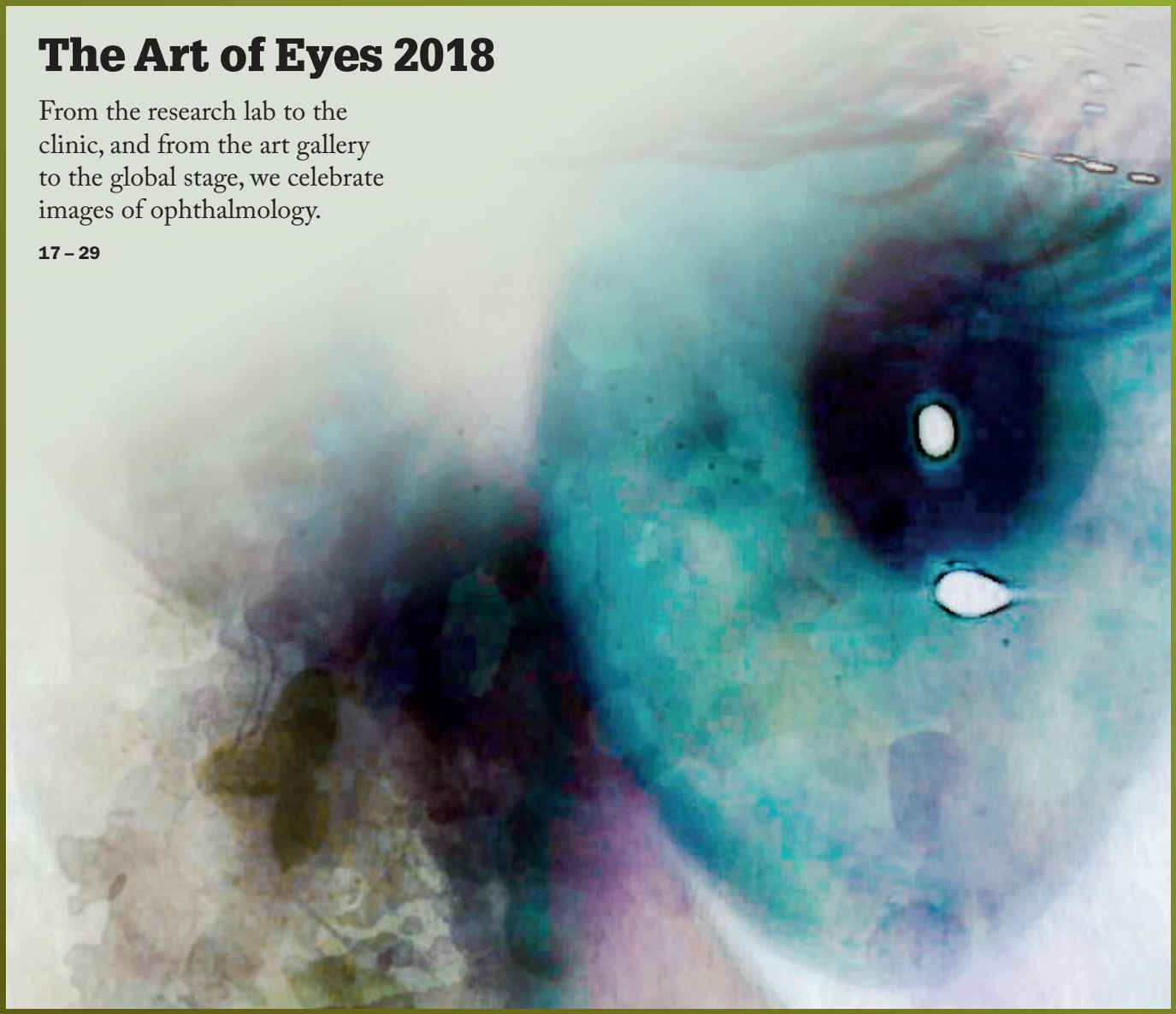
JULY 2018 # 23

the Ophthalmologist™

The Art of Eyes 2018

From the research lab to the clinic, and from the art gallery to the global stage, we celebrate images of ophthalmology.



POWER TO PREVAIL

As demonstrated in phase 3 clinical trials evaluating BCVA,* as measured by ETDRS letters, in patients with Wet AMD, Macular Edema following RVO, DME, and by ETDRS-DRSS† in DR in Patients with DME,[1] as well as your clinical experience

Start with EYLEA for proven efficacy outcomes[1]

AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema;
DR = Diabetic Retinopathy; RVO = Retinal Vein Occlusion.

Dosing driving efficacy outcomes across all indications.[1]
Learn more at EYLEA.us/dose

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

EYLEA® (aflibercept) Injection is indicated for the treatment of patients with

- Neovascular (Wet) Age-related Macular Degeneration (AMD): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months).
- Macular Edema following Retinal Vein Occlusion (RVO): The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly).
- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) in Patients with DME: The recommended dose is 2 mg administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 20 weeks (5 months).

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.

EYLEA® (aflibercept) Injection
For Intravitreal Injection

- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Please see adjacent Brief Summary.

*Best-corrected visual acuity.
†Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: an established grading scale for measuring the severity of DR.

Reference: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2017.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

10/2017
US-LEA-13945

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR) in Patients with DME

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.7) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

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

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1)*], treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: June 2017
Initial U.S. Approval: 2011

Based on the May 2017 EYLEA® (aflibercept) Injection full Prescribing Information.

REGENERON

Image of the Month

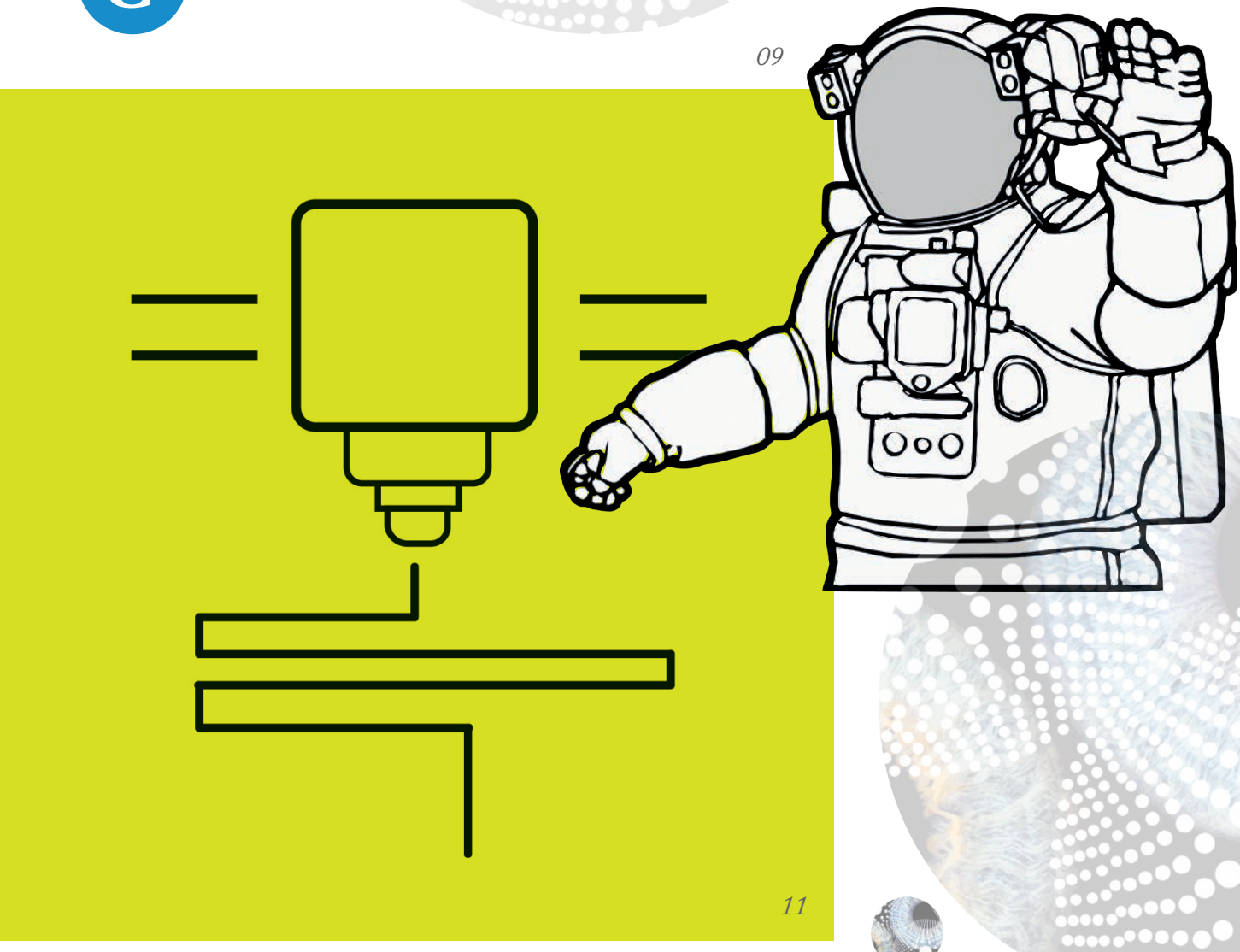
Post-peak Posterior Problems

This fundus image is from a 25 year-old female patient who presented with sudden vision loss after a hypertensive peak, and features a stage 4 papilledema, tremendous venous loop, vascular sheathing, neovascularization, ghost vessels, peri-papillary and peri-macular exudates, and intraretinal hemorrhages.

Credit: Imane Tarib, Military Hospital Mohammed V-Rabat, Morocco.

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

Contents

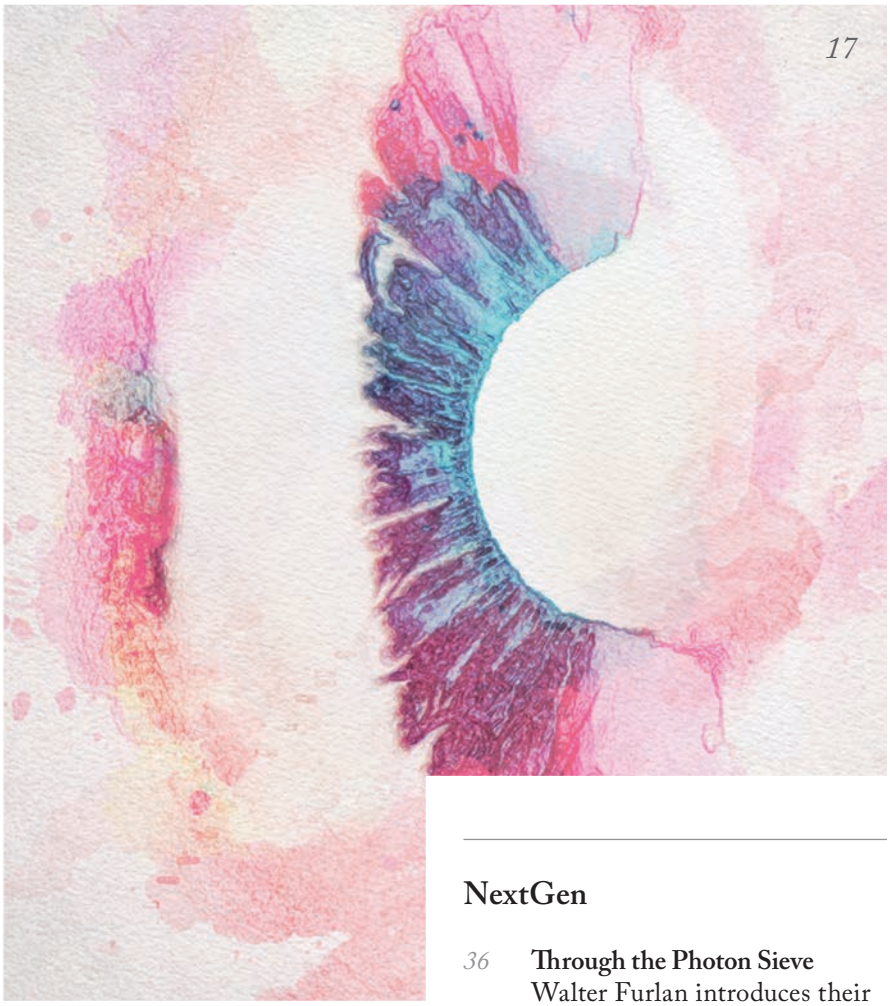


On The Cover

An artistic image captured using a cell phone. Find out more and celebrate the most beautiful images in ophthalmology, in The Art of Eyes 2018.

Upfront

In My View



Feature

In Practice

NextGen

Sitting Down With

Erratum
In our June article, "The Peer-to-Peer Network" by Jessica Griffith, a quote was attributed to Sunir Garg (Wills Eye Hospital, Philadelphia, PA, USA). In fact, this quote should have been attributed to Sumit Garg (Gavin Herbert Eye Institute, University of California, Irvine, CA, USA). The author apologizes for any inconvenience this might have caused.

the Ophthalmologist

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JULY 20, 2018

VANCOUVER, BC, CANADA

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An Eye on Our Planet's Future

Can ophthalmology be more sustainable?

Although I don't consider myself an 'earth mother', I do care – and worry – about the fate of our planet. My household recycles, I drive an economical car, and I am mindful of reducing waste overall. In my local town, I was pleased to see a collective ban on plastic drinking straws issued, and many bars and restaurants now offer cheerfully striped cardboard straws. Even McDonalds are "responding to customer feedback" by ditching the disposable plastic straw. Similarly, many groups are calling to end the use of plastic cutlery, cotton buds, and a whole array of disposable plastic items.

Why am I sharing stories of plastic drinking straws and cotton buds with an audience of ophthalmologists? Because I recognized that sustainability should extend to all practices – from the routine and mundane to the most specialized – including ophthalmology. In our June issue, we sat down with Alan Crandall, who made an interesting point about attitudes to waste and recycling when asked what we could learn from developing countries: "Over there, there's no such thing as a single-use instrument, but their complication rate is no higher than ours; do we really need to focus on disposables so much?"

Does ophthalmology focus too much on disposables? Certain instruments and equipment necessitate being disposable because of the nature of their use – and unsuitability for decontamination. But I am left wondering if more could be done to 'green up' ophthalmology – whilst still achieving favorable outcomes for patients, of course. Surely, there is more scope for reuse and recyclability of some instruments, as well as their packaging. A study of cataract surgery waste reported that three participating US medical centers generated 2.3–3.9 kg of waste per phacoemulsification case – 100 percent of which was either landfill or biohazardous material. Contrast that with the Aravind Eye Hospital in India, which generated 0.25 kg of waste per case on average – of which two-thirds was recycled (2).

It seems as though there could be more than a few ways to reduce ophthalmology's ecological footprint, and I'd be surprised if there weren't any environmentally-conscious institutes and clinics out there who are already making efforts to reduce waste. In this ever-changing world, where environmental issues are becoming increasingly important to many, it will be interesting to see how general attitudes might change – and how industry may follow suit.

