophysical prospection, we study modern techniques of research and surveying, such as ground-penetrating radar, LIDAR laser scanners and magnetometry. This subject matter in itself is very interesting, but it's the final payoff of identifying large areas of "no digging required" is what counts!

The real difficulty is getting back into the habit of studying really hard! I haven't tried to learn a book or article by heart for over 40 years! When studying medicine, to learn a book within a fortnight, was possible, but it's a skill that gets lost with age; you have to retrain your brain… There are so many sites of prehistoric findings – several hundred important ones

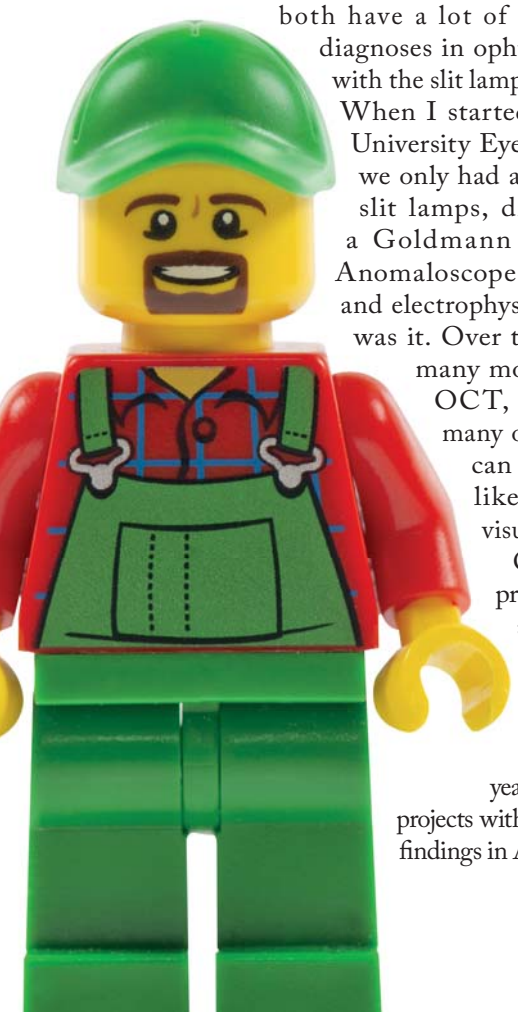
in Austria alone, and many thousands worldwide – that one should probably be aware of! In other words, there is no shortage of archaeological challenges!

How are your interactions with the much younger students?

I think I'm well accepted; I treat them like colleagues, and they do the same. At first, they were amazed to have a student at my age (when I first entered the lecture hall, all were really quiet – probably thought I was the Prof…), but they've accepted it by now. Out of about 50 students in the class, I'm the only one in this age group, but it's fun! We go to seminars and on field trips together. For example, there are some Paleolithic sites close to Vienna (you might have heard of the famous "Venus of Willendorf"), and we go on excursions – six students, two lecturers and two professors – and we take pictures and do some actual digging. We also learn how to dig properly, and how to handle what is discovered.

You mentioned LIDAR laser-based topography scanning techniques – sounds familiar...

There are certainly some similarities with ophthalmology: both have a lot of "visual diagnostics". Most diagnoses in ophthalmology can be made with the slit lamp and the ophthalmoscope. When I started at the Second Vienna University Eye Clinic – Fuchs' clinic – we only had a handful of instruments: slit lamps, direct ophthalmoscopes, a Goldmann perimeter, the Nagel Anomaloscope, plus some ultrasound and electrophysiology instruments. That was it. Over the last 40 years, we got many more "toys": topographers, OCT, ocular biometers, and many other instruments that we can use now, but still, quite like archeology, it's a very visual specialty.



One of the research institute's priorities is aerial archeology and, as the name suggests, surveys of the earth's surface from an airplane are made – which is nice, especially as I've held a pilot's license for 40 years, so I'm currently looking for projects with aerial surveys of prehistoric findings in Austria!

What other transferrable skills have you been able to apply to archeology?

If you've been doing ophthalmic surgery for several decades, you really have learned to have a light touch. When you're digging in the ground, you're supposed to remove the soil ("stratigraphic units") very slowly so as not to disturb the stratigraphic layer that you're working in. One has to find slowly out what type of shards might be deposed. Is there charcoal, are there bone structures, can you see any discoloration, pigment? You don't want to break the shards, they can be very delicate, so I learned very quickly to treat the findings carefully. Rarely is pottery ever in one piece; the nice colored kylix from Mycenaean times that we found last year was broken into many small pieces, and one does not want to lose any of them…

So you're almost rebuilding them like you used to rebuild very damaged eyes!

This is a similarity I have not thought about! Just imagine reconstructing something that has been in the ground for several thousand years – e.g. since the Bronze Age in Aegina. And on another excavation site, I found a sewing needle from the Paleolithic (stone age) era that was dated as being from 19,000 years ago. It was quite satisfying….

Any advice to others on how to approach retirement?

My advice for people close to retirement is: find a hobby that truly delights you. For me, retirement was kind of a shock, although, in the end, it was rather a small one. I knew that I would retire – everyone knows that, if we make it – but it is still an awkward experience to lose your regular schedule. For years, getting up at 5:50 am, being in the clinic by 7 am at the latest, starting surgery at 9 am after rounds, finishing surgery in the afternoon, doing the administration, and getting home at seven or eight in the evening was my routine. And then all of a sudden – no one misses you…

My advice for people close to retirement is to find another tight schedule to follow as soon as possible after retirement. Find a hobby – or more – that you love, and start with it immediately after retirement – don't waste time!

George Beiko is Assistant Clinical Professor at McMaster University, and currently practices at St Catharine's in Toronto specializing in cataract, anterior segment and refractive surgery. George also lectures at the University of Toronto.

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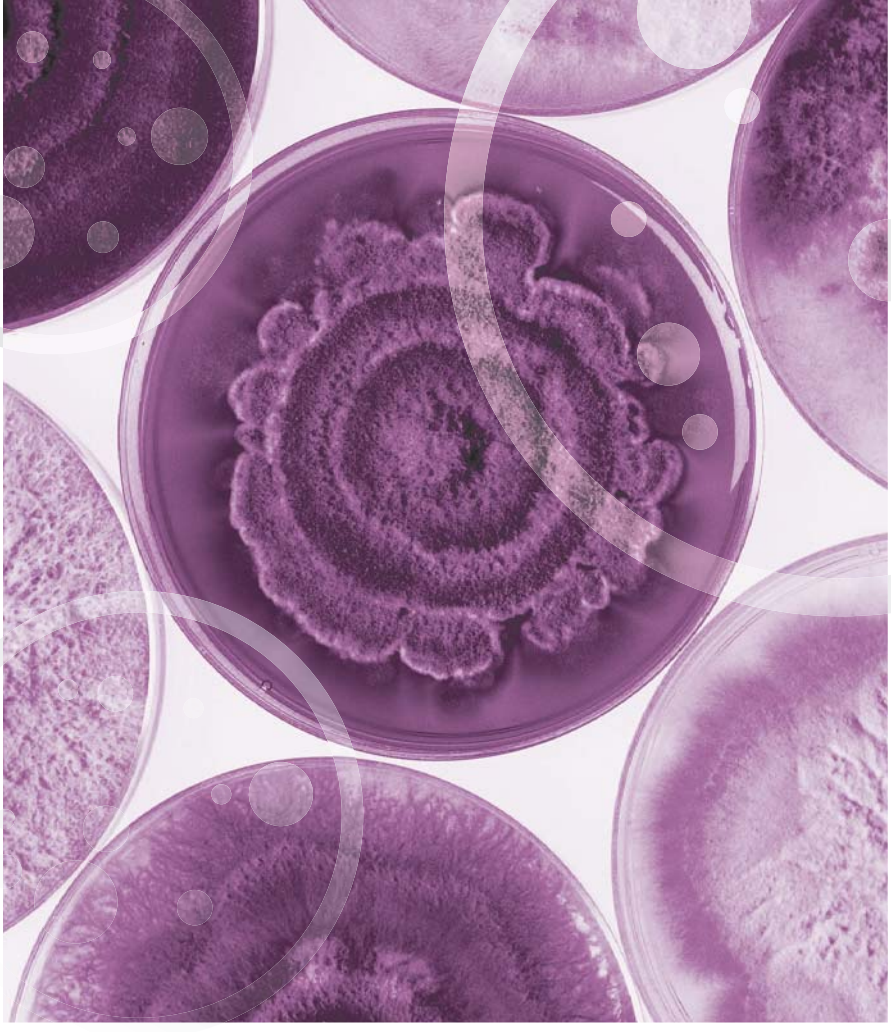
Nature's Petri Dish

The advantages of SLET and how to perform it

By Virender Sangwan



For over 10 years, I have been performing cultivated limbal epithelial transplantation (CLET) for limbal stem cell deficiency (LSCD), and have performed over 1,000 procedures. But I think that simple limbal epithelial transplantation (SLET) is a much better technique.

