ASSOCIATION FOR OCULAR CIRCULATION
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Accepting the Lifetime Achievement Award Presentation

Charles E. Riva
Good morning everybody. Please accept my sincere apologies for not being with you in person. Nothing would have pleased me more than joining you all in beautiful Chicago but to take a short return transatlantic trip would have been rather difficult for me at this time.

Thank you very much, Leo, for your kind and gratifying words. My feeling when I got the message about this award was of real surprise. I did not know that such an award existed. Nevertheless, I accept it with immense pleasure and want to share it with all the people I had the privilege to work with during my life as a researcher. I deeply thank the ophthalmic and vision science community for having granted me during 40 years the freedom and pleasure to do a wonderful and enjoyable activity and learn new things every single day. Is it not unusual to have the opportunity to do what one always wants to do and be rewarded for it?

In this acceptance talk, I would like to share with you some of the milestones which have marked my scientific undertaking. No doubt, good fortune and key encounters played a large part in my carrier.
After obtaining the diploma in physics in 1964 from the ETH in Zürich, I applied to graduate school. At that time most of my classmates opting for a PhD chose atomic physics. Luckily, I met Prof. Berg, who encouraged me to go into the less crowded but, nevertheless, fast growing field of optics. His advice was pertinent since before I completed my thesis, which was related to optical noise and information capacity of image storing media (as revealed by the German title of my thesis), I already had offers from a number of US research laboratories. Among them was the Retina Foundation (RF) in Boston. I did not know what kind of research was being done there and why it needed physicists. Nevertheless, I accepted the generous invitation of the RF (now called ERI) to visit the institute.
After meeting Dr Charles Schepens, the founder of the RF and Oleg Pomerantzeff, the director of the Physics lab, who had studied optics in the renowned Institut d’Optique in Paris. I was quite enthusiastic about working in the future at the RF and in 1968, moved to Boston with my wife and first child. I was surprised to see that all the other scientists in the Physics Lab were French. The atmosphere of the lab was quite friendly (we used to call the director “Oncle” Oleg) and stimulating. Money for research came from a NEI grant to Dr Schepens and was plenty.
By the mid-sixties, retinal blood flow was estimated from the passage of fluorescein through the retinal vasculature (left). It was recorded from sequential fundus fluorescein angiograms. From the arterial and venous passages the arterio-venous MCT of the dye was determined. The recording process was time consuming. My first task was to improve this technique by recording the so-called dilution curves on-line. For this purpose, I built a fundus fluorophotometer (Appl. Optics, 1972), which did that (middle) using only 1/1000th of the amount of dye injected for fluorescein angiography. This small amount permitted multiple, sequential injections, which made possible the study of the effect of various induced physiological conditions on RBF. Some years later we built a new device to simultaneously record both the arterial and venous dilution curves (right).
At that time, it appeared important to determine not only the flow of fluorescein through the retina but also whether the dye was leaking out of the optic nerve capillaries in glaucoma. The hypothesis was that an abnormal leakage might reveal an alteration of the vessel wall in this disease. With the fluorophotometer we could also record simultaneously dilution curves of fluorescein and indocyanine green to investigate the diffusion process of fluorescein in the optic nerve. ICG does not normally diffuse out of the retinal vessels, whereas fluorescein can leak into the tissue if the vessel wall is altered. By comparing both dilution curves, we had a means to extract the component resulting from leakage and have a quantitative assessment of this leakage.

We found no leakage of fluorescein from the vessels of the normal optic nerve. The