Ruth Steer
Managing Editor

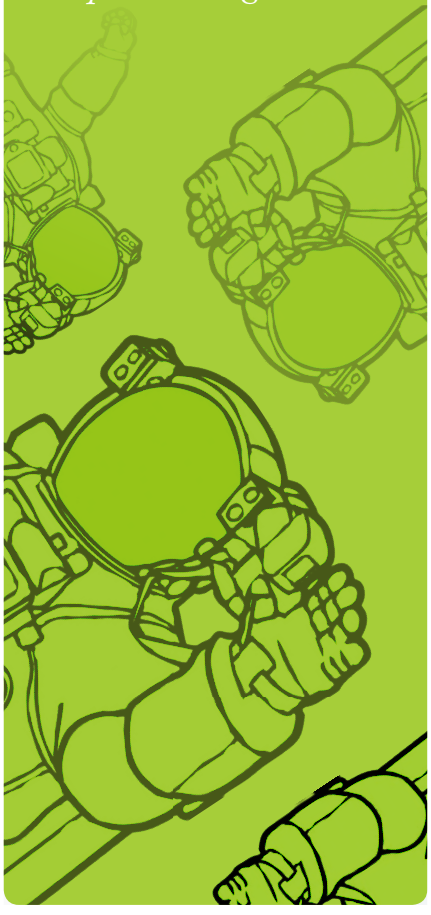
References

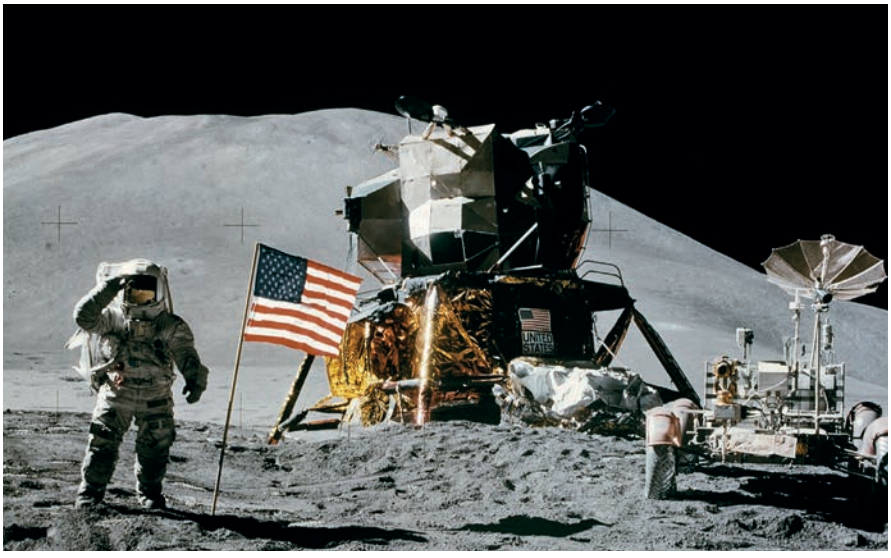
1. *Alan Crandall, "The Selfless Surgeon", The Ophthalmologist, 54, 50–51 (2017). Available at: http://bit.ly/alancrand.*
2. *Miriam Karmel. "Reducing waste in cataract surgery". Accessed June 21, 2018. Available at: http://bit.ly/catwaste.*

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





Battlestar Bulge

Heavier astronauts could experience more visual changes in microgravity

We've covered the ophthalmic issues caused by spaceflight before (1, 2) – but now, there's a new twist in this cosmic tale. It appears that changes in the eye observed in astronauts may be linked to their weight (3).

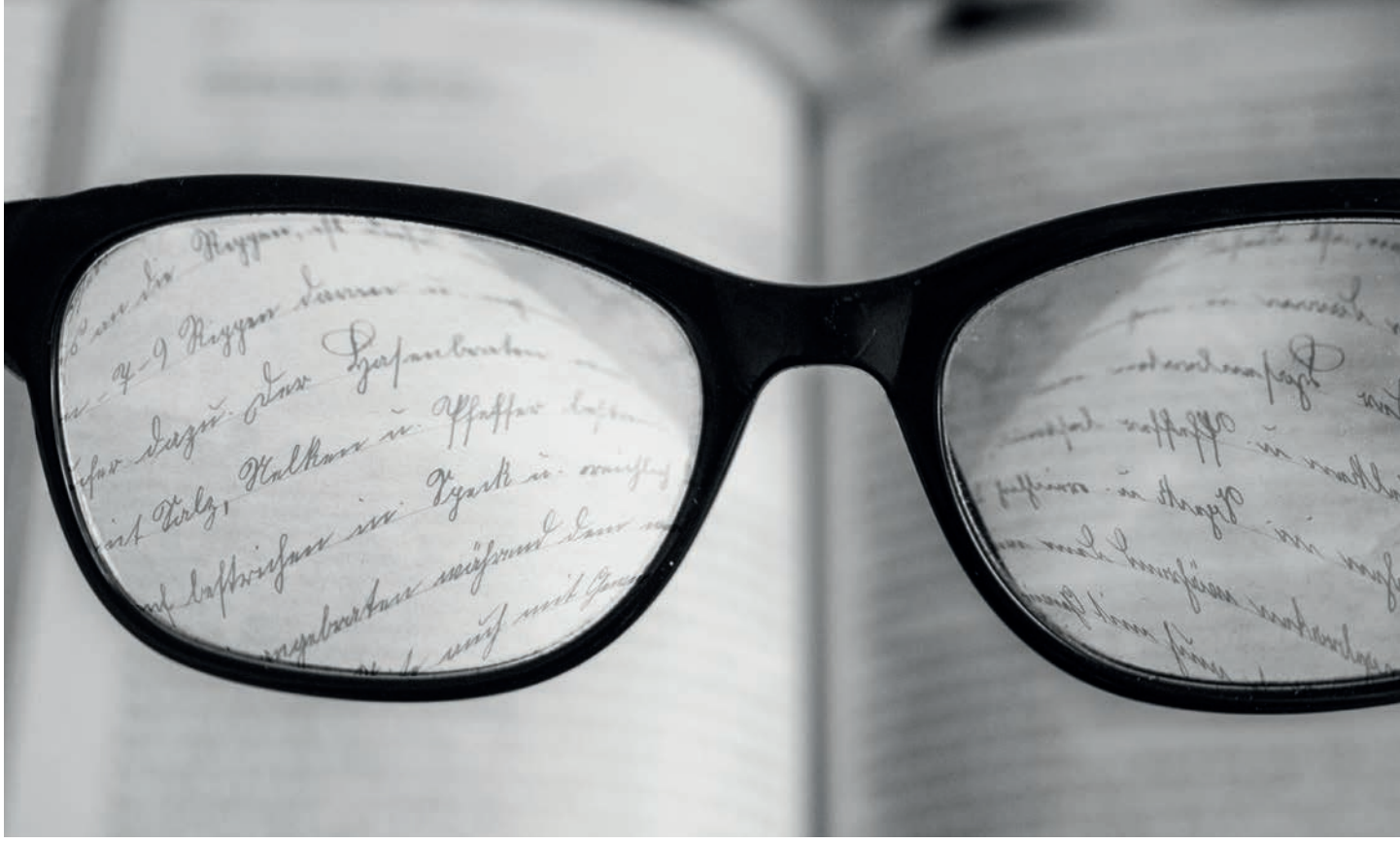
Jay Buckey, first author of the associated study, has a long-standing interest in the effects of microgravity on the human body – and has experienced them first hand, having flown in space as a specialist astronaut on several missions. "The more someone weighs the more likely they are to experience visual changes on long-duration spaceflights," he explains. "From our work using numerical modeling to understand the effect of weightlessness on the eye, and from our previous studies, we had a strong feeling that the loss of tissue weight was an important, and unique, change that occurs in microgravity."

But the work doesn't only have implications in space. "These findings are relevant to people with visual changes due to idiopathic intracranial hypertension, which is a condition also affected by body weight," Buckey says. Their model shows that the more someone weighs, the higher their intracranial pressure – something supported by clinical data; however, during microgravity exposure, the model suggests that heavier people will have a greater initial reduction in intracranial pressure compared with people who weigh less. What happens to these pressures when someone spends a relatively long time in space? Not currently known, says Buckey.

"This study provides another piece of the puzzle to help us understand why these visual changes occur," says Buckey – but many questions remain to be answered. In space, it's still ophthalmology – but not quite as we know it…

References

1. *R Steer, "Miami, we have a problem", The Ophthalmologist, 37, 10–11 (2017). Available at: bit.ly/miamiproblem.*
2. *M Schubert, "(Ophthalmic) space oddity", The Ophthalmologist, 27, 16–17 (2016). Available at: bit.ly/spaceodditeye.*
3. *JC Buckey et al., "Microgravity-induced ocular changes are related to body weight", Am J Physiol Regul Integr Comp Physiol, [Epub ahead of print] (2018). PMID: 29768035.*



Short-distance Learning

The link between myopia and academic achievement isn't news to ophthalmologists – but just how strong is the link, and what could be causing it?

A recent study has delved deeper into the association between book learning and short sight (1), led by Denize Atan, an academic ophthalmologist specializing in neuro-ophthalmology at Bristol Medical School and Bristol Eye Hospital, UK. Though Atan's clinical role centers on managing patients who have neurological conditions affecting vision, her research role centers on performing genetic epidemiology and genetic modeling to further understand the visual pathways in the central nervous system.

"Our first approach was to look for genetic correlations between measures of visual and cognitive function. For more than a century, observational studies have reported links between myopia and higher levels of educational attainment or intelligence, so this was one possible example of an association between visual and cognitive function that might have a common genetic basis," says Atan. "However, our analyses seemed to suggest that genetic correlations between intelligence and refractive error explained only a very small part of the story."

Causal relationships are traditionally investigated by randomized controlled clinical trials, but as a randomized clinical trial exposing children to different levels of education would be unethical, Atan and her colleagues took a different approach, using Mendelian randomization.

"The results of our study showed that exposure to more time in education contributes to the rising prevalence of myopia. We found that every additional year of education was associated with an increased myopic refractive error of −0.27 D/year," says Atan. By contrast, the study found little evidence that myopia led to a longer time in education – in other words, myopia does not appear to lead to better educational outcomes.

The study was not designed to assess how education increases myopia risk – but previous studies and experiments provide some clues, says Atan. "Very simply, those who spend more time in education may have less exposure to natural light. Large differences in ambient light exist between well-lit classrooms (500 lux) and bright sunlight (up to 120,000 lux), and randomized controlled trials have consistently shown that more time spent outdoors during childhood protects against the development of myopia."

Atan hopes the study will lead to further research and discussion with the aim of reducing the rising tide of myopia. "Given the benefits of time spent outdoors on mental health and the protection it provides against obesity and many chronic diseases, there may be several other reasons why our children ought to spend more time outside," she adds.

Reference

1. *E Mountjoy et al., "Education and myopia: assessing the direction of causality by mendelian randomisation," BMJ, 361, k2022 (2018). PMID: 29875094.*

Hot Off the Press

What if, instead of waiting for a donor cornea to become available, you could just print one?

Corneal transplants are among the most common solid tissue transplants – over 30,000 are performed each year in the US alone (1). But with around 10 million people in need of transplants globally, the number of donor corneas cannot meet cut demand.

Now, a team at Newcastle University in the UK has succeeded in 3D-printing a human cornea equivalent (2). The proof-of-concept study, led by Che Connon, Professor of Tissue Engineering, mixed stem cells from a healthy donor cornea with alginate and collagen to create a "bio-ink", which was 3D printed in concentric circles to form the shape of a cornea in less than 10 minutes. We spoke with Connon to find out more...

Why 3D print a cornea?

I've been working in corneal biology for over 20 years, and it has recently been observed that stromal cells can be influenced by the shape of the cornea – specifically, a curved surface creates alignment of these cells, and alignment is important for maintaining the transparency and function of the cornea. We believe that the shape of the cornea is not only important for refraction and so on, but also for the way the cells behave. So we needed to find a way to create a curved tissue to facilitate the right cell behavior as well as its refractive properties – and 3D printing has been gaining a lot of attention recently, so we decided to try it. One of the benefits of this approach is that you can have fine control over the final product you produce, and you can produce a tissue with multiple features. We have been looking at the mechanical properties of the limbus and the effect of stiffness on epithelial differentiation – and from our understanding, on a printed cornea we wanted to create a different degree of stiffness at the edge than in the center.

How did you create your "ink"?

This was probably our biggest challenge – we needed a "bio-ink" with which to print our 3D construct, and it needed to have specific properties. It needed to keep the stromal cells alive, and be extrudable, so that it could get through the printer needle. Finally, once printed it needed to retain its structure and remain stiff. We achieved this using a unique combination of collagen – which is, of course, the main structural component in the cornea – and alginate, which is a polysaccharide extracted from seaweed.

How do you envision the 3D-printable cornea being used?

We hope that eventually the corneas will be printed on demand, as 3D printing offers this flexibility, and the machines we've been working with are relatively cheap. We've been collaborating with the Newcastle University spin off company, Atelerix, which offers a hydrogel that keeps cells alive at room temperature for several weeks in a sealed storable tube. So thinking ahead, we could see our technology on the shelf in the doctor's surgery. One day, you could potentially have a printer in the corner of your surgery – simply plug in a tube of bio-ink containing the live cells, creating the tissue you need on the spot!

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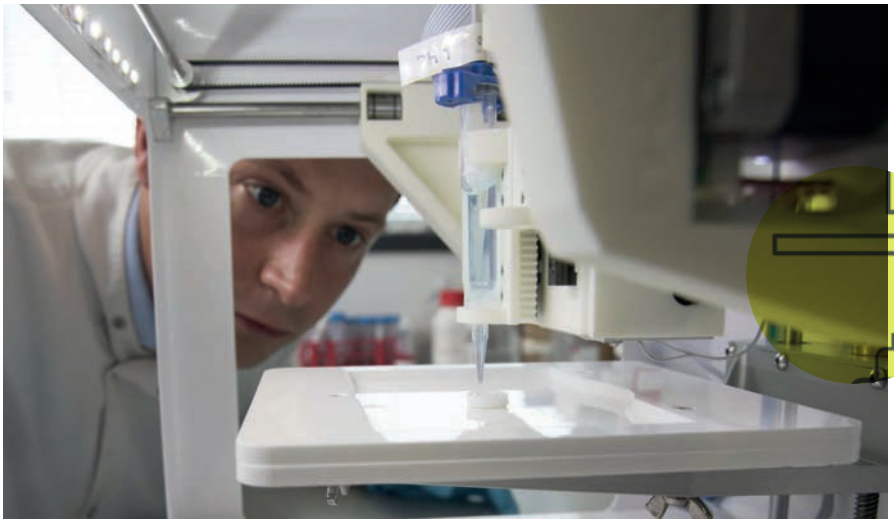
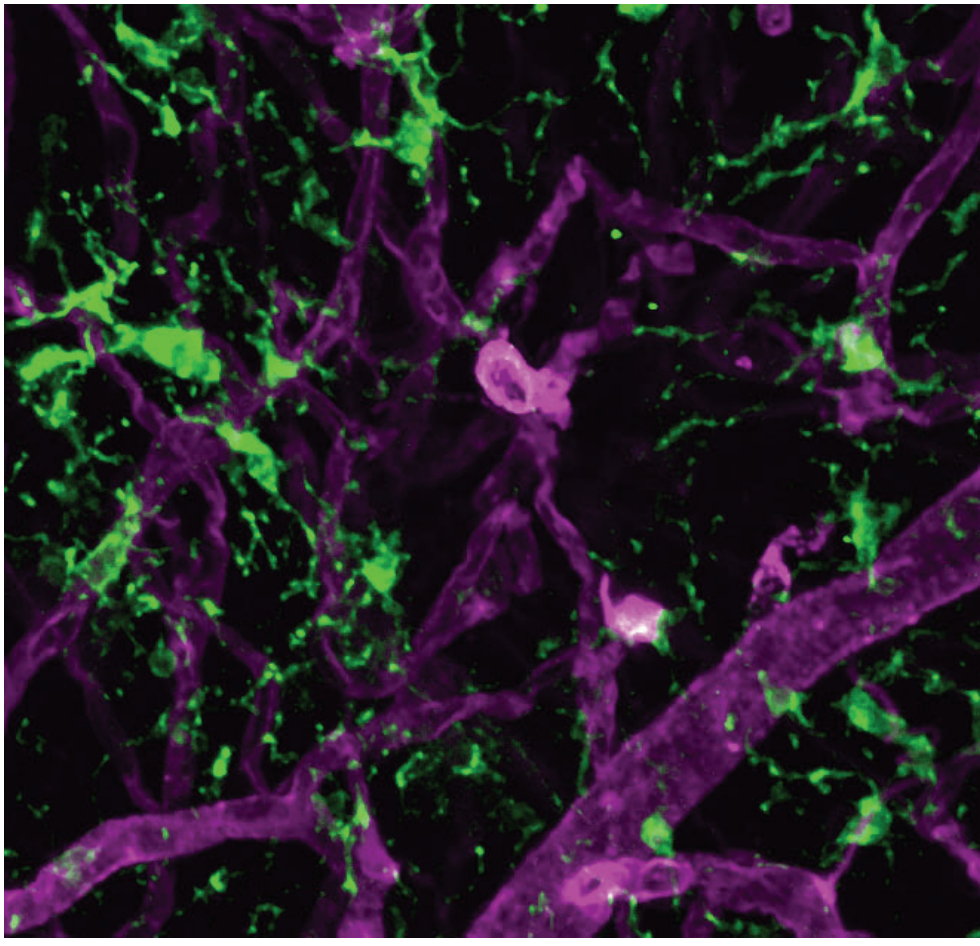
2. *A Isaacson et al., "3D bioprinting of a corneal stroma equivalent", Exp Eye Res, 173, 188–193 (2018). PMID: 29772228.*