CLET versus SLET

In the CLET procedure, a limbal biopsy is harvested from the healthy eye at the first patient visit. These cells are then cultured for two weeks, before being implanted in the patient's eye. CLET might have shown effective results (1–3), but the procedure is not a commercially-viable or scalable option. A very high quality cGMP laboratory is needed to culture the cells, which is very expensive, and there are associated regulatory hurdles. There are also logistical considerations, such as the two-week gap between the two procedures and transport of cell cultures to clinics, as well as the risks of contamination with the materials used to enable cell culture, such as fetal calf serum. Furthermore, despite 40 percent of patients needing CLET being children, the procedure is only successful in around 40 percent of pediatric cases (4).

SLET is similar, but much simpler (See "Step-by-Step SLET") – and there is a nice story as to how it evolved (See "The Evolution of SLET"). As in CLET, a limbal biopsy is taken from the healthy eye, but instead of being cultured and expanded in the laboratory, the cells are implanted onto an amniotic membrane attached to the surface of the diseased eye (5). SLET uses the environment of the eye as a natural petri dish. The cells are in their normal environment on the cornea and everything they need – serum, tears, oxygen – is present at physiological concentrations. Dr Nidhi Gupta from Shroff's Charitable Eye Hospital, Delhi says "SLET is like a natural pregnancy and CLET is like IVF" – it's an interesting analogy. The setup brings various benefits; it is an easier procedure than CLET, it is less costly as there is no need for a laboratory, there is no risk of contamination, and only one patient visit is required compared with the two needed for CLET (Table 1).

In my experience, SLET delivers excellent outcomes (Figure 1). When you observe patients over a period of time, you can see that the cornea clears – indicating modulation of corneal scarring – and that vision improves. Independent investigators have reported good outcomes with the procedure (6), and a multi-center trial across eight sites in India (Visakhapatnam, Delhi [SCEH and AIIMS], Ambala, and Kolkata), Mexico (Mexico City) and the USA (Boston and Miami) has shown good long-term outcomes with SLET (7). Furthermore, in a case series of 125 patients, we have shown that SLET was effective for long-lasting corneal

At a Glance

- *CLET is an effective procedure for LCSD in adults, but it has several drawbacks.*
- *CLET is expensive, it isn't easily replicable, and it has shown limited effectiveness in children.*
- *SLET offers a lower cost and simpler alternative; it uses the eye's environment as a natural 'petri dish' for limbal cell transplants.*
- *I overview the benefits of SLET versus CLET, and describe how to perform the surgery.*

"I implore people to be open and improve SLET – and to share their results with the community."

regeneration, as well as being equally effective in both adults and children (8).

Replicating success

One of the key benefits of SLET is that it is easily replicable. Even if I taught surgeons the CLET technique, there are many who wouldn't be able to replicate it because they'd need investment from a hospital or a big organization, as well as regulatory approvals and funding for maintenance costs. CLET has EMA approval, but it costs over €50,000 to grow the cells for one patient – there aren't many who can afford this type of treatment. It is because of this cost that I believe CLET cannot be a commercial success, although it is an academic and biological success. On the other hand, SLET is a commercial success model because minimal training is required – teaching is the only rate-limiting step. Training programs and videos are shared freely with no limitation, and there is no IP – it is an open platform technology. Rather than being possessive and attached to what I have developed, I implore people to be open and improve it – and to share their results with the community. And this has been happening – several surgeons have reported on modified SLET techniques such as Hernández-Bogantes et al. (9) on the 'mini SLET' procedure and Amescua et al. (10) on the

CLET	*SLET*
Two-step long procedure	One-step quick procedure
Difficult and needs laboratory resources	Can be taught and replicated easily
Expensive	Less expensive
Needs human/animal blood products and fibrin	No blood products but requires fibrin glue
Risk of contamination	No risk of contamination
Culture-related risks, issues with transport and failure of growth	No culture-related risk
Primary biopsy can be stored for repeat surgery	Secondary biopsy required for repeat surgery
Poor outcomes in children (<40 percent success rate) (4)	Better outcomes in children (71 percent) (8)
Modifications not tried	Multiple modifications tried
Pterygium surgery not tried	Used for pterygium surgery
No role in reducing stromal scar	Role in reducing stromal scar (8)

Table 1. Comparison of CLET and SLET

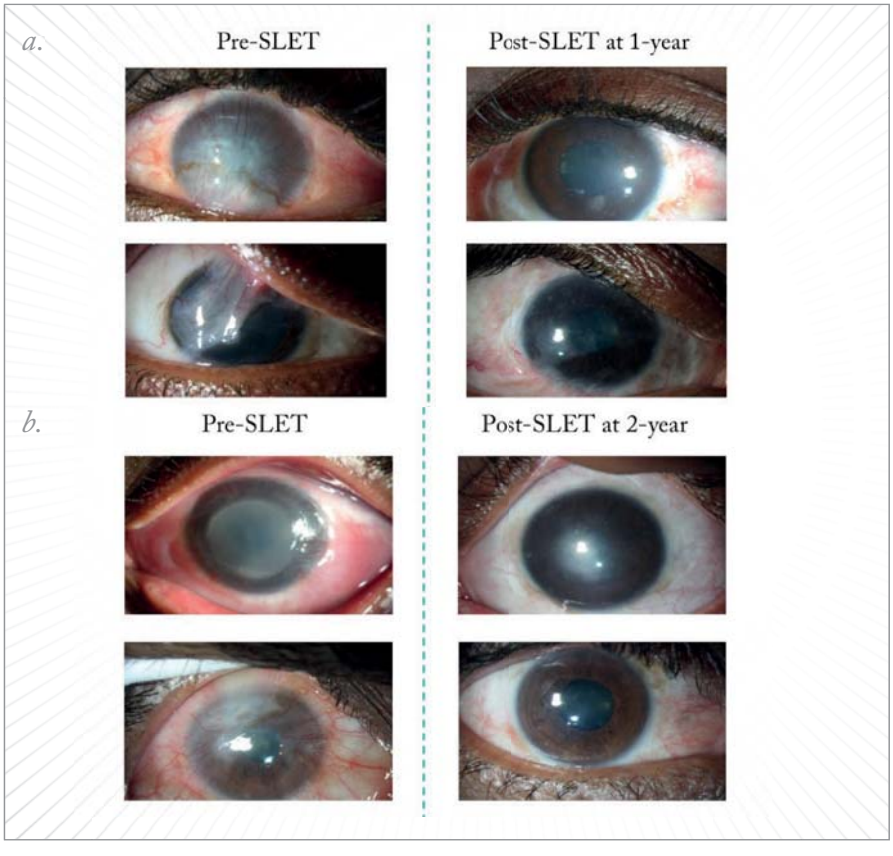
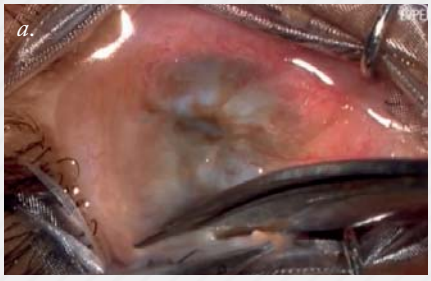
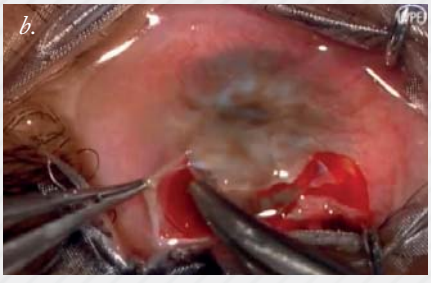


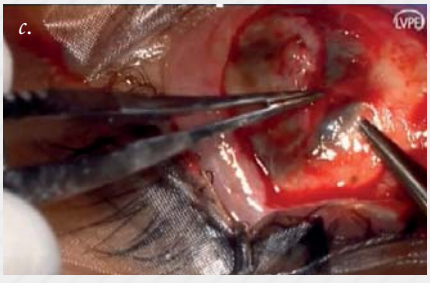
Figure 1. Examples of pre-SLET and post-SLET outcomes at 1 year (a) and 2 years (b).

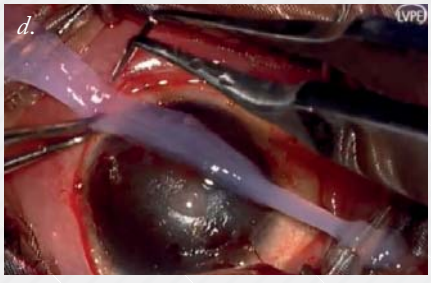
Step-by-Step SLET (5)

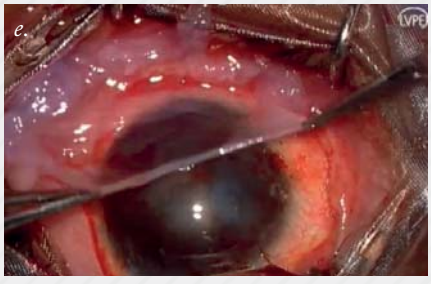
- *Harvesting the limbal biopsy.* Biopsies can be taken from the healthy eye in cases of unilateral disease, or even from a healthy area in the same eye. If disease is bilateral and extensive, lab-related or cadaveric biopsies can be obtained.
- *Preparing the corneal surface for surgery.* A peritomy is performed and the vascular pannus covering the cornea is excised (a–c).
- An amniotic membrane graft is placed on the ocular surface and secured in place with fibrin glue (d–f). Peripherally the amniotic membrane is tucked under the free margin of the conjunctiva (g), and the excess amniotic membrane is trimmed using Vannas scissors.
- *Implanting donor tissue.* The donor limbal tissue is held gently and sectioned into 8–10 small pieces with Vannas scissors, before being positioned in a circular fashion around the corneal center (h-i). The transplants are fixed in place with fibrin glue, and a soft bandage contact lens is placed on the eye at the end of the procedure (j).

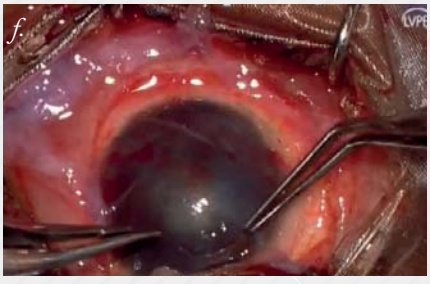


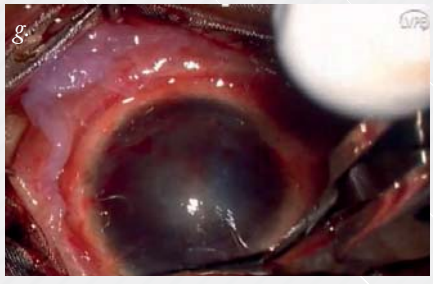


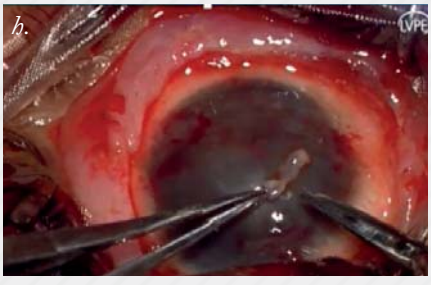


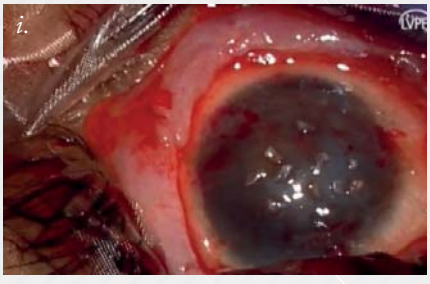


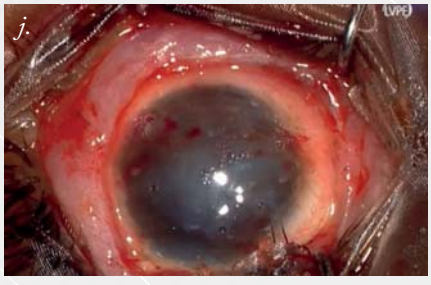












'double sandwich' technique. There have also been reports of using the surgery for other unique (and sometime surprising) indications, including the treatment of ocular surface squamous neoplasia (11) and pterygium (9). It is a list that just keeps growing! We have started using mesenchymal stem cells (MSCs) extensively for ocular surface disorders (12), and in the future, we are planning to investigate how we can combine SLET with MSCs to accelerate healing and expand its potential applications. For now, I feel very happy that this technique is effective, and that other surgeons are adopting it. I hope more continue to adopt this simple, yet effective, procedure.

Virender Sangwan is Director of the Center for Ocular Regeneration (CORE) and Dr. Paul Dubord Chair in Cornea at the LV PRASAD EYE INSTITUTE, Hyderabad, India.

The evolution of SLET

The story of SLET began when Sheila MacNeil – a professor of tissue engineering at Sheffield University, UK – contacted me via email with an interest in researching limbal stem cells. In a conversation over video messaging, she had an interesting proposition: "You know Dr. Sangwan, we should have a teabag approach to the stem cell transplant," she said. Frankly, I was unable to make the connection and told her so. But then she explained: "Right now you are growing cells in the laboratory, then transplanting them – it's complicated. But why not approach it like tea, where people have the different components, such as milk or sugar, ready to prepare it. We can make a biosynthetic membrane with micropockets, take an explant biopsy and grow the cells on the surface of the eye." A lightbulb went off, and that was the moment I always attribute to the genesis of SLET.

Sheila said we'd need to perform some research and apply for a grant, but I didn't want to wait. Within a week I was performing the surgery, and by the time we presented our idea to the Wellcome Trust in London, UK, I had completed five cases showing proof of the concept. Now, around five years later, the human trial of the synthetic membrane is underway, but to me, the much bigger idea is SLET.

When entering that first surgery, I was a bit anxious to the extent of whether it would work or not. More than anything I felt stupid. I have probably performed the largest number of CLET procedures in the world and I couldn't believe I hadn't thought of this idea. But this is what comes from the collaborations you build outside of your field, and what can result from the conversations you have with others. It is so important.

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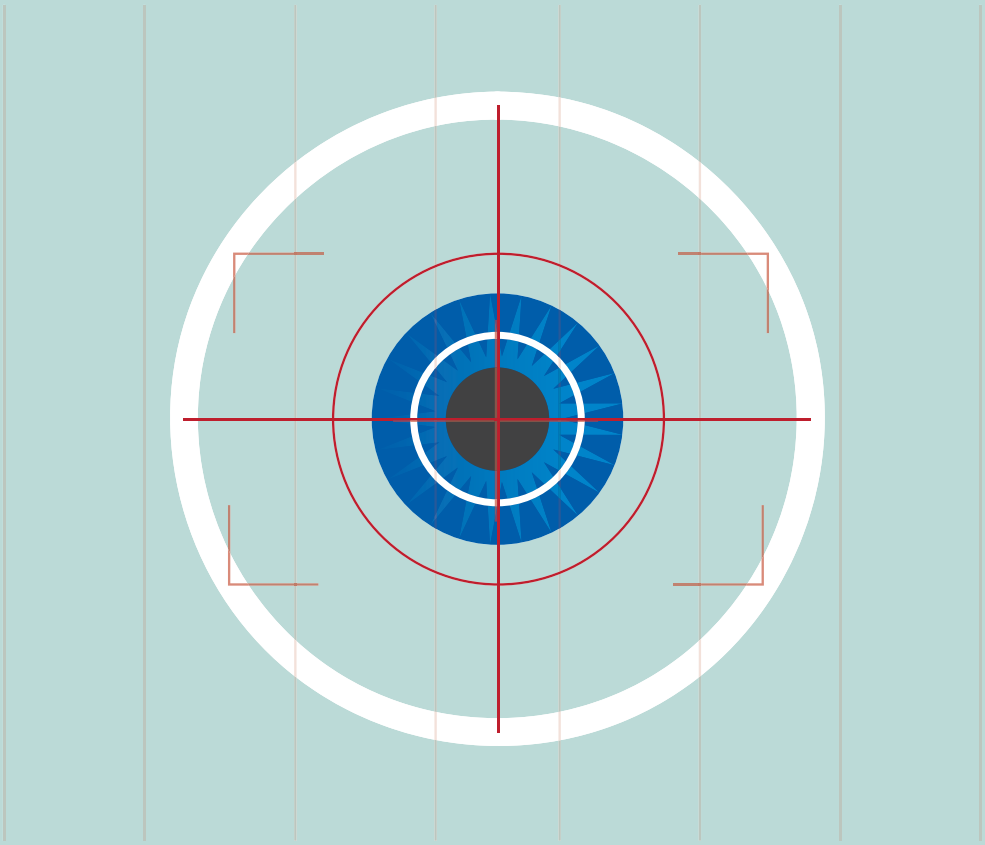

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CATS Cuts Errors

How using mathematical modeling to account for corneal variability can make applanation tonometry more accurate

By Sean McCafferty

The critical task of measuring IOP lies with a 60-year-old method so error-prone that relying on its readings may be sight-threatening for many patients. How did we come to rely so heavily on Goldmann applanation tonometry (GAT)?