3D printer used to print the corneas, with co-author Steve Swioklo. Credit: Newcastle University, UK.

The Magic of Microglia

Researchers discover the protective potential of microglial cells in retinal detachment



Retinal microglia (green) and the retinal vasculature (purple). *Credit: Dong-Ho Park, Connor Lab.*

It is fair to say microglia are misunderstood. Best known for being the resident immune cells of the retina, microglia have traditionally been overlooked in favor of other glial cells. But now, a team at Massachusetts Eye and Ear Infirmary, Boston, USA, has thrown microglia into the spotlight by discovering that they play a protective role in response to a common complication: retinal detachment (RD).

"Our results provide clear evidence that microglia protect photoreceptors from cell death in acute RD," says Kip Connor, senior author on the associated paper. After inducing acute RD in murine retinae, the team found that retinal microglia were rapidly activated in response, migrating to the injured area within 24 hours where they associated with infiltrating macrophages. When microglia were depleted, photoreceptor death increased. The team also discovered that activated microglia cells phagocytosed injured and dying photoreceptors.

"These findings provide the first insight into how microglia respond and function during RD, but our original hypothesis was the polar opposite of what we discovered," says Connor. "We thought that these cells would contribute to inflammation and cause harm. In actuality, these cells were aiding photoreceptor survival in acute retinal detachment."

Although the current standard of care for RD – surgical reattachment – is highly effective from a physical point of view, in some cases, patients experience permanent vision loss, accompanied by changes in color vision. The difference between a positive and negative outcome all comes down to timing. "Speed is critical," says Connor. "Studies in both human and animal models have shown that photoreceptor cell death is induced as early as 12 hours after RD, and increased severity and duration of detachment results in a significant decrease in overall visual regeneration." Early intervention could potentially preserve the photoreceptors, improving the visual acuity of patients that undergo both early and late stage reattachment procedures.

But do microglial cells present a potential solution? "Our findings begin to identify a new role of microglia, which appear to perform multiple functions in response to retinal injury," says Connor. "Our hope is that future studies will allow the development of specific therapeutics that enhance microglial function, resulting in greater visual outcomes and quality of life for patients suffering from sight-threatening diseases."

Reference

1. *Y Okunuki et al., "Microglia inhibit photoreceptor cell death and regulate immune cell infiltration in response to retinal detachment", Proc Natl Acad Sci U S A, [Epub ahead of print] (2018). PMID: 29915052.*

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 editor at edit@theophthalmologist.com

Presbyopia in the Farsighted Future

What will management of the disability look like in 10 years?

By Blake Williamson, cataract and refractive surgeon, Williamson Eye Center, Baton Rouge, LA, USA

I'll start with a bold claim: within 10 years, I believe the majority of ophthalmologists will not be treating presbyopia with spectacles but rather with either topical drops or refractive surgery. Perhaps a wild idea given that our current solutions have limitations – but when you consider the technology that will be available 10 years from now, it doesn't seem so far-fetched.

Presbyopia is a huge problem – there are 1.8 billion presbyopes worldwide, and the number increases each year. The inability to read at near has always been a disadvantage, but with Johannes Gutenberg's invention of the printing press in 1439 – which led to the rise of mass communication, global literacy and the transformation of society – the problem became magnified. Centuries later, with the advent of the in-home computer in 1984 and the iPhone in 2007, awareness and complaints about the disability have skyrocketed.

Today, reading glasses and bifocals are the most common treatment – a poor effort, when you think that reading glasses were invented by Italian clergy in the 13th century and bifocals have been around since Benjamin Franklin brought them to market in the 1770s. Innovation is sorely needed in the presbyopia space – and I think ophthalmologists and industry have finally started to answer that call. Five years ago in the US, there were essentially five commonly used surgical options: blended vision LASIK, monovision cataract surgery, multifocal IOLs (two choices), and accommodating IOLs. Just 10 years from now, we are likely to have some 31 different options including: laser vision correction (blended vision LASIK, multifocal LASIK); inlays (synthetic inlays, PEARL, allograft inlays/onlays); IOLs (monvision cataract surgery, multifocals, EDOF, small aperture, trifocals, accommodating); adjustable IOLs (light adjustable lens, refractive indexing IOL; and scleral approaches (scleral implants, lasers).

"Just 10 years from now, we are likely to have some 31 different options."

Several of these future solutions will move the needle for refractive surgery in the presbyopia space, but I believe the most disruptive surgical technologies will be Allotex's inlay/onlay, RXSight's Light Adjustable Lens (LAL), and refractive indexing with Perfect Lens. Why? Because several

other technologies have been available for years on the EU market (trifocals, EDOFs, and so on) – yet the penetrance of refractive surgery for presbyopia treatment remains low.

"Giving patients the ability to 'test drive' multifocality is an absolute game changer [...] I believe the era of adjustable IOLs will be as disruptive as the era of foldable IOLs."

The allograft from Allotex is an improvement on the original tissue addition techniques by José Barraquer. Synthetic inlays have remained a niche market because of concerns such as haze, but allografts offer a promising alternative; the pristine biocompatibility of human corneal tissue has been known for decades, and improvements in metrology, tissue banking and laser technologies will solve many of the problems that older tissue addition techniques had. The possibility of onlay procedures without the need for a femtosecond laser cutting a deep flap/pocket are particularly attractive, not to mention the procedure can be easily reversed through removal at the slit lamp.

The LAL will be disruptive because it will be the first lens giving surgeons the ability to adjust the IOL sphere and cylinder after surgery. I believe this will calm many surgeon's fears about missing their refractive target and not having direct, easy access to an excimer laser in their center. Further, as monovision with cataract surgery is by far the most frequent surgical treatment for presbyopia in the US, the LAL will create a "premium channel" for monovision – and surgeons will be even more confident of hitting their targets.

Lastly, the Perfect Lens will use principles of refractive indexing to give surgeons the opportunity to make monofocal lenses multifocal… And then convert back to monofocal, if the patient doesn't tolerate multifocality. As no special lens is needed, you can potentially have patients who chose a monofocal IOL years ago opt for retreatment of their lens to provide better near vision. Giving patients the ability to "test drive" multifocality in vivo is an absolute game changer. And, along with the LAL, I believe the era of adjustable IOLs will be as disruptive as the era of foldable IOLs.

Having said all that, refractive surgeons know that we now have excellent surgical treatments for presbyopia, but the market isn't approaching maturity. And this is where the "Topical Presby-lution" (as I like to call it) comes in. There are four eyedrops currently undergoing trials in the US aiming to be first to market: Novartis EVO6, Presbyopia Therapies PRX100, Orasis CSF1, and Allergan AGN-199201 and AGN-190584. Most of these enhance depth of field via a pinhole effect and EVO6 reduces lens stiffening; some of these medications can be synergistic with each other or combined with refractive surgery to enhance outcomes. In my view, eyedrops will have the biggest impact for plano presbyopes. The vast majority of the global presbyopia population are clustered between -0.50D and +0.50D, and understandably, most surgeons are hesitant to operate on the pristine cornea of a plano presbyope who has 20/20 distance vision. The ability to treat this population medically, and then later surgically with the option for adjustment to provide LASIK-like outcomes, could have a huge impact for this population as well as surgeon confidence.

"Ultimately, a change in mindset combined with the advanced technologies heading our way will allow us all to better serve our patients."

Lastly, the majority of refractive exams are performed by optometrists who have no surgical options to offer their patients. The financial upside for selling reading glasses in their clinics is less compared with participating in collaborative care with a surgeon to simultaneously improve their patient's lifestyle. Ultimately, a change in mindset combined with the advanced technologies heading our way will allow us all to better serve our patients. We are now living in the presbyopia revolution, and it's about time.

Hello Femto!

FLACS has not reached its 'peak' – here's why

By Mitch Jackson, cataract and refractive specialist, and founder and CEO of JacksonEye, Lake Villa, IL, USA

Back in the early days of phacoemulsification technology, there were people who didn't believe in it. Now, we have 'naysayers' who say femtosecond laser-assisted cataract surgery (FLACS) has reached its peak. But I believe FLACS is here to stay.

I am a 'femto guy' – I use it in over 80 percent of my cases. Why? Because it offers me better outcomes for my patients than conventional phaco surgery. In terms of safety, FLACS delivers less energy into the eye, and is associated with less endothelial cell loss, corneal edema and a 50 percent lower rate of vitreous loss (1–3). Most importantly, FLACS delivers significantly faster visual recoveries to patients; one day after surgery, FLACS patients who had dense cataracts removed can see three lines better than patients who received phaco surgery (4). FLACS also has superiority as a cataract refractive tool. As effective lens position is partially determined by where you place the capsulotomy – important for multifocal or EDOF lenses – an advantage of FLACS is that the capsulotomy can be centered more precisely on the optic axis. There's no way a manual capsulorhexis can be placed as perfectly! Also, astigmatism can be managed using femto through the placement of precise, customized arcuate incisions. Recently, LENSAR received approval to create anterior capsule 'nubs' to enhance accuracy of alignment when toric IOLs are used for astigmatism correction. Cyclorotation errors are minimized significantly with this new femto adjunct to my armamentarium.

So what are the naysayers saying about FLACS? Cost is admittedly the biggest disadvantage, but if you're a high volume cataract surgeon, this is not so much of an issue. Sure, if you're only performing one or two procedures a month, it doesn't make much financial sense to own a laser. But if you're not a high-volume surgeon, FLACS is not inaccessible; if you have a nearby center you can pay a 'per click' fee to use the technology. At my center, I'm happy to let anyone use the femto systems once they're certified.

Another commonly reported disadvantage of FLACS is time efficiency. In my practice, we went from 4.2 cases an hour to 3.8 cases when we converted to FLACS. But from that small amount of time efficiency lost, I've gained a lot by having better surgical outcomes and happier patients, which to me is a huge offset. There are also many ways to maximize efficiency of FLACS in your OR – I call mine the 'no motion efficiency system'. I have all equipment in one room, and as my system doesn't have a detachable bed, I sit in the same spot and the patient can be slid in head- or feet-first depending on which eye is being operated on; there is no movement of equipment between cases, which saves time.

It is true that lower cost technologies exist, such as Zepto (Mynosys), but you've got to remember that you're not gaining access to lens fragmentation or astigmatic treatment; you're just getting a capsulotomy. miLOOP (Iantech) offers lens fragmentation, reduces phaco time, and it is extremely useful for dense cataracts; but even so, miLOOP doesn't do all the things that femto can do – it's more of an adjunct. Both Zepto and miLOOP add a nominal cost to the procedure which, in the US, isn't billable to the patient unlike use of femto, which is billable to the patient as long as astigmatic correction is performed.

In short, I believe that FLACS is 'alive and kicking' and has multiple advantages for both surgeons and patients alike. I think that as long as the big companies keep supporting the technology and driving it forwards, FLACS is here to stay. I would like to see it continue to move forward as it has done a lot for my patients – I am a 'pro-femto' guy, after all, and I'm excited to see what else may be on the horizon.

Jackson reports that he is a consultant for Bausch & Lomb and LENSAR.

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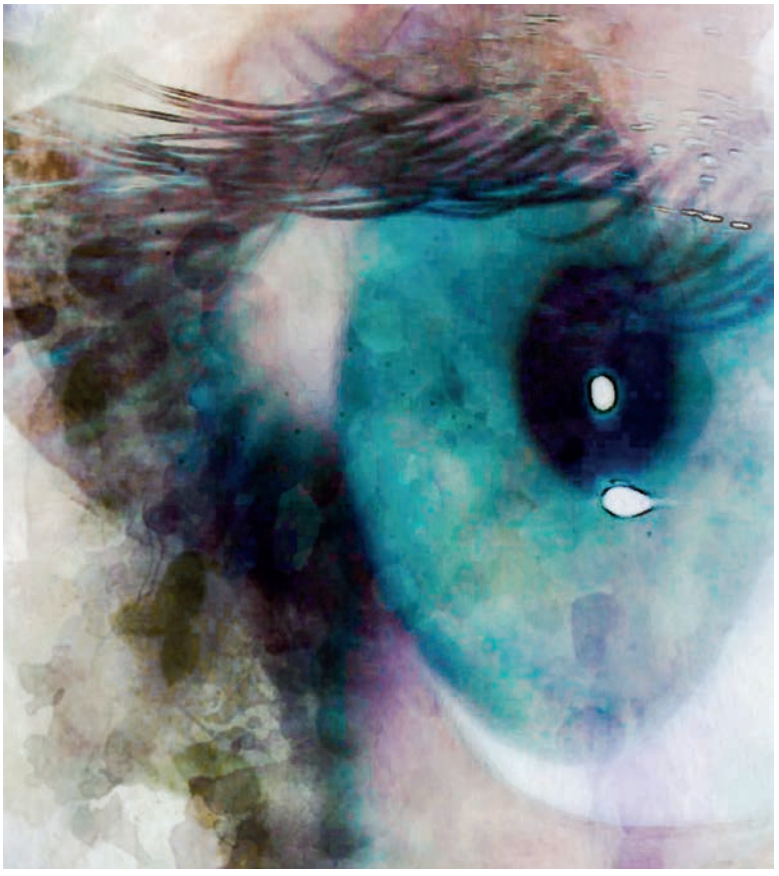
The ART of EYES 2018

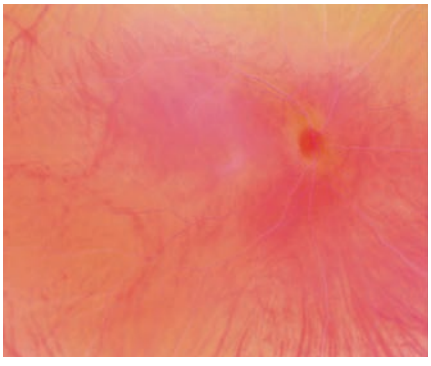
We present a collection of beautiful images across the whole spectrum of ophthalmology, from the research lab to the clinic to the art gallery. Welcome to The Art of Eyes 2018.