Fundamentally, GAT's problem stems from its assumption that the cornea is an infinitely thin membrane requiring no force to applanate – other than that produced by the IOP, which is simply not true. In fact, biomechanical variations in the cornea modulate the applanation forces acting on the tonometer prism, and these force variations are then incorrectly interpreted by GAT as IOP variations. In fact, fully 50 percent of patients deviate from 'nominal' cornea sufficiently to induce clinically significant inaccuracies in GAT IOP readings. So although GAT may provide accurate measurements for patients with 'nominal' corneas, many others are failed by the technique.

Corneas may diverge from the 'nominal' in four main aspects: thickness, rigidity, curvature and tear film. In particular, IOPs are often over-estimated in eyes with thick corneas and under-estimated in eyes with thin corneas (1); this in itself can result in glaucoma misdiagnosis. Measurement errors can also occur with steeply curved corneas; these will be significantly over-estimated during GAT. Similarly, flat corneas (commonly found after LASIK surgery) are associated with IOP under-estimations. Even the tear film can have an effect – inter-patient variations in the adhesion forces associated with tear film surface tension will confound true IOP measurement.

These issues have been recognized for many years. Proposed remedies have included measuring and correcting for central corneal thickness (CCT); however, this – albeit the current standard of practice – addresses only one of several error sources, and therefore is at best an incomplete correction. Conversely, multiparameter algorithms, intended to correct the effects of multiple error sources, have proved too cumbersome for clinical use. In summary, the situation is highly unsatisfactory – but how can it be addressed?

Model answers

Our solution was to develop CATS – a tonometer prism that automatically corrects for the major sources of corneal variation. In brief, development required i) detailed mathematical modeling to predict the optimal topology for the prism

At a Glance

- *Goldmann applanation tonometry (GAT) is known to return clinically significant IOP reading errors in about half of patients, resulting in suboptimal clinical decisions – and even glaucoma misdiagnosis*
- *Accurate GAT tonometry requires that IOP readings are corrected to allow for corneal biomechanical variations associated with measurement error, but to date this has been impractical with the exception of incomplete CCT correction*
- *We used advanced mathematical modeling to design an optimized correcting applanation tonometry surface (CATS) for the existing Goldmann tonometer interface to minimize IOP errors*
- *Clinical studies have demonstrated that the CATS prism reduces IOP measurement errors to below ± 2 mmHg in 98 percent of patients, compared to only 50 percent with the existing GAT.*

surface; ii) construction and validation of prism prototypes; and iii) testing CATS in clinical studies.

The first step was to develop a mathematical model of the cornea. Non-linear, hyperelastic finite element modeling (FEM) simulations allowed us to analyze effects of corneal properties on IOP measurement, which in turn made it possible to design a prism surface that would – in theory – improve measurement accuracy (2). We used our model to flatten the (simulated) IOP isobaric curves with respect to error-generating corneal parameters and thereby derive an optimized topology for the prism surface (Figure 1).

According to our model, the optimal prism surface should not be flat (as in GAT) but should be comprised of a polynomial-approximated central concavity surrounded by a convex annular rim. Such topology was predicted to allow the prism to minimize the intra-corneal stress as well as tear-film adhesion, and thereby reduce each measurement error by ~50 percent.

"CATS is associated with ~50 percent reductions in errors related to central corneal thickness, corneal rigidity and curvature variations."

The next step was to manufacture and validate prototypes of the optimized prism. Accordingly, CATS prototypes were inserted into standard Goldmann tonometer armatures and used to measure IOP in cadaver eyes (2). The method, in brief, used a specially designed chamber (Figure 2) to stabilize enucleated globes while IOP measurements were taken by GAT, CATS and manometry. The object was to achieve a prism design that gives the same pressure reading in a 'nominal' cornea as GAT. This bench testing period was also intended to demonstrate accuracy and repeatability of IOP measurements: specifically, to test IOP measurement bias and variability by comparing CATS and GAT prism measurements relative to true IOP values as given by manometric pressure transducers. We were delighted to find that, as predicted by our model, the optimized CATS prism was substantially equivalent to GAT in eyes with nominal corneal parameters (2).

The final step was to investigate CATS performance in patients with varying corneal parameters. Initial clinical studies aimed to identify any biases. Each time we found a bias, we optimized the prism design and went back to patients with the new models; we went through three such iterations. Next, we assessed the ability of the optimized CATS system to correct for identified sources of IOP measurement error. Comparing tonometer-measured IOPs with readings from intracameral transducers is difficult in patients, so for our first study (3), we opted to compare GAT and CATS readings, and to correlate corneal variability with any differences identified in the GAT versus CATS comparison. Specifically, we looked at the following corneal parameters: CCT, corneal resistance factor measured by the ocular response analyzer, and corneal curvature. (We did not assess corneal tear film, as this parameter is better suited to measurement under the static conditions of cadaver eyes). After analyzing data from 109 eyes, the findings were clear (3): IOP measurement differences between CATS and GAT were evident, and correlated with known error parameters (corneal thickness, stiffness and curvature). The effect was very obvious: for CCT, for example, whereas IOP measurement inaccuracies of >±2 mmHg were found in 46 percent of all patients when using GAT, IOP measurement errors of >±2 mmHg were found in only 3 percent of patients when using the CATS prism (3). Overall, as predicted by our model, CATS is associated with ~50 percent reductions in errors related to CCT, corneal rigidity and curvature variations.

One limitation of the study outlined above was its lack of a comparison between tonometric IOP readings and true intracameral pressure readings. We have now remedied this with a follow-up study (4) that shows similar findings to the initial study: in short, we assessed the correlation between GAT errors and corneal variations in cataract surgery patients, and performed additional cadaver eye studies. Prior to surgery, we measured CCT and CRF with an ocular response analyzer. During surgery, we modulated the pressure on the inside of the eyes sequentially to 10, 20 and 40 mmHg, using a bottle height-modulated intracameral transducer, and simultaneously measured the IOP from outside to assess the accuracy of the tonometers. Finally, we corroborated our findings in 21 fresh cadaver eyes, with IOPs modulated between 5 and 60 mmHg, again comparing tonometer-measured pressures with those reported by an intracameral pressure transducer inside the eye. Encouragingly, we found that CATS gave very repeatable measurements, both within and between practitioners. We also found that GAT significantly underestimated IOP (by 5.2±1.6 mmHg – Figure 3), and that this underestimation was greater

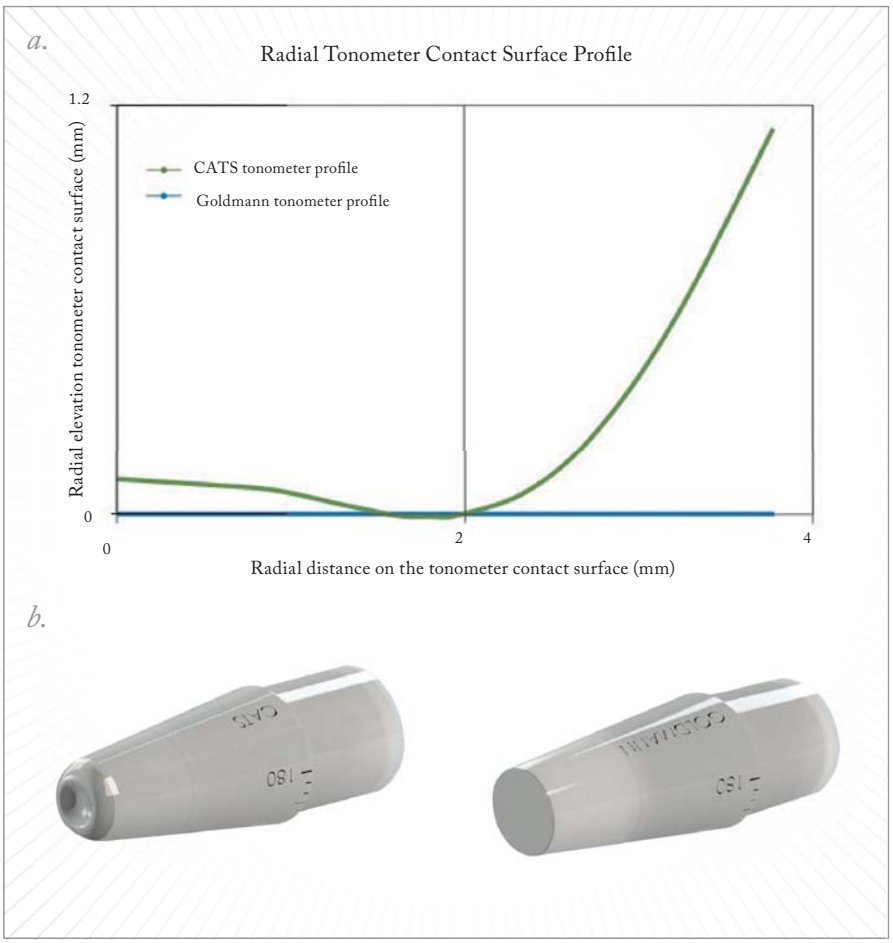

Figure 1. (a) Optimized radial profile of the CATS tonometer prism surface designed to minimize the corneal mechanical and tear film hydrostatic contributions to measured IOP in applanation tonometry; (b) Different tip morphologies of CATS and Goldmann applanating tonometers: note the central concavity and annular convex rim in the CATS device.

for patients in the supine position (7.9±2.3 mmHg). These errors were highly correlated with patient CCT. Thus, the results from patients both corroborated in vitro data and validated our mathematical modeling.

CATS out of the bag

It is now clear that a CATS prism permits more accurate IOP measurement – and it does so without requiring any changes to the standard GAT technique. All practitioners to date have easily accommodated to the CATS prism: it really is just a case of taking the GAT prism off and putting the CATS prism on, and needs no additional examination time or specialized data interpretation.

Another significant user benefit of CATS relates to centration. GAT will measure applanated mires at any point on the flat prism surface – but precise IOP measurement requires the cornea to be accurately centered on the prism face, which is subjective and so constitutes another source of error. CATS is an autocentrating system; the mires line up

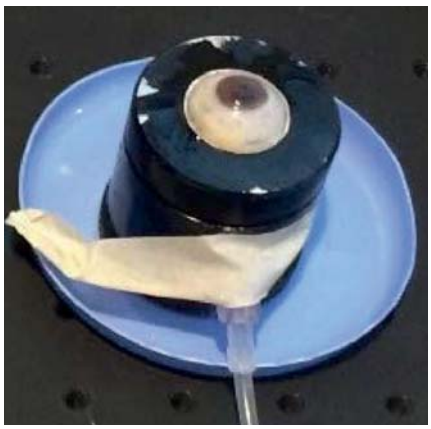

Figure 2. Cadaveric eye experiments. Apparatus for stabilizing the ocular globe while exposing the cornea for measuring IOP (2).

exactly only when the cornea is centered on the applanation surface. Hence, it is more difficult to take a inaccurate CATS measurement!

What will these advantages mean once CATS is approved and released on to the market? We will soon find out – we have completed our clinical trial for FDA clearance, and hope to reach the market in early 2018. When we do, there will be real benefits for patients. For example, I recently tested a glaucoma suspect with an increased cup-to-disc ratio and a CCT of 490 microns; the IOP as measured by GAT was only 16, but with CATS the pressure reading was 22.

Detecting such significant IOP elevations will have profound implications for many patients. Groups that may particularly benefit include those with low pressures, say around 10 mmHg, after stent or trabeculectomy surgery – such low pressures are often read incorrectly. In fact, at 5 mmHg, the GAT system may give you a zero reading! But CATS can still measure pressure accurately at that level, perhaps because the cornea is not buckling, as it does with GAT, but is conforming to the prism surface. So the greater accuracy of CATS will change clinical decisions for the better – the IOP measurement is 'real', and requires neither interpretation nor correction.

"With CATS, the IOP measurement is 'real', and requires neither interpretation nor correction."

CATS eyes up the future

In the immediate future, CATS will be easily and broadly adopted: it is compatible with the in-office GAT systems used by virtually all ophthalmologists, and its operation is identical to the GAT device. Also, there are no hidden expenses or inconveniences associated with CATS: it doesn't disrupt patient flow, and doesn't need maintenance or user training. Indeed, CATS could be cost-saving in that it will eliminate the need to purchase, maintain and use expensive pachymeters (as it already corrects for CCT). In the longer term, we expect the device to help in the assessment of: i) patients on eye drops who perhaps should not be on drops; ii) patients with progressive visual loss; and iii) specific populations including keratoconus patients, pediatric populations, post-LASIK patients and even veterinary indications. First versions of the device will likely be reusable units; later iterations will most likely have the added convenience of being disposable.

In summary, compared with GAT our CATS prism detects higher IOPs in eyes with thin corneas, and lower IOPs in eyes with thick corneas; higher IOPs in less rigid corneas, and lower IOPs in more rigid corneas; higher IOPs in flatter corneas, and lower IOPs in steeper corneas. It does this with high repeatability and without detectable bias, and should result in better clinical decisions for many patients. Clinical data (3) validate our mathematical modeling approach (2).

Finally, CATS couldn't be simpler or easier to implement – yet its impact will be dramatic; it will allow accurate measurements of IOP in the 50 percent of the population who do not have a 'nominal' cornea and are, therefore, not adequately served by GAT. And that's a lot of people!

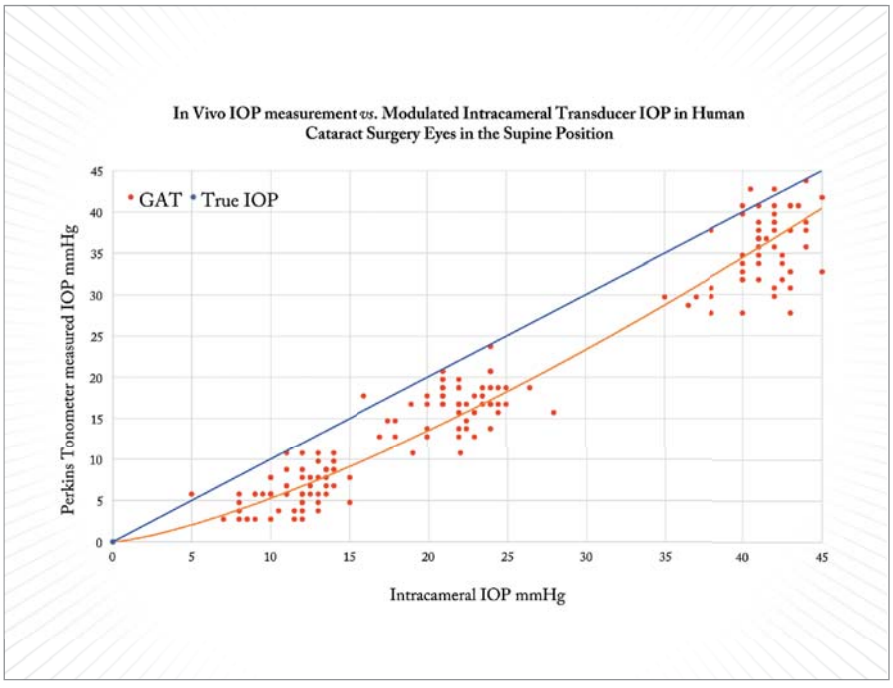

Figure 3. IOP measurement versus modulated intracameral transducer IOP in human cataract surgery eyes in the supine position. The observed differences are highly correlated with CCT.