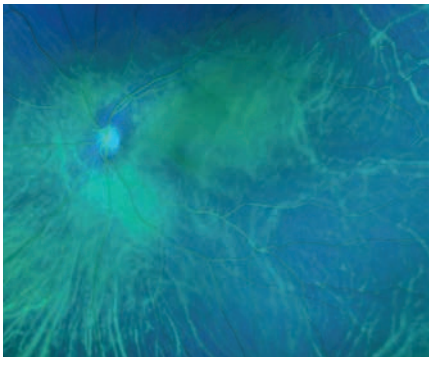
TEMWANI

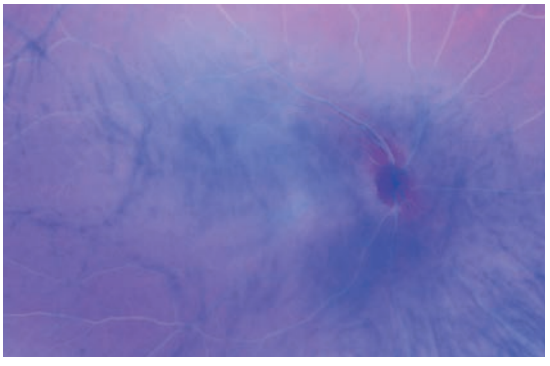
Temwani had a tumor over his left eye. It was successfully removed, and his vision has improved dramatically. He has been able to return to school. *From the Orbis Visions of Zambia project.*

ART OF OPHTHALMOLOGY









ATTACHMENT

"The best camera is the one you have with you." *Chase Jarvis*. Art is created in the mind and manifested through the mediums you have at your disposal. It is up to the artist to possess the desire and will to master the medium and produce art. This image was captured on a cell phone attached to a Haag-Streit slit lamp (top left image).

CELL PHONE EFFECT

During my time teaching I taught my students "you can't cheat in art, you can only use your resources wisely." Cell phone photography is not cheating, it is just another tool in our arsenal (top right image).

TRYPTIC

Post-production of a photograph can provide for unlimited possibilities. This is the same photograph of a single retina with various post-production techniques.

Kelly Aileen Oldstein, Certified Ophthalmic Photographer at Chester County Eye Care, and owner of Kelly Aileen Photography, Chester County, PA.

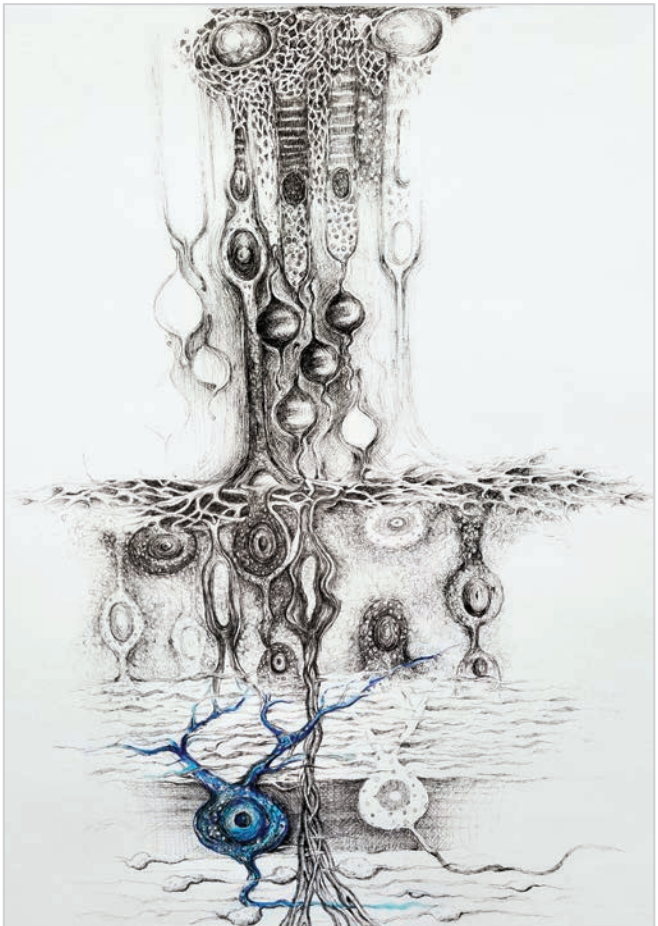
FROM MICROSCOPE TO WATERCOLOR

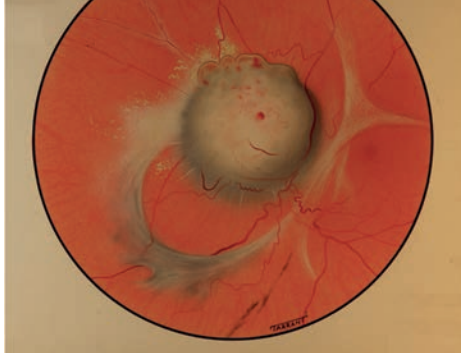
These images are from Project VISIONS, an initiative that aims to make science in vision accessible through art. The creators, Dorota Skowronska-Krawczyk, Assistant Professor at the UC San Diego Shiley Eye Institute, and Eva Henry, a Toronto-based artist, report that the project was born from a mutual belief that the beauty of science should be shared with those who do not have formal scientific training. More information on Project VISIONS and the full gallery can be viewed at www.the-visions.com

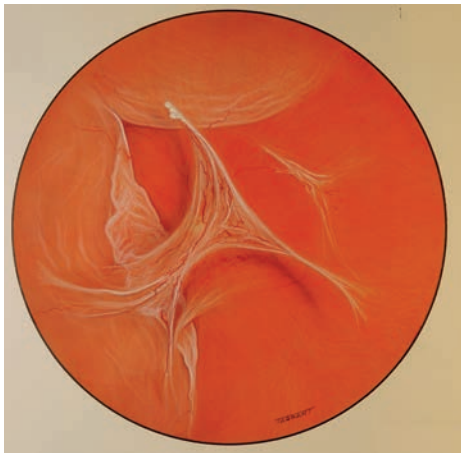
Project VISIONS: Dorota Skowronska-Krawczyk, Assistant Professor, Shiley Eye Institute, University California San Diego (UCSD), CA, USA (http://dsklab.ucsd.edu), and Eva Henry, Artist, Toronto, Canada (http://www.evahenryart.com).

RETINAL GANGLION CELLS ,WATERCOLOR (right).

RETINA CROSS-SECTION, INK AND WATERCOLOR (bottom left).



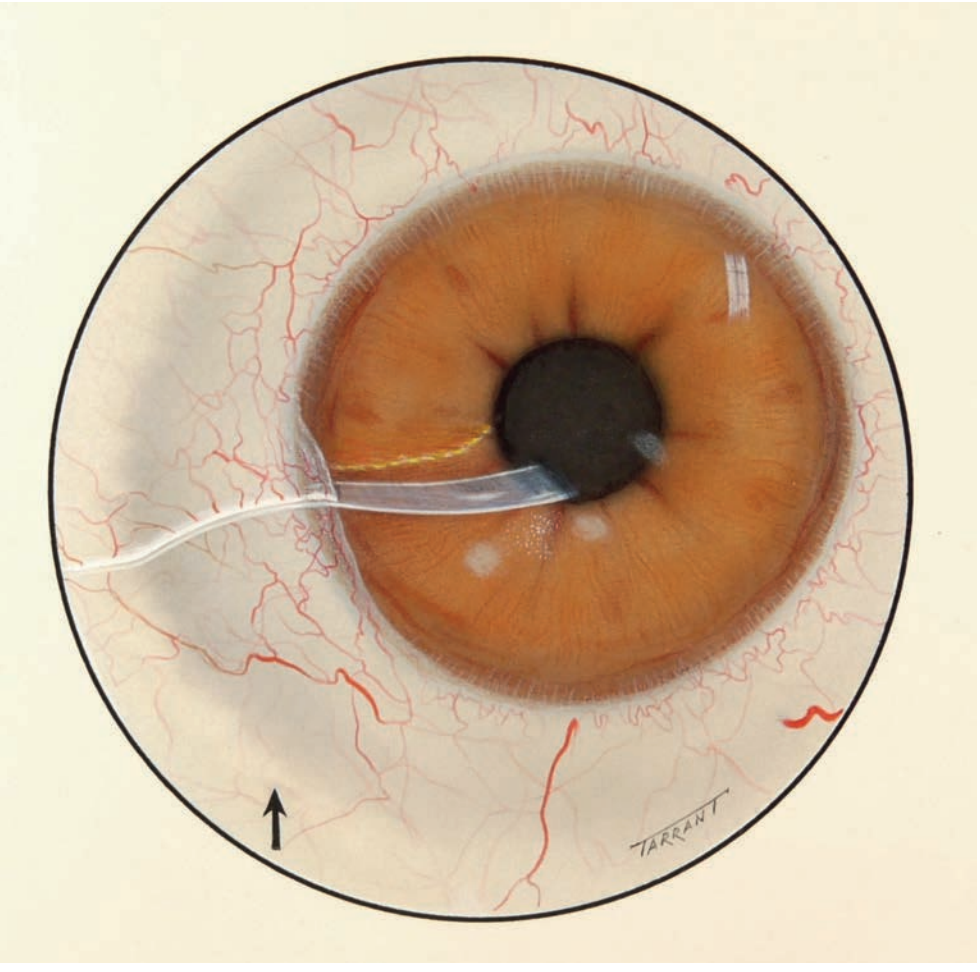




A VISION OF OPHTHALMIC HISTORY

These illustrations are by Terry Tarrant, a renowned medical illustrator, employed by the Institute of Ophthalmology in London, England. Tarrant worked in the Medical Illustrations Department from 1950 until 1984. The Institute is now part of UCL. Tarrant's images were created following indirect ophthalmoscopy of patients, and were an important adjunct to medical records. With an incredible eye for detail, Tarrant was known to produce the finest medical illustrations of the fundus, external diseases of the eye and details of instruments and operating procedures, and painted hundreds of medical cases - including retinal breaks, detachments and degenerations. Many of his images were published in papers and textbooks, and were invaluable for the education of ophthalmology trainees worldwide. His paintings are on display at Moorfields Eye Hospital and in the Joint Library of Ophthalmology, located in the UCL Institute of Ophthalmology, London, UK, where the originals are kept in the archive.

NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology and The Joint Library of Ophthalmology, Moorfields Eye Hospital & UCL Institute of Ophthalmology.



OPTIC NERVE, 1959

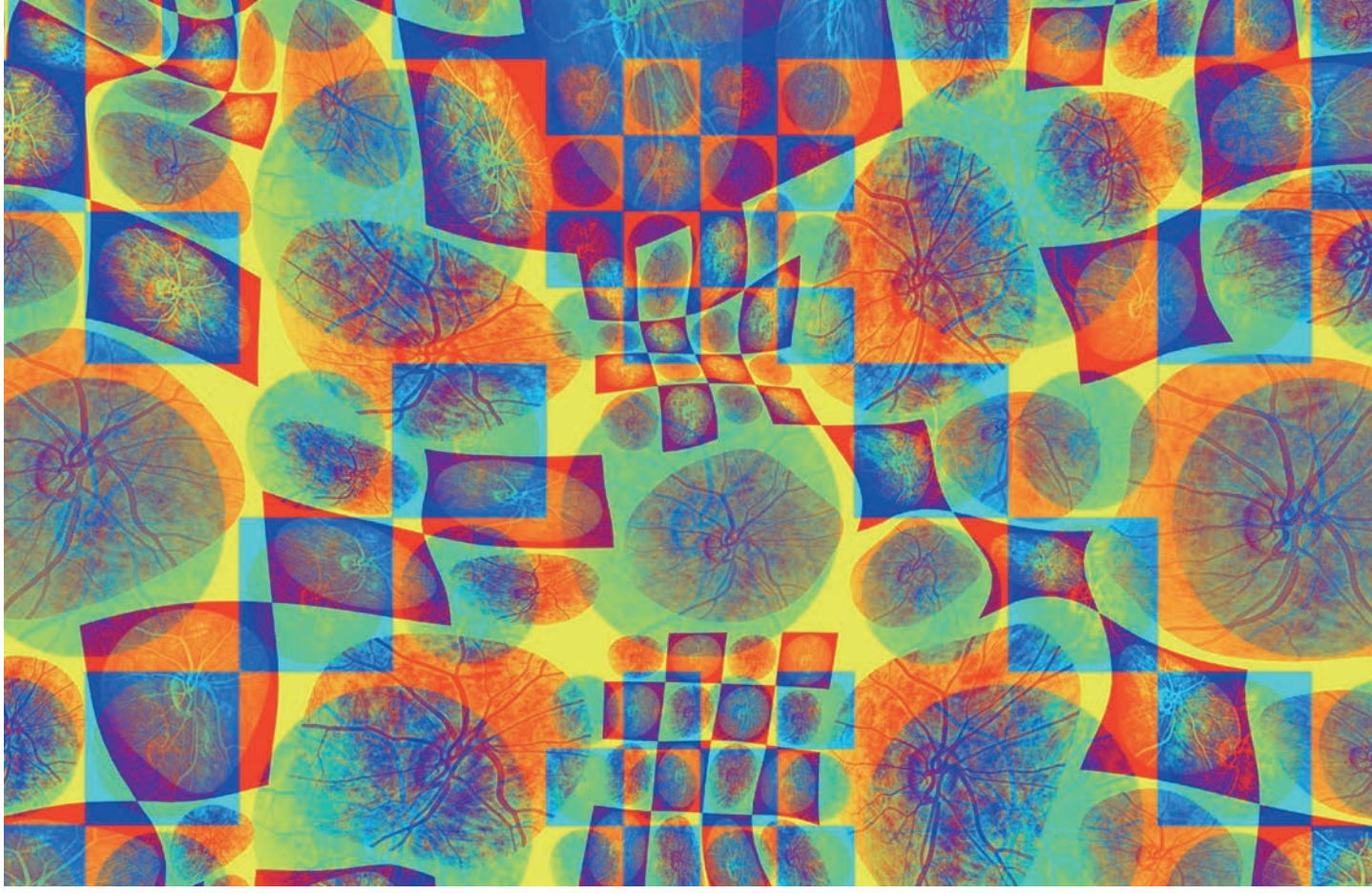
The central retina is illustrated with the optic disc obscured by a large neurofibroma that is lifting and detaching the surrounding retina (top left).