Sean McCafferty is Founder, President and CEO of Intuor Technologies, LLC. After an undergraduate degree in mechanical engineering, he worked as a product development engineer before attending Ohio State University's Medical School and completing a residency in ophthalmology at the University of Arizona. Subsequently, he completed an MSc in optical engineering expressly to allow his ideas to become reality in terms of products for the ophthalmic industry.

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HUMANITY IN SCIENCE AWARD

the Analytical Scientist

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Richard Jähnke

Meet the Winner

Richard Jähnke

Richard Jähnke from the Global Pharma Health Fund (GPHF) has received the 2017 Humanity in Science Award for "development and continuous improvement of GPHF Minilab™ (www.gphf.org), which represents a breakthrough for the rapid and inexpensive identification of substandard and falsified medicines in low- and middle income countries in Africa, Asia and Latin America".

Richard received his award at a special jubilee reception in Berlin, Germany on October 2, 2017 hosted by KNAUER to celebrate the company's 55th birthday this year. Richard's work will feature in an upcoming issue of The Analytical Scientist.

Could it be you in 2018?

Analytical science has been at the heart of many scientific breakthroughs that have helped to improve people's lives worldwide. And yet analytical scientists rarely receive fanfare for their humble but life-changing work. The Humanity in Science Award was launched to recognize and reward analytical scientists who are changing lives for the better.

Has your own work had a positive impact on people's health and wellbeing? Details of the 2018 Humanity in Science Award will be announced soon.

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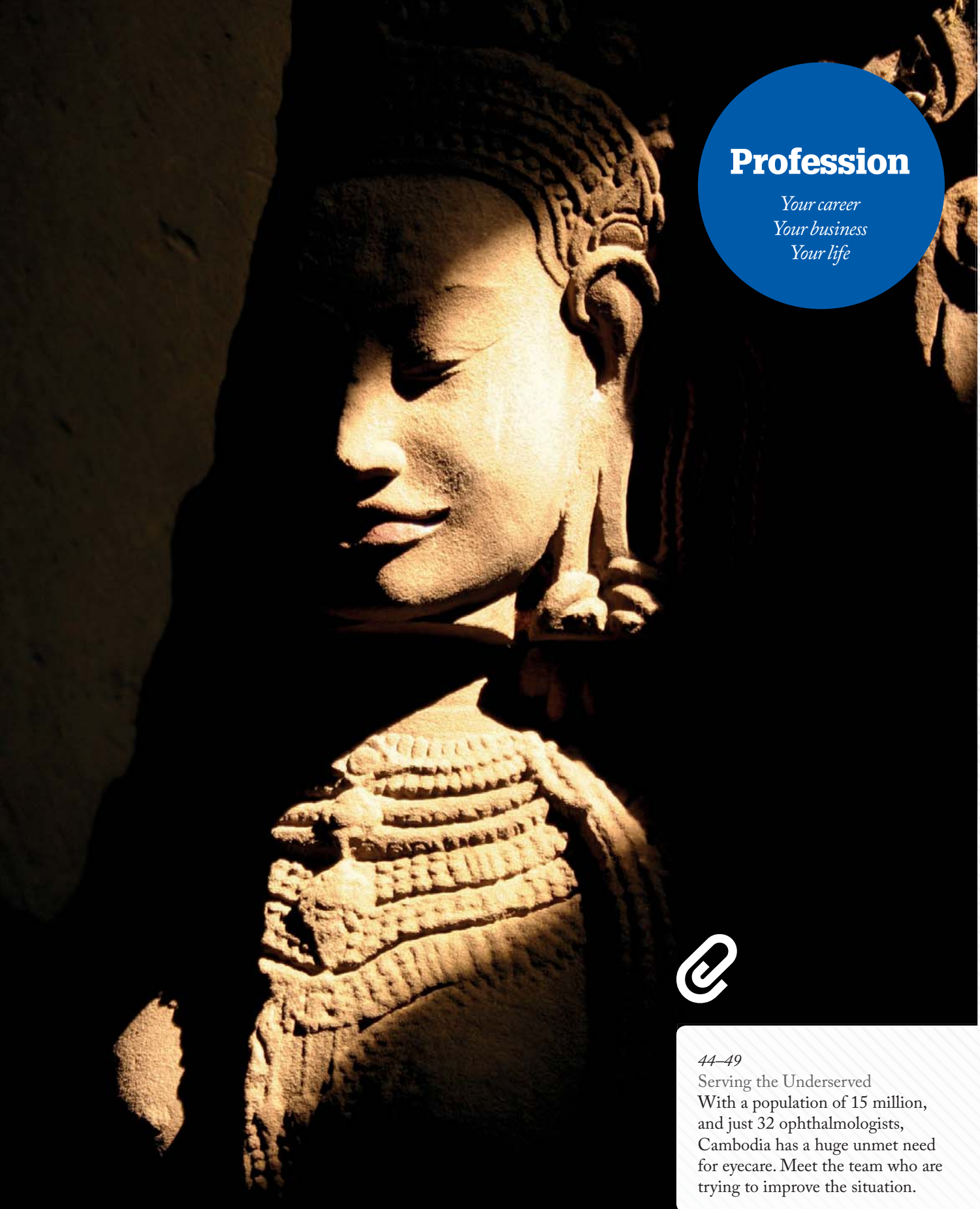

Profession

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Serving the Underserved

The Khmer Sight Foundation: helping to deliver and develop eyecare programs to a country in serious need

By Priyanka Mandal, Swetha Rambhatla and Sunil Shah

Cambodia is a country of 15 million people with a pre-history dating back to 6000 BC. In the 12th century, Cambodia had the largest empire in Southeast Asia, with its seat at the world-famous city of Angkor. However, it faced tragedy in recent times; from 1975 until 1979, mass genocide by the Khmer Rouge regime resulted in the death of around a quarter of the population. The government arrested, tortured and executed supposed enemies of the regime, specifically professionals and intellectuals. In practice, this included anyone with an education, foreign language skills and even people who required glasses – the regime inferred that these people spent too much time reading.

Despite the Khmer Rouge's official dissolution in the 1990s, the lasting impact is evident throughout the country. There are only 32 ophthalmologists – 23 with surgical training – to serve the whole population, making it one of the most underserved countries in the world. As a result, there are 180,000 completely blind Cambodians, a figure that rises by 10,000 each year despite 90 percent of cases being either treatable or preventable. Cataract – a highly treatable condition in the West – is the single leading cause of blindness, with a current backlog of approximately 300,000 Cambodians who require cataract operations. Other leading causes of blindness include pterygium, corneal scarring and glaucoma.

The Khmer Sight Foundation (KSF) is a not-for-profit organization that was set-up in 2015 by the late Kim Frumar, an Australian ophthalmologist, and Sean Ngu, the Secretary of State for Cambodia. The intention? To provide and develop sustainable eyecare services for the people of Cambodia. KSF has a two-pronged approach to tackling this issue. First, it runs weeklong missions at a central facility in Phnom Penh, performing free cataract and pterygium operations. Second, it trains local Cambodian ophthalmologists through theater sessions, labs and lectures. For the next year, KSF has a specific agenda

At a Glance

- *Cambodia has a small population of 15 million, but there are only 32 ophthalmologists – and only 23 who are surgically trained*
- *The incidence of blindness is high and on the increase, despite 90 percent of all cases being preventable*
- *The Khmer Sight Foundation (KSF) was initiated to bring eyecare to Cambodians who need it most*
- *Here, we share the story of the first mission, and look to the future of KSF – and preserving the sight of the Cambodian population.*

– to undertake 18 weeks of charitable ophthalmic missions with the help of 120 internationally recruited surgeons from the UK, Germany, Italy, Austria, Singapore and India. The first mission ran for seven days in April 2017. Here, we share the story…

Mission logistics

The first mission was delivered at the Preah Ang Duong hospital in Phnom Penh, and involved a team of 11 healthcare professionals from the UK (consultants, fellows, senior ophthalmology trainees, an anesthetist, a senior optometrist and junior doctors). The first day was spent setting up the facility with the required equipment; through generous donations from a number of ophthalmic companies, four phacoemulsification machines, 2,500 IOLs, 500 viscoelastics, medications and a whole host of other equipment were flown to Phnom Penh.

"There is a current backlog of approximately 300,000 Cambodians who require cataract operations."

As 85 percent of the Cambodian population lives in rural provinces, KSF arranged a pre-mission screening program, which saw local medical student volunteers traveling to different provinces to identify patients with eye disease. The medical student volunteers spoke fluent Khmer and English and were vital to the successful running of the mission. Each day of the mission, these patients were collected from their rural province by coach (a different province each day) and brought to the Preah Ang Duong hospital; the journeys were often long and patients had often set out far in advance before reaching the community bus stop. On arrival at the hospital, information on medical history and visual acuity measurements were collected before the patients were assessed clinically through slit lamp examination. If indicated, the patient was offered same day surgery – a big decision to make in the space of minutes. If patients had a condition that the team did not have the facility to treat, they were either told to return to a certain mission where the team would consist of that specialty or referred to local specialist services. Once the patients from the provinces had been assessed, the clinic opened up to the local citizens of Phnom Penh. Patients who earned less than $100 USD per month were entitled to free treatment.

Those patients identified for theater were consented, and biometry and/or further imaging was obtained, if

required. In the theater, scrub nurses from the hospital and further volunteers assisted, while local Cambodian ophthalmology trainees observed. As many patients presented with mature cataracts, senior surgeons performed the majority of operations. Surgeons had access to a full range of foldable, PMMA and anterior chamber lenses, as well as iris hooks, tension rings and vision blue. Small incision cataract surgery (SICS) – a small-incision form of extracapsular cataract extraction – was employed for certain patients. The procedure is particularly useful in resource-poor settings because it results in a self-sealing, sutureless wound. In pterygium procedures, autologous blood was employed as a sealant for the conjunctival autografts, which was again advantageous as sutures or fibrin sealants were not required. Postoperatively, the patients from the provinces slept in the hospital overnight before receiving a one-day postoperative check-in clinic. Patients were also followed up 4–6 weeks after surgery. Throughout the week, senior ophthalmology trainees delivered lectures and a dry lab, which was well received by Cambodian trainees.

In total, over 400 patients were seen in clinic and 200 patients received operations. The immense gratitude

"We also encountered several unusual – and unforgettable – cases during this mission."

from those seen both in the clinic and post-operatively was unforgettable; as the team left the hospital at the end of each day, the theater doors opened to a sea of smiling, eye-patched patients affectionately waving goodbye. In practice, the theater did not run at full capacity during this first mission – of six operating tables only four were used – but it is hoped that more surgeries could be performed in future missions.

Unforgettable clinical cases

As well as the unforgettable memories of gratitude, we also encountered several unusual – and unforgettable – cases during this mission. For example, a three-month-old baby was brought to the hospital with her mother, who was concerned because the child had not been opening their eyes. Unbeknownst to the mother, the child had been born with bilateral anophthalmia, so the team had to explain that the child would never see. Sadly, there have been cases of infanticide in Cambodia related to congenital defects, so arrangements were put in place for the police to visit the family on a regular basis to ensure the child's safety.

There were also a few cases where patients had severe pathology but could not be treated because management was outside the teams remit. One such case was a young woman who presented with bilateral cataracts, diastolic blood pressure of 150 mmHg and Cushingoid features (Figure 1). It was surmised that she might be suffering from congenital adrenal hyperplasia, and she was referred to local services. One gentleman presented with unilateral exophthalmos secondary to a brain tumor (Figure 2); presumably he was unable to afford treatment. Another gentleman was brought to the hospital with pathology highly suspicious of thyroid eye disease. KSF has managed to refer these patients to local services for treatment.

In some cases, the proposed outcome

Figure 1. Young woman with bilateral cataracts, Cushingoid features and diastolic blood pressure of 150 mmHg.

Figure 2. A gentleman with unilateral exophthalmos secondary to a brain tumor.

was unattainable; for example, an 11-year old girl was identified in the provinces with a unilateral cataract. During cataract extraction, a Toxocara scar and tractional retinal detachment were discovered (Figure 3). The team explained to the patient and her family that her sight would always remain poor despite intervention – they were extremely grateful to the team despite the bad news.

The future of Cambodian eyecare

The first mission was a success. But what does the future hold? The Cambodian government has recently increased the number of ophthalmology postgraduate training posts, and KSF, in conjunction with the government, is currently developing an ophthalmic 'super-center' in Phnom Penh. This complex, the first of its kind in Cambodia, will consist of a school of optometry and act as the center for postgraduate ophthalmology training, as well as the location of future KSF missions. KSF is also working to develop international fellowship opportunities for Cambodian ophthalmologists. One day, we hope that the country can become self-reliant in the provision of high quality, safe and effective eyecare.

Priyanka Mandal and Swetha Rambhatla are trainee ophthalmologists and KSF volunteers. Sunil Shah is a consultant ophthalmologist at the Birmingham and Midland Eye Centre, Birmingham, UK, and International Medical Chair of KSF.

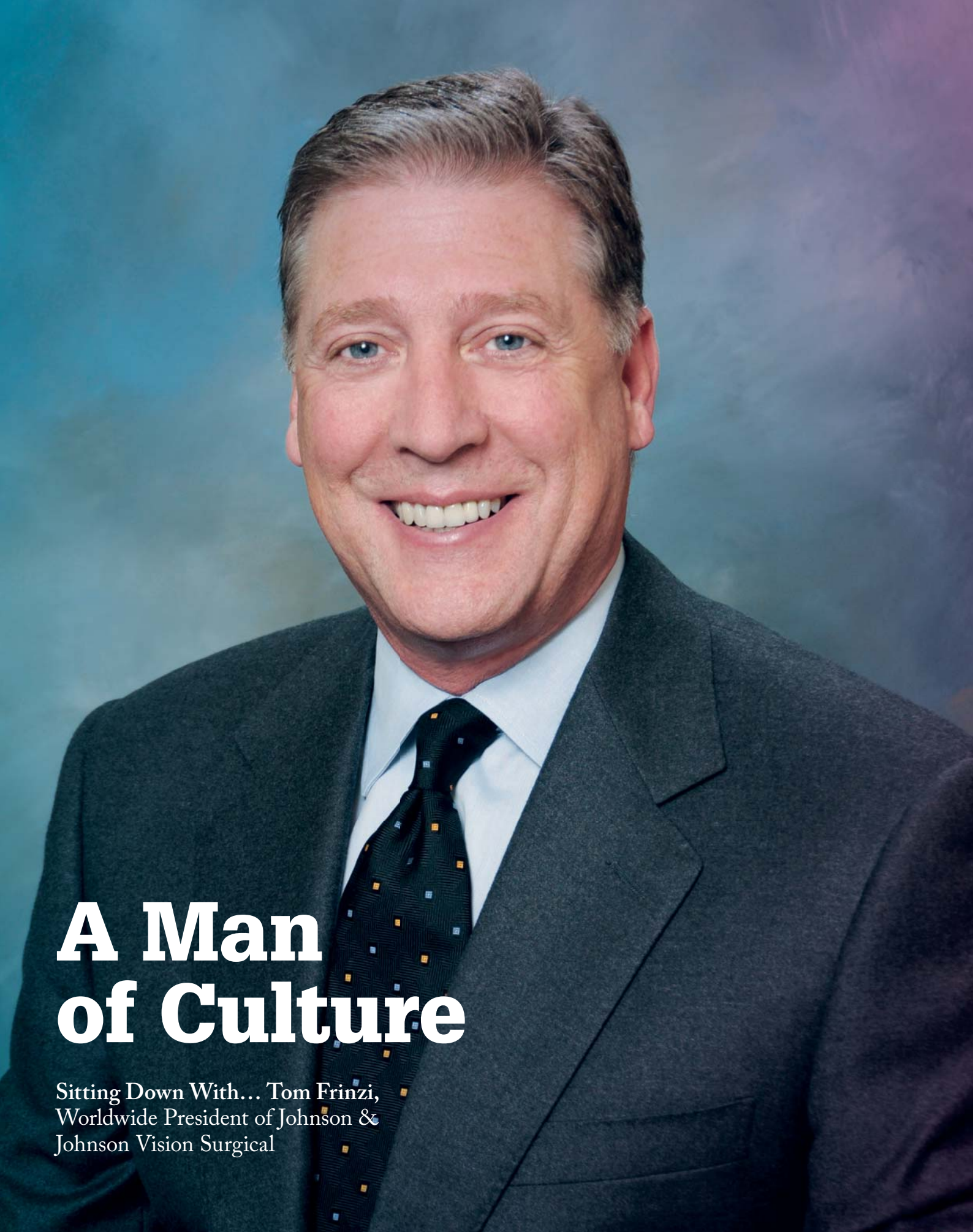
The authors would like to acknowledge and thank the following for their hard work and dedication in making this mission a success: Sean Ngu, Teresa De Leon, Sunil Shah, Leon Au, Rao Rambhatla, Dong Park, Siddharth Subramani, Shi Zhuan Tan, Kenneth Yau, Andrew Walkden, Patrick Gunn, Priyanka Mandal and Swetha Rambhatla.