RETINA, 1971

White scar tissue distorts the retina and obscures details of the optic nerve head and blood vessels (middle).

CORNEA, 1967

A reflection from a slit lamp beam is horizontal to emphasize the area of scleral guttering adjacent to the cornea (bottom).

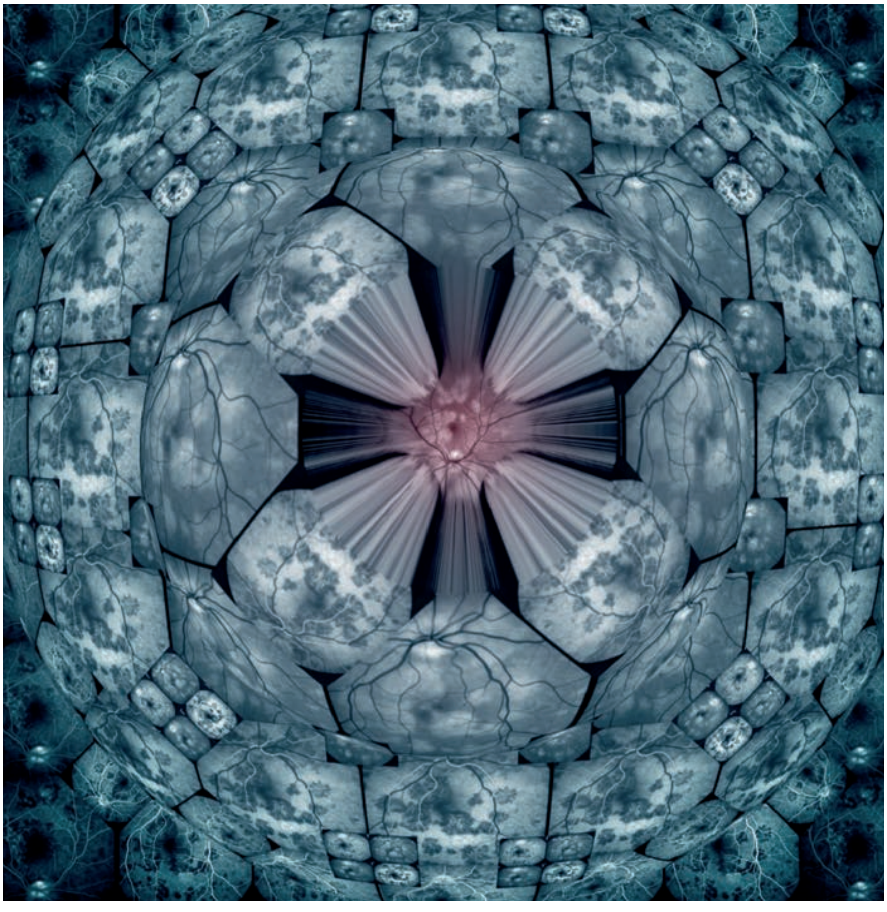


"As an ophthalmic photographer, my training had always been to rigorously document diseased retina for specialists in ophthalmology. But as a creative photographer, I found retinas to be visually fascinating. These quilts were distilled from everyday images I found around me. My personal images have always been reflections of self: I'd always photographed from the inside out. The work emerges from black and white digital images which are layered, manipulated, and colored. The patients are anonymous and unidentifiable. The finished work is presented in galleries as a traditional fine print. In the end, these documentary clinical images become art which is looking back at us."

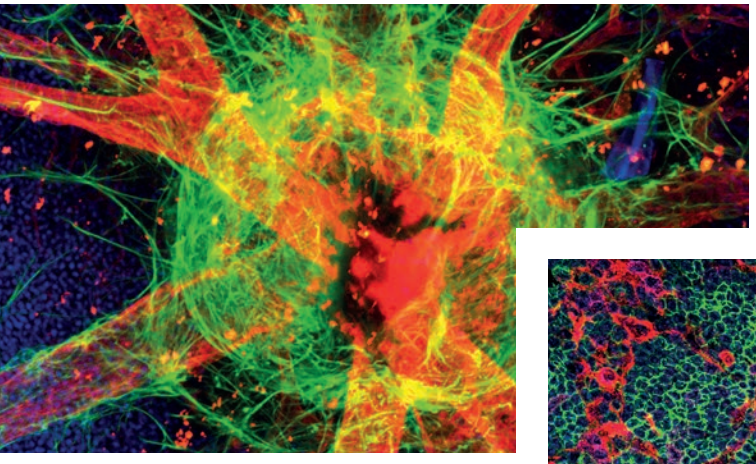
Pat Saine, former ophthalmic photographer and owner of Blue Plate Books, Winchester, VA. http://www.pjsaine.com/.

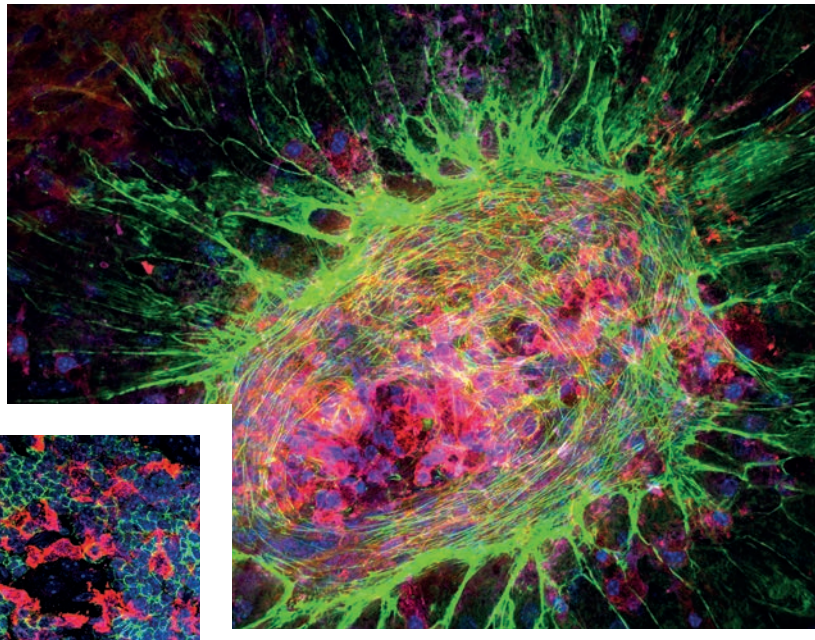
GEOMETRI (top).

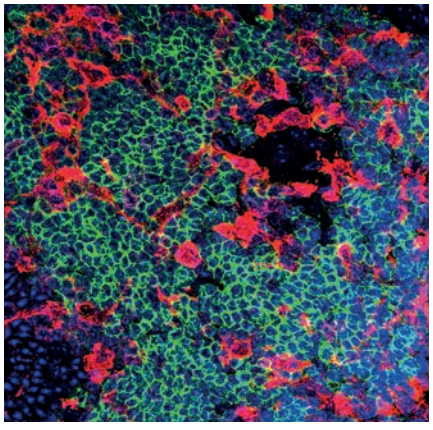
RETINA BLUES (bottom).

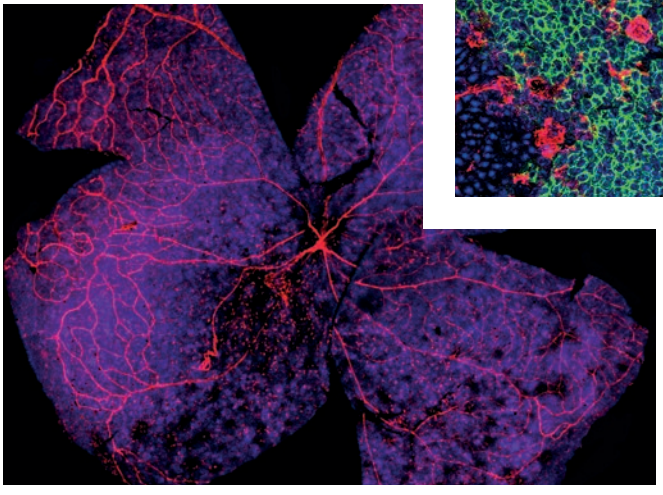


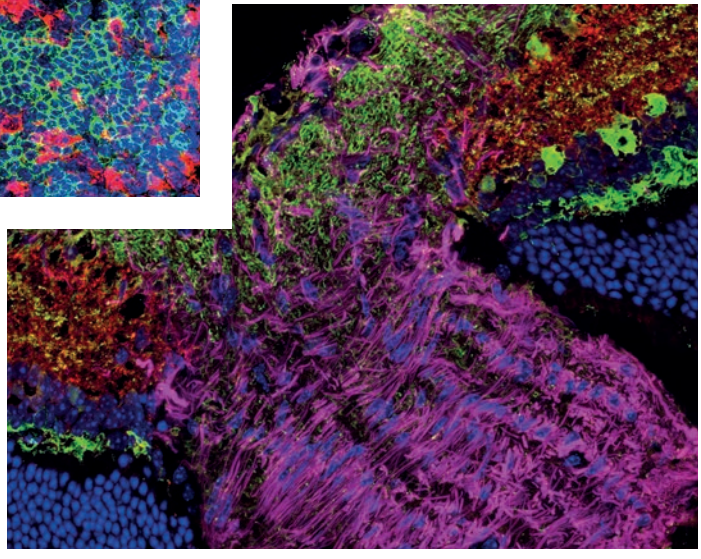
RESEARCH











OPTIC HIGHWAY

A normal mouse retinal flatmount depicting the optic nerve showing the retinal vasculature stained with isolectin (red) and GFAP (green) and DAPI (top left).

A MAGENTA MASS

A mouse RPE flatmount with laser injury showing choroidal neovascularization. Staining shows phalloidin (RPE stained), isolectin (blood vessels), and DAPI (top right).

TECHNICOLOR UVEITIS

A tertiary retinal lymphoid aggregate in a mouse with spontaneous uveitis. The staining shows the presence on microglia (red), B cells (green), and T cells (magenta) and DAPI (center).

VIOLET BLOOM

A mouse retinal flatmount showing the retinal vasculature stained for isolectin (red) and DAPI. The mouse was virally infected with Zika virus (bottom left).

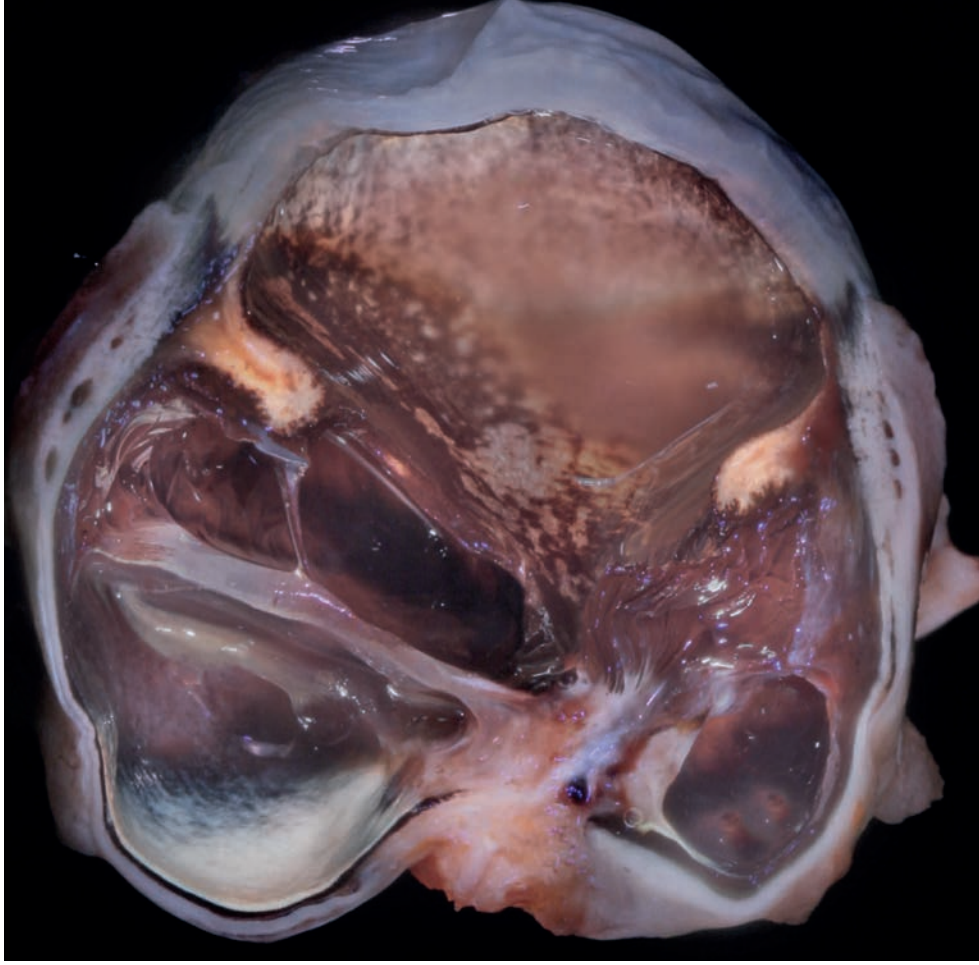
SPOTTING SYNAPSIN

A normal mouse optic nerve head stained for synapsin, PKC-A, and GFAP and DAPI (bottom right).

This selection of images were contributed by Jennifer Kielczewski, a Staff Scientist with the National Eye Institute, Biological Imaging Core (BIC) in Bethesda, MD, USA. Her research interests include using imaging techniques to study retinal pathologies, ocular inflammation, and neuronal degeneration in diseased animal models.

CAT FIGHT

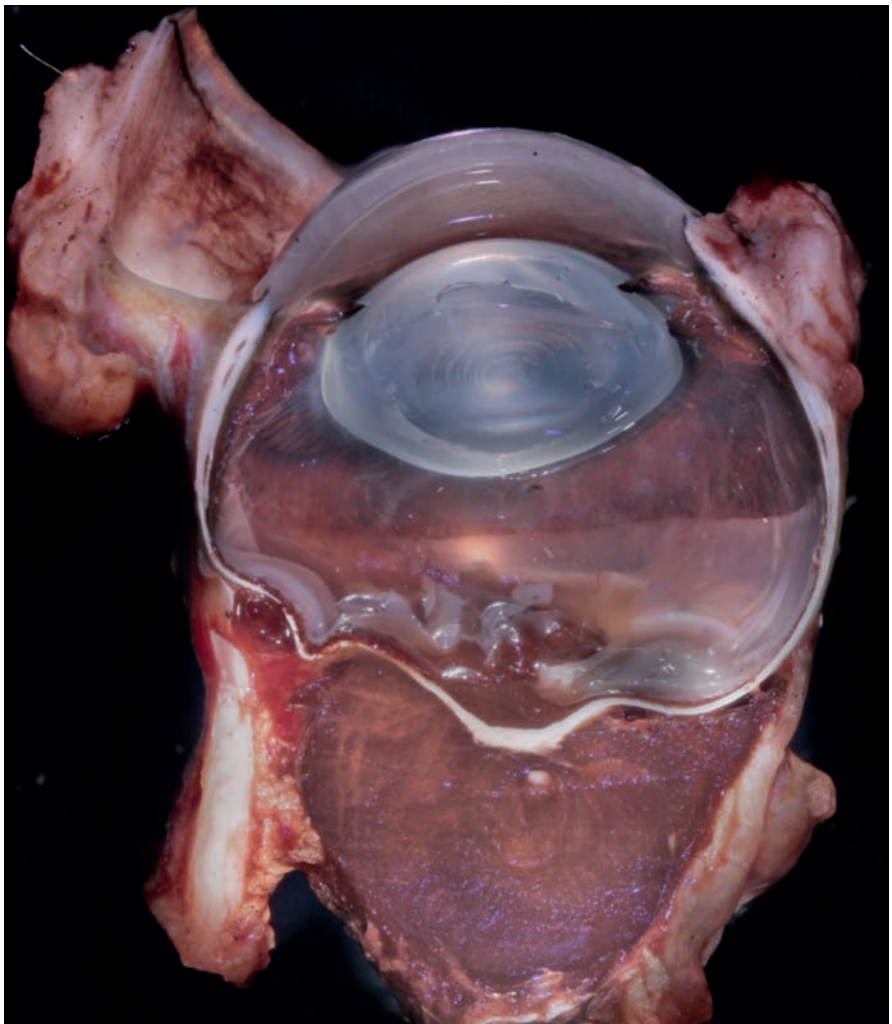
This is the globe of an adult cat with posterior scleral rupture due to presumed blunt trauma. The anterior chamber is collapsed and the pigmented iridal tissue lines the posterior cornea. Pigmented uveal tissue (likely ciliary body) stretches backwards and contacts fibrotic tissue at the posterior scleral rupture site. The lens capsule was ruptured and only recognized microscopically associated with the fibrotic tissue at the site of the posterior scleral rupture.



CHOROIDAL MELANOCYTOMA

In this canine globe, a choroidal melanocytoma extended through the posterior sclera and formed a mass behind the globe. Though locally destructive, this type of benign melanocytic tumor rarely metastasizes.

The Comparative Ocular Pathology Laboratory of Wisconsin (COPLOW), USA. Further images can be found on the COPLOW Facebook page: bit.ly/COPLOW.



GLOBAL OPHTHALMOLOGY

VISIONS OF ZAMBIA

This selection of images are from "Visions of Zambia," an exhibition of portraits by artist Tim Benson in support of Orbis. The project, a collaboration between Orbis and Benson, was conducted to raise awareness of avoidable blindness through sharing the stories of patients at the Kitwe Hospital Eye Annexe in Zambia, Africa. As part of the project, Benson traveled to Zambia to meet patients and health staff trained by Orbis medical volunteers. The resulting oil paintings capturing children and adult patients, parents and carers, as well as traditional healers, are available for purchase with 80 percent of the proceeds going to the support of global Orbis work.

Larry Benjamin, Consultant Ophthalmologist and Orbis Volunteer and Trustee, says: "Tim Benson's visit to Kitwe Eye Annexe in Zambia, a hospital that is very dear to me and one which I have been heavily involved with, has shone a light on the people and the emotions of those receiving treatment. His beautiful work captures the hopes and fears of patients and their families as they seek help for their vision loss."

For more information on the project or paintings please contact visions@orbis.org.uk

ALISHA

Alisha was just four months old when she had her first surgery to correct her eyesight. She has undergone treatment for both cataract and squint. Originally, her mother's family told her not to take Alisha to hospital, for fear that they might remove her daughter's eye (top right).

Artist Tim Benson at the Kitwe Eye Hospital (right).

READY FOR SURGERY

This photo is from an Orbis cataract training program in Kingston, Jamaica. The patient was marked to be wheeled back to surgery.

James Lehmann, Focal Point Vision, San Antonio, TX, USA.

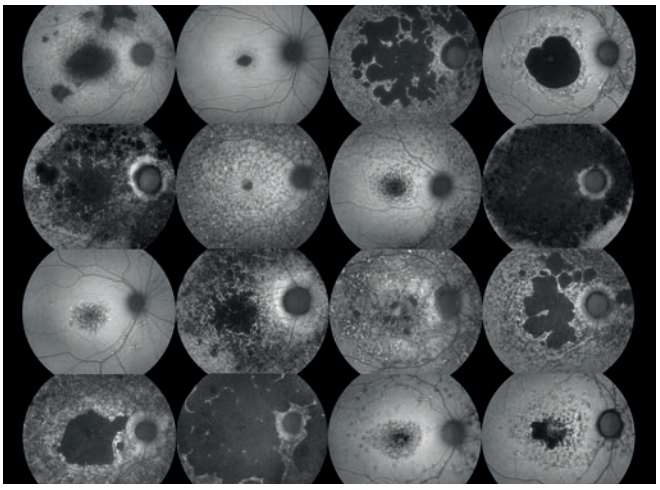
VISION 2020: UGANDA

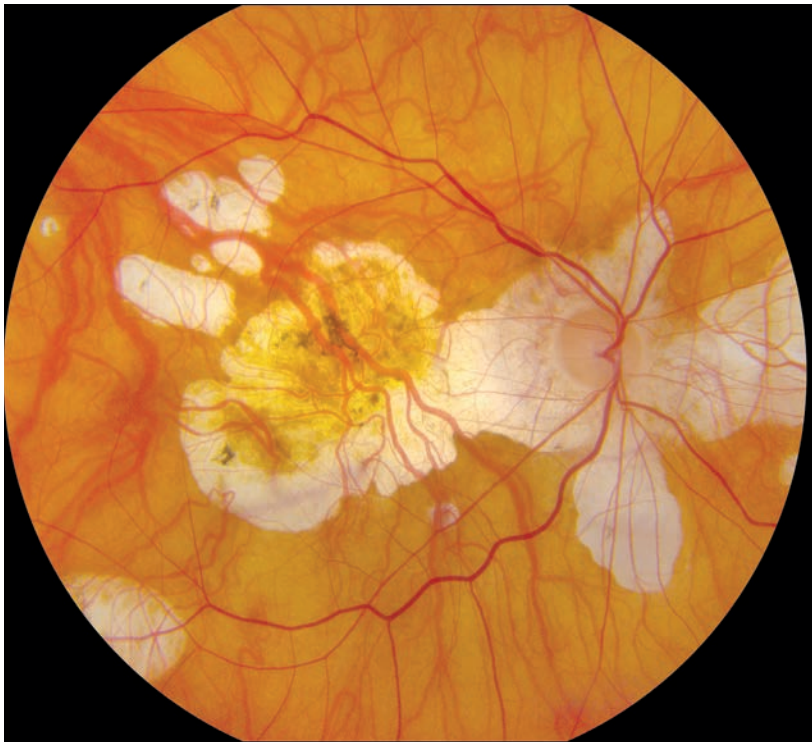
These photos by Terry Cooper were taken as part of a VISION 2020 programme on outreach eye clinics in Uganda funded by THET (the Tropical Health and Education Trust). The programme, led by Cooper, consists of a series of training workshops for eye health workers followed by live clinics.

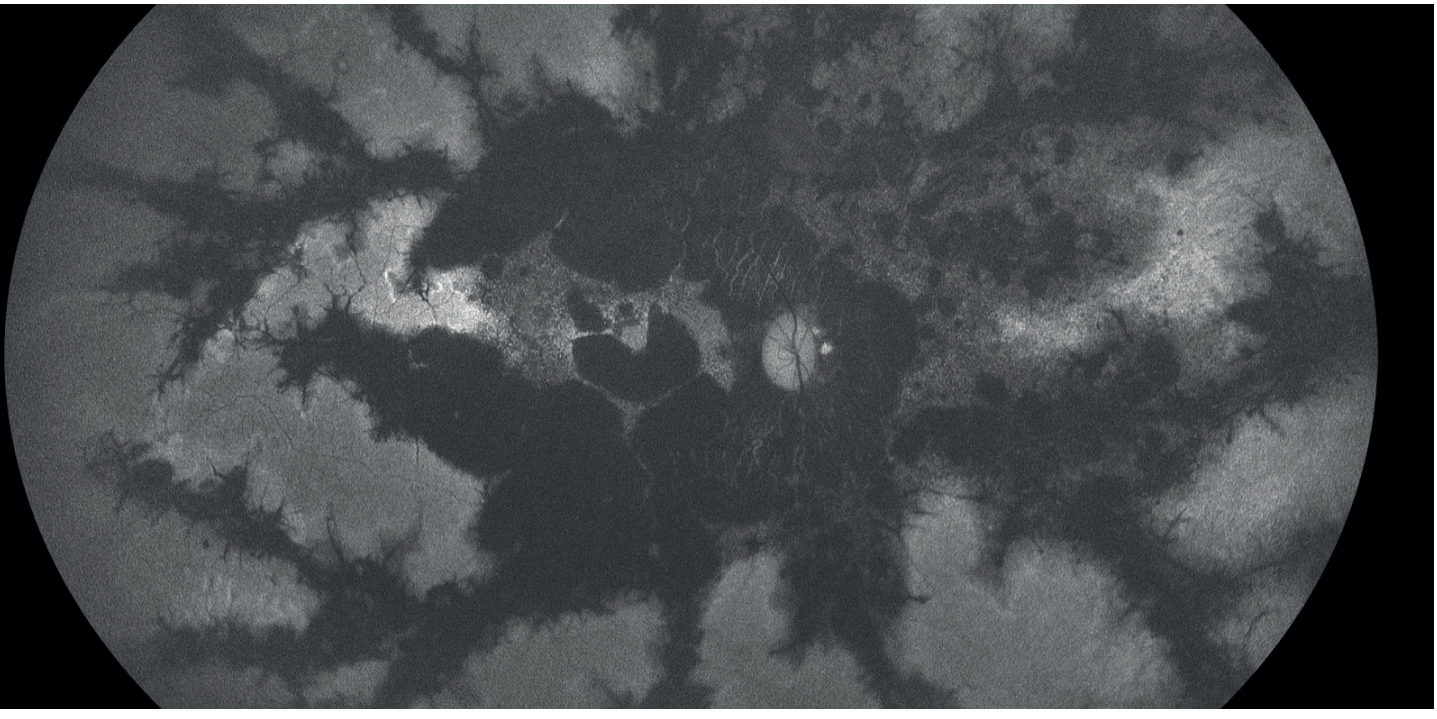
Terry Cooper, London, UK, www.terrycooper.photography


ECONOMY

IN THE CLINIC







MANY MOONS

Sixteen different fundus autofluorescence images that display phenotype variations in Stargardt Dystrophy (top left).

TIE DIE

Color fundus photograph of an individual with myopic degeneration (top right).

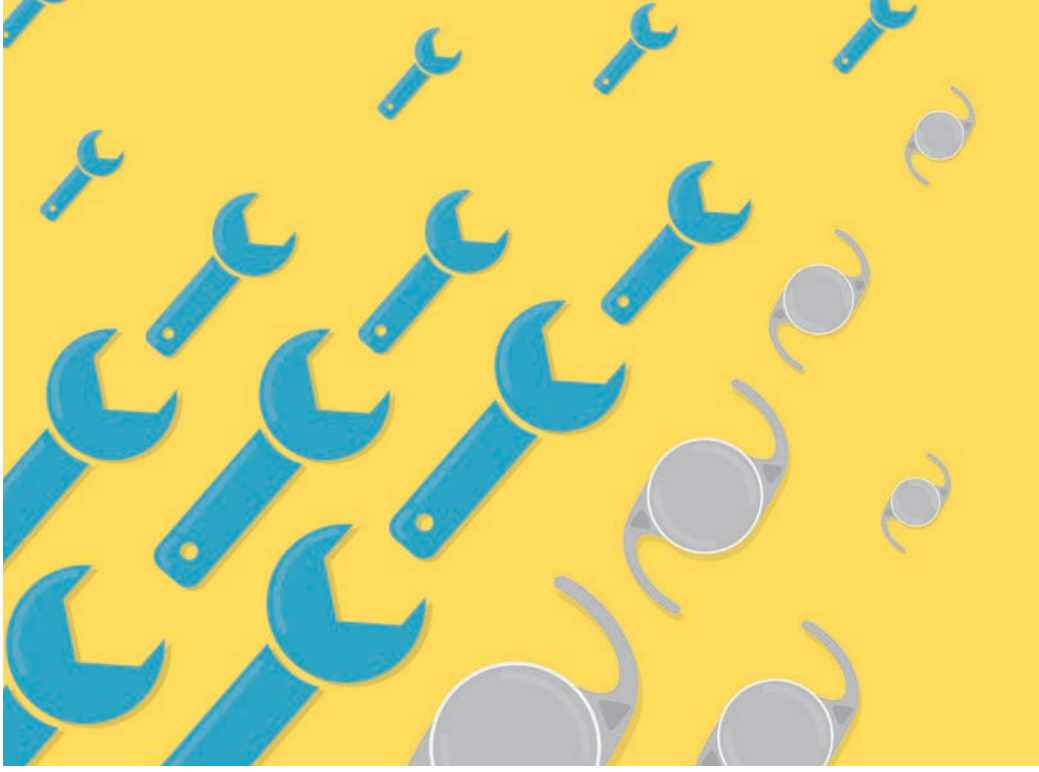
RORSCHACH RP

Ultra-widefield autofluorescence image of retinitis pigmentosa (bottom).

Robert Mays, Ophthalmic Photographer, NEI/NIH, Bethesda, MD, USA.

In Practice

Surgical Procedures
Diagnosis
New Drugs



Troubleshooting Yamane

Top tips for intrascleral haptic fixation – and its application in complicated cornea cases

By Karolinne Rocha

The Yamane technique (sutureless needle-guided intrasceral IOL implantation with lamellar scleral dissection) was first published in 2014 by Shin Yamane of Yokohama University Hospital, Yokohama, Japan (1). Two years later at the ASCRS 2016 annual meeting, Yamane was awarded the Grand Prize for his video on the technique (available at http://bit.ly/ASCRSYamane). But in the years since Yamane's technique was introduced, there have been several reports of complications – such as IOL tilt and decentration, and haptic erosion through the conjunctiva and sclera. Turnbull and Lash reported that there was an 'ultrathin line' between success and failure; the line turned out to be the need for an ultrathin wall 30G needle instead of a regular 30G needle (2). Here, I share my own experiences to help other surgeons when performing the technique.

At a Glance

- *Since its introduction in 2014, the Yamane technique of two needle intrascleral haptic fixation has been increasing in popularity*
- *Possible complications associated with the technique include IOL tilt and decentration, conjunctival erosion, iris capture, vitreous hemorrhage, cystoid macular edema, vitreous traction and retinal tear*
- *I overview top tips to master the Yamane technique – including some of my own modifications*
- *Complicated cornea cases in which the technique has helped achieve good outcomes for my patients are presented.*

My experiences with Yamane

From my experience so far, I have found that there are some modifications that help me perform the surgery. The first thing is the initial marking (Figure 1). Using a toric marker, I mark 0 and 180° for the main incisions. I then mark 2 mm from the limbus and 2 mm down from my main incision, and 2 mm from the limbus and 2 mm from the second incision. I find these angles help make it easier to pass the haptics, especially the second one which can be tricky when you first start performing the procedure.

Using the right lens and the right needle for the procedure is also important. We now have the CT-Lucia (Zeiss) available in the US (prior name EC-3 PAL); this is a 3-piece IOL with PVDF haptics that are very malleable and resistant. I find that the PVDF haptics create a much better flange than PMMA haptics, and can prevent erosion through the conjunctiva. I also find that the TSK 30G needle (available in Europe from TSK Laboratory Europe B.V. and in the US from Dermatologic Lab & Supply, Inc.) is best to use with the CT-Lucia (Figure 2).