Getting Involved

For more information about KSF please visit *www.khmersight.com*. KSF plans to continue running missions and relies on the help of volunteers. If you would like to volunteer please email *founder@khmersight.com*. For surgical volunteers, please email *sunil.shah@khmersight.com*.

Volunteering with KSF gives medical practitioners the opportunity to change the lives of those less fortunate. It enables volunteers to learn about a country and its culture from the inside, as well as to develop their team working skills. On a practical level, the missions run for only seven days each, so the program is an accessible way to volunteer.

Figure 3. Young girl with cataract, Toxocara scar and retinal detachment.



A Man of Culture

Sitting Down With… Tom Frinzi, Worldwide President of Johnson & Johnson Vision Surgical

What excites you about ophthalmology?

Sight is precious and people value it. Not too long ago, a study at Johns Hopkins validated that people considered vision loss as one of the worst health conditions that could befall them. Helping people see the world a little better or sharper makes it gratifying to go to work each day. I have been fortunate to be a part of that journey for over 30 years. And it has also been a lot of fun.

How else have you stayed motivated over those 30 years?

My journey with J&J began back in 1980; I moved into the field of ophthalmology in 1984 and that division was sold in 1995. Now, some 22 years later – having stayed in ophthalmology through that transitional period – I find myself in the fourth quarter of my career back with J&J. It's been an exciting journey for me, both personally and professionally, and what motivates me now is the opportunity to really build a leading eye health company. Innovation is alive and well in the field of eye health, and to be with a quality company like J&J is really exciting. We made a major acquisition in the form of the AMO business and then, within 6–7 months, we made another acquisition in the field of dry eye – both of which demonstrate J&J's commitment to eye care and prove that we're bringing innovation and technology on a broad scale.

Eye health is probably one of the biggest segments in all healthcare and it grows at about 5–6 percent annually. But even though those demographics are exciting, it's relatively underserved: about 50 percent of the world's population could benefit from some form of vision correction yet only 10 percent are being treated. What a wonderful opportunity we have to narrow that down for patients, not only through technology but through truly partnering with ophthalmologists and optometrists around the world. Improving education through training and bringing value to practices with an overall focus on improving patient experience. They're the kind of things that motivate me – it is a great time in our field.

"I admire people who aren't afraid of taking risks, who think boldly and creatively about opportunities and who aren't afraid to stretch themselves."

Who has been your inspiration?

I think that everybody should have access to good mentors throughout life. I have been very fortunate; my father and brother have been my lifelong mentors. Professionally, two particular individuals in ophthalmology – John Gilbert, a retired executive from J&J, and Bill Link, who I met when I joined Chiron Vision – have taught me a great deal throughout my career and helped me grow and develop into who I am today. Bill and I have had a wonderful relationship, which has moved from him being my boss and then my mentor, to then being a colleague and a friend. Outside of ophthalmology, I admire people who aren't afraid of taking risks, who think boldly and creatively about opportunities and who aren't afraid to stretch themselves.

What important lessons have you learned from your competitors?

I think ophthalmology is blessed to have really good competitors – competition makes us all better. Alcon has been a formidable competitor and well-respected. Its marketing and commercial execution, as well as its focus and consistency through the years is certainly something to be admired.

Any advice for executives making their way up the ladder?

For me, it has always been about doing the best job you can in the role you currently have. Try not to be so obsessed with the next move or the move after that. Be less political and more focused on your performance and acting with integrity. J&J is a values-based company, where what you deliver and how you do it are equally weighted, which creates a culture that is certainly positive, and I do believe that culture trumps everything in a company.

What makes a good president and CEO?

Having a good team around you, and having the right culture. If you can develop the right culture in an organization, amazing things are possible. But it's also important to recognize the value and importance of the team around you; your job as a leader is to remove impediments and allow people to be the best they can be.

Getting the whole organization – from the receptionist up to the CEOs office – rallied around a few vital objectives and breakthrough opportunities is really going to make a difference in the business. If you have that kind of focus and that kind of alignment from a culture that rewards productivity, has a strong sense of values and cherishes the individual, you're likely to be successful.

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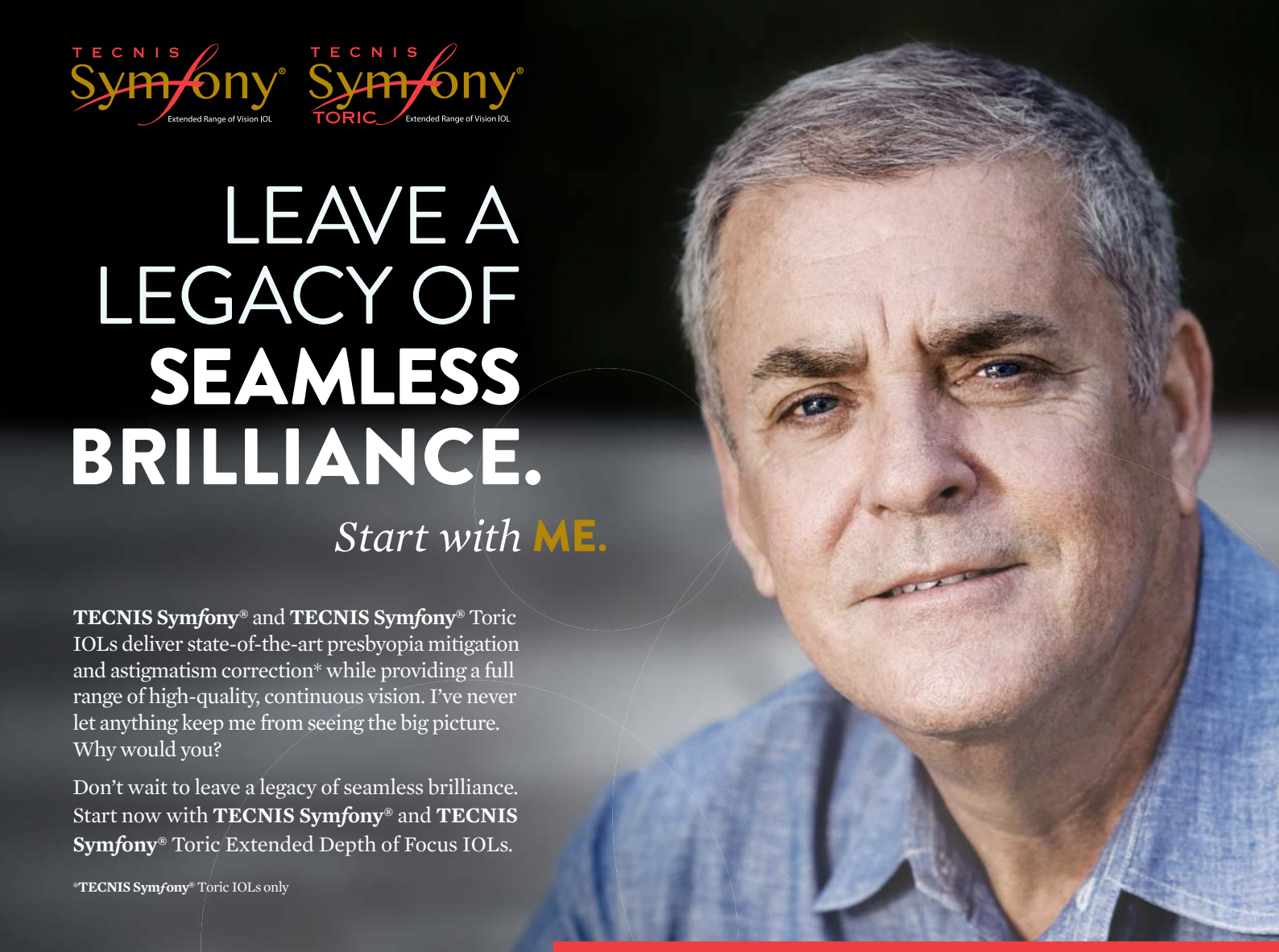

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