For IOL centration, a modification I have made is to control cauterization of the haptics. One thing I have noticed is that many surgeons just perform the cautery without knowing how much to cauterize on each side. Using calipers, I mark 1 mm on each side of the haptics, and when using cautery, I stop at that mark. Why 1 mm? Because we know from post-operative OCT that 1 mm of the haptics are needed to make a flange diameter of 0.3 mm – the perfect size for the scleral tunnel created by the 30G needle. If the eye's anatomy needs a wider flange to ensure centration, you can just mark the haptic a little more on each side.

Further things I have learned are to perform a really good anterior vitrectomy; you can use triamcinolone staining to make sure that there is no vitreous. Ensuring that you don't pull the lens all the way when passing the first haptic is also helpful as it gives you space to work with the second haptic. I also find it easier to perform the procedure if I sit temporally rather than superiorly. Additionally, the 'ideal' lens for the procedure might not always be available to you. In one of my first patients, I used the MA60AC lens with PMMA haptics; I am monitoring

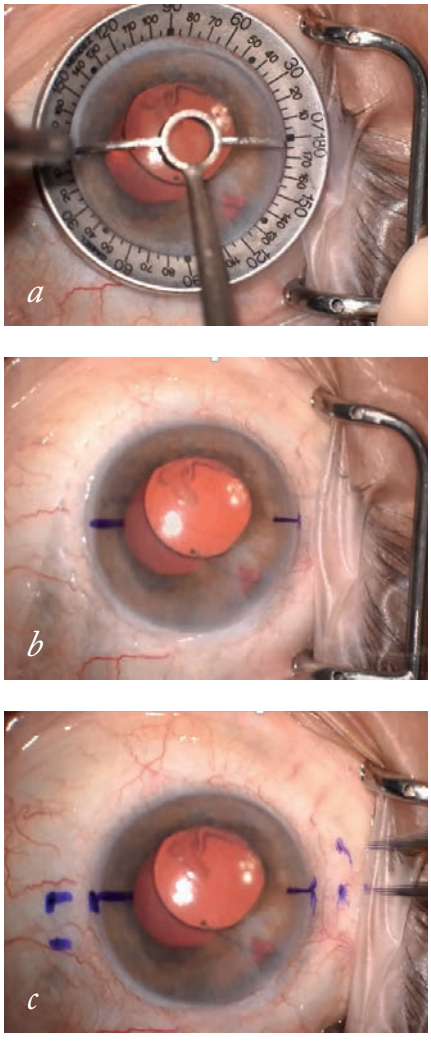


Figure 1. Initial marking for the surgery using a toric marker to mark the two incisions at 0 and 180°, (a, b) and marking 2 mm from the limbus and the incisions (c).

Advice from the master himself

In an email correspondence shared with the Cedars Aspens Group, Yamane advised the following, saying it takes four to five cases to master the technique:

IOLs

"I now use X-70 (Santen, Japan), which has 7 mm optics and PVDF haptics. You can use ZA9003 (J&J Vision) and MA60MA (Alcon)."

Scleral tunnel

"It is difficult to control the length of the scleral tunnel. I wanted to create a 2 mm length, however in most cases the lengths were about 1.5 mm as measured by OCT."

"Too short a scleral tunnel may result in IOL dislocation, and too long a tunnel may lead to intraoperative distortion of the cornea. A too small angle of the 30G needle can lead to this situation."

Haptics

"You can control the length of the haptics by cutting down the longer side."

"Too small a flange has the risk of IOL dislocation (during wound healing). Too large a flange is difficult to be pushed into the scleral tunnel. If so, you should enlarge the entry site of the tunnel using the 30G needle."

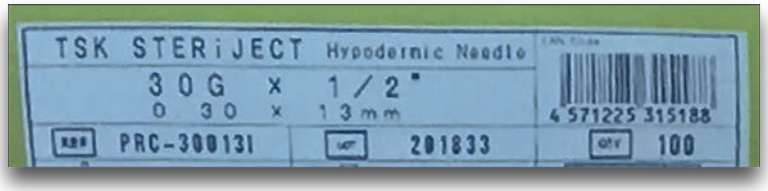


Figure 2. TSK 30G needle for the procedure.

them to see if they develop an erosion that might require a patch, but so far he has been doing great. I would say for these cases you must tell your patients, "No eye rubbing!"

Application in corneal cases

As a cornea specialist, I find the Yamane technique very useful. Here, I outline examples of complicated cases where it has really helped me – and my patients.

Case 1 – Yamane technique and DSAEK

This pseudophakic bullous keratopathy (PBK) patient had a complicated surgical history (Figure 3). They had an anterior chamber IOL, and had basically lost their cornea. For patients like this, it is much better to move the lens to the posterior chamber, otherwise there is always an increased risk of postoperative endothelial cell loss. You could perform a suture technique for scleral IOL fixation, but you'd need four needles to pass the sutures. Yamane is really great for these cases as you only need to pass two needles in the pars plana, then pass the haptics and you're done. Five weeks after surgery this patient had a binocular distance-corrected visual acuity (DCVA) of 20/50.

Case 2 – IOL dislocation in PBK patient

This PBK patient had a dislocated 3-piece IOL in the anterior chamber (Figure 4), and had a history of a complicated cataract extraction three years earlier. I first tried

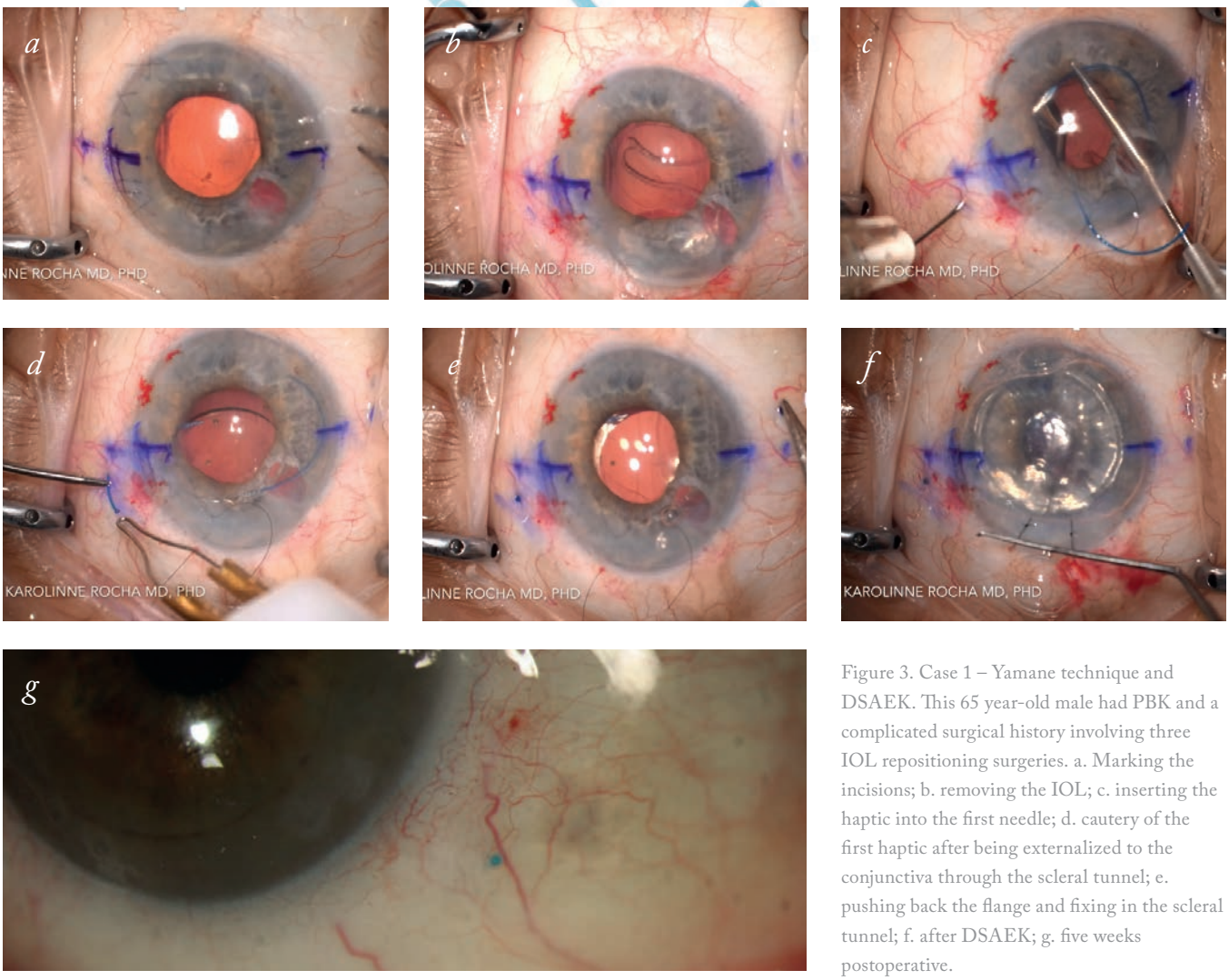


Figure 3. Case 1 – Yamane technique and DSAEK. This 65 year-old male had PBK and a complicated surgical history involving three IOL repositioning surgeries. a. Marking the incisions; b. removing the IOL; c. inserting the haptic into the first needle; d. cautery of the first haptic after being externalized to the conjunctiva through the scleral tunnel; e. pushing back the flange and fixing in the scleral tunnel; f. after DSAEK; g. five weeks postoperative.

flipping the lens, as I didn't know it was a PMMA lens, but it needed to be removed. A new lens was inserted using the Yamane technique – in this case, I only had the MA60AC lens – and a corneal graft applied. Twelve weeks after surgery, the patient was doing well, and had a DCVA 20/30.

Case 3 – Ocular trauma

This was a complex case of a Seidel positive patient who needed corneal sutures for a ruptured globe (Figure 5). But when I started to perform the full thickness transplant I discovered that they had a fibrosis, and that their lens was basically dissolving. Instead of leaving the patient aphakic, I was able to pass the needles and perform the Yamane technique, before finalizing with a full thickness corneal transplant.

Final thoughts

Yamane is an incredibly useful technique, and I have been very successful with it so far, especially with corneal cases. The small modifications I have made to the procedure have really helped me with my cases, and I hope they help other surgeons master the technique too!

Karolinne Rocha is Director of Cornea & Refractive Surgery at the Storm Eye Institute, Medical University of South Carolina, Charleston, SC, USA.

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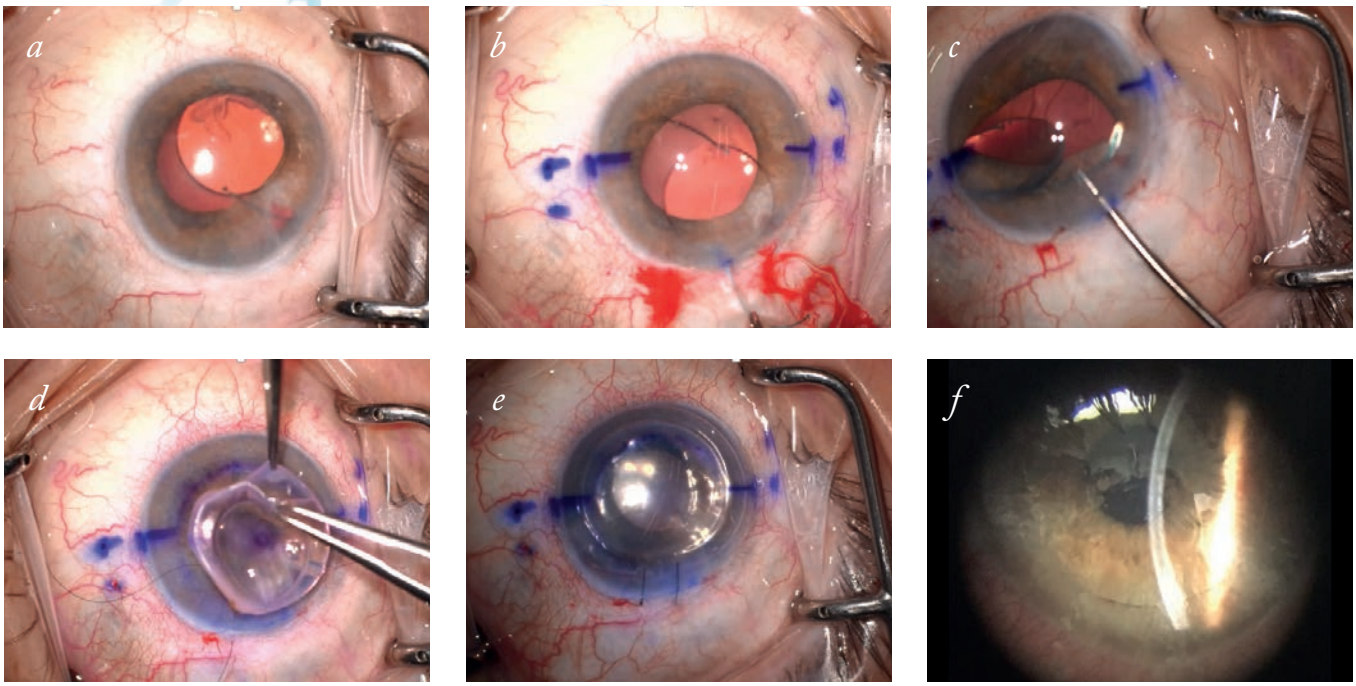

Figure 4. Case 2 – Dislocated IOL in PBK patient. This 62 year-old male had PBK and a complicated cataract extraction three years prior. a. Dislocated IOL; b. removing the dislocated IOL; c. passing the second haptics of the newly inserted IOL into the needle; d, e. during and after the corneal graft; f. seven weeks postoperative.

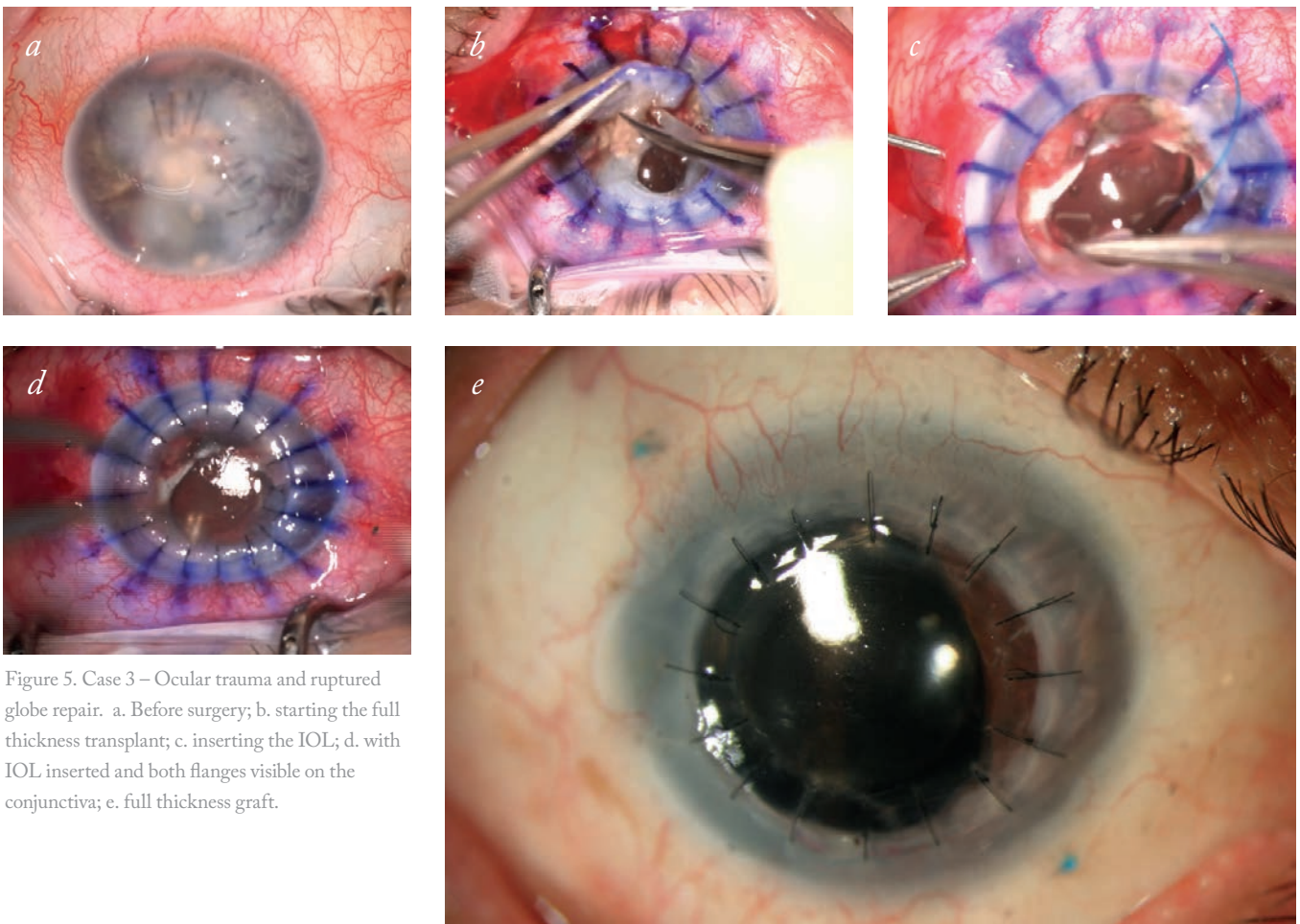

Figure 5. Case 3 – Ocular trauma and ruptured globe repair. a. Before surgery; b. starting the full thickness transplant; c. inserting the IOL; d. with IOL inserted and both flanges visible on the conjunctiva; e. full thickness graft.

NextGen

Research advances
Experimental treatments
Drug/device pipelines

Through the Photon Sieve

Introducing a new concept for presbyopia correction that turns the disadvantages of currently available inlays into advantages for patients

By Walter Furlan

What are the surgical options for presbyopes who don't want glasses or contact lenses? One possibility is to implant a corneal inlay. These devices are intended to increase depth of focus, and thus improve near vision without significantly affecting distance vision. The inlay procedure is fast and simple: using a femtosecond laser, the surgeon creates an intracorneal pocket of appropriate position and dimensions, and inserts the inlay. Recovery is usually complete in one or two days.

At a Glance

- *Corneal inlays for presbyopia may be associated with drawbacks including compromised contrast sensitivity and degraded stereoscopic acuity*
- *These issues are largely a consequence of the diffraction of light through the thousands of micropores required to allow nutrient diffusion across the implant*
- *By exploiting the photon sieve concept, we have created the diffractive corneal inlay (DCI), a device that diffracts light by design*
- *The DCI is the basis for a corneal inlay that not only avoids issues of degraded contrast sensitivity and stereoscopic acuity, but also corrects presbyopia and higher order aberrations on a personalized basis.*

At present, corneal inlays are available in two forms: the refractive inlay and the small aperture corneal inlay (SACI), as represented by the Kamra product. Refractive inlays are very simple, being no more than small lenticules that can locally modify corneal power and/or curvature – and thereby modulate depth of focus – when correctly positioned. The SACI, by contrast, is an opaque disc with thousands of micro-pores and one larger central aperture. The central aperture exploits the pinhole effect so as to increase the depth of focus of the eye. Implantation of a solid disc, however, would block the flow of nutrients to cells of the corneal stroma; to prevent this, the SACI must be made permeable. Hence the SACI micro-pores – more than 8,000 of them, in a size range of 5–11 µm diameter.

Unfortunately, although SACI implantation can result in good clinical outcomes, there are some drawbacks. First of all, only about 20 percent of the incident light passes through the disc's central aperture. Secondly, as much as five percent of incident light is diffracted by the disc's pores. The net effect of these handicaps is that the improvement in near vision provided by a SACI procedure comes at a significant cost to contrast sensitivity. For this reason, patients only ever receive SACI in one – the non-dominant– eye, never both, the idea being that the non-SACI eye will compensate for the compromised vision in the SACI eye. But this monocular approach results in the additional issue of degraded stereoscopic acuity (1)! Might there be a better way?

Seeing the light

Of course, SACI manufacturers are aware of the limitations outlined above, and have investigated various mitigating strategies. In particular, they have tried to minimize the diffractive effect of the micro-pores by decreasing their diameter and distributing them randomly on the disc. It occurred to my colleagues and I, however, that the pores could be turned to our (and patients') advantage. Our inspiration came from the photon sieve – a device that uses an array of pinholes to focus light by means of diffraction and interference, thus capitalizing on the very features that SACI manufacturers were trying to eliminate. Another great benefit of the photon sieve is that its optical characteristics can be modulated by varying the size of the pinholes and the pattern of their distribution – suggesting that devices based on the photon sieve concept could be customized for a variety of specific applications. We knew that photon sieves had already been applied in X-ray microscopy, and used as alternatives to lenses or mirrors in telescopes, so why not try them in vision correction? It seemed like a relatively simple proposition to test; all we needed to do was distribute the pores in a precisely designed pattern, and a SACI-type disc should be turned into a diffractive lens that brings near objects into focus.

So we set out to merge the photon sieve and the SACI pinhole-effect concept to develop a novel corneal implant – the diffractive corneal inlay (DCI: Figure 1). The DCI's disc pores would not just permit the flow of nutrients, but also deliberately and precisely diffract light to create a new focus for near distance. Furthermore, we expected that by optimizing the spatial distribution of the pores, we would be able to vary the relative intensity between near and far foci, and also correct higher order ocular aberrations. In this way, the DCI would be customizable according to specific patient need. In other words, our approach turns the diffractive effects of SACI from a disadvantage into a significant advantage, and in doing so provides an entirely new concept in corneal inlays!

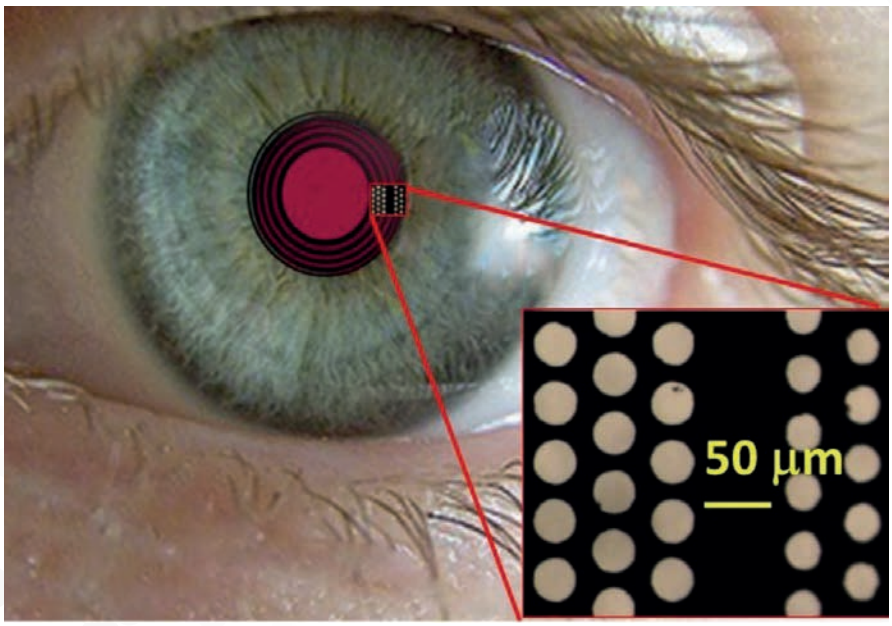

Figure 1. Simulated appearance of the DCI. The inset shows holes created by a femtosecond laser on a graphene oxide sheet..

Theory was brought closer to practice by my colleagues and I in the Diffractive Optics Group, a multidisciplinary collaboration between a number of institutions. Together, we designed and performed a series of optical bench experiments to measure the polychromatic axial Point Spread Function (PSF) associated with different inlay designs, recording PSF along the optical axis under polychromatic illumination. In this way, we showed that the DCI's performance was superior to that of the Kamra SACI (2). And given that the DCI permits passage of a very high proportion of incident light, it seems likely that patients could receive DCI implants in both eyes – avoiding yet another drawback of SACI.

Looking ahead

In the near term, we are clearing the path to the clinic via two clinical investigations of the DCI device. One is aimed at testing the performance of soft contact lenses printed with a DCI array of pores. The other seeks to simulate the implant with a VAO visual simulator (Voptica, Murcia, Spain). At the same time, we are also investigating earlier-stage concepts, not least various transparent DCI designs that could be the basis of new types of multifocal IOLs.

We are also investigating the application of novel materials for our device. To date, we have known that DCIs could be fabricated from the same material used for SACIs – namely, polyvinylidene fluoride. We believe, however, that we can improve on this aspect of corneal inlay devices too, and are currently engaged in proof-of-concept studies using graphene oxide. We chose graphene because its properties make it excellently suited for ocular implantation; for example, it is highly biocompatible with corneal tissue (3), has an ultrahigh refractive index, has linear optical absorption characteristics and can be manufactured in sheets thin enough to be implanted into the cornea without inducing refractive effects and even, can be held between two contact lenses in preclinical studies. We are very excited about this development.

Personalizing refraction

But perhaps the most exciting feature of the DCI is its potential to be personalized according to the specific needs of each patient. The design of the device incorporates several free parameters that allow DCI customization according to requirements regarding reading/working distance and pupil size in different environmental conditions, and may even permit compensation for particular higher order aberrations. In practice, we would probably make each device in contact lens form initially, to confirm that it adequately corrects a given patient's vision before proceeding to device manufacture and implantation. Of course, to bring this promising innovation to the market will require collaboration with industry, and we are actively inviting and pursuing such discussions.

Walter Furlan is a Physicist in the Departmento de Óptica y Optometría y Ciencias de la Visión, Universitat de València, Spain. *He would like to acknowledge his colleagues in the Diffractive Optics Group: Juan A. Monsoriu and Vicente Ferrando (Universitat Politécnica de València, Valencia, Spain); Laura Remón (Universidad de Zaragoza, Spain); Salvador García-Delpech and Patricia Udaondo (Aiken Clinic / Hospital La Fe de Valencia, Valencia).*

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No Rest for the Dedicated

Sitting Down With… Steve Charles, founder and owner, Charles Retina Institute, Memphis, Tennessee, USA

Why did you study engineering before medical school?

I wanted to be an engineer from a young age. My maternal grandfather, who I lived with during World War II while my father was in the Navy, was a mechanical engineer. He taught me to drive a car, to row a boat, and how to swim. He was a diesel engine designer, and when he took me to his work, I thought I was designing engines too! So I always knew I wanted to be an engineer – but I wanted to engineer something worthwhile. I could never have worked building machines that made cigarettes, or gambling machines or weapons systems. I wanted to be creative, and to do something meaningful.

My other grandfather, who died before I was born, was a famous surgeon, and his oldest son, my godfather, was a leading colorectal surgeon. My father was a college professor, an art historian and a fantastic lecturer. I've ended up doing all three: engineering, surgery and teaching.

You're known as an entrepreneur and prolific inventor…

I find that people often call me an entrepreneur – but I don't like it; I don't see myself in that way. I do mechanical, electrical and systems engineering, and I don't do it for the money. For me, it's about making something useful.

From a product development perspective, it's true that I've been involved in quite a few startups. If you create enough threat to big companies, they tend to think, "I guess we have to buy the technology!" In that way, startups serve a very helpful purpose. But I haven't launched an ophthalmology startup since Alcon bought a company from me in 1991. I have set up two new companies in neurosurgery because my dad died of a brain tumor at just 61. In ophthalmology, I now work exclusively with Alcon as they allow me to stay embedded with the engineering team. I'm very fortunate that Alcon treats me as a systems engineer, not just a surgeon, so I can serve as a conduit between those two disciplines.

Because of intellectual property laws, I like working with just one company – but I'm not in this field to name products after myself. It's not an ego game and it's not about money.

Of your inventions, which do you think has had the most impact?

I've invented a lot of instrumentation that I'm very proud of, but I think ultimately your technique is king – and technique isn't tied to my machines, or anyone else's. So my contribution to new techniques is what I'm most proud of. The intersection of technique and technology is crucial, but technique has to lead.

Where do you see the future of vitreoretinal surgery?

I'm really focused on better visualization. Our surgical instrumentation is very good already, and so are our techniques. It's something I've worked on for 44 years, as have others, but there's still room for improvement. I've got a whole project – which will be an Alcon project, so I can't share too many details – working on better visualization, higher magnification, better depth of field, and so on.

What are your interests outside of your work?

I have three wonderful daughters – one is a GYN surgeon, one is a family physician and the other is a team-building expert. We're very close, and I also have four grandchildren who are just phenomenal.

I don't personally believe in entertainment. I haven't seen a movie in 30 years, and I haven't gone on a vacation for 22. I don't read fiction or go to concerts. I don't really have a social life! I do fly a jet, but it's not a hobby, it allows me to travel extensively for work despite not living near a good transport hub. I am involved in social issues; I worry about domestic violence, racism and the state of the planet, and I work with inner-city kids. I'm not a political animal – as my niche is building machines for vitreoretinal surgery and teaching – but I definitely take an interest.

Any plans to retire?

Never! I'm going to do this for as long as I can, as hard as I can. I have zero interest in slowing down. People always tell me I'm passionate about my work, but I don't think that's the right word for it. I'm not a religious person, but I believe if you can do something to help people, you should be doing it, rather than retiring to take up fishing or golf!

What advice would you offer to a young vitreoretinal surgeon?

Learn some science and collaborate with your colleagues – go watch other people operate, attend meetings, read the literature. Be a physician and a surgeon first, not a businessman. And remember there's a difference between a surgeon and a physician. Be both. I pride myself on seeing a patient with a limp and asking, "Is somebody looking after your knee? Tell me what treatment you're getting, because every time I see you the swelling seems worse." You can't be an expert in every area, but you can take an interest in the whole patient.

Don't obsess over reimbursement, coding, billing and private equity. Personally, I pay no attention to the business of medicine. I have no idea what I make when I perform a vitrectomy, I just take care of my patients. These days it seems like there's too much focus on how much you're making, and it's exhausting. Some people think, "Well I've borrowed all this money and I have to pay it back." Yes, you did, but the taxpayer paid way more for your education than you did if you went to a public medical school! The world doesn't owe you – you have to give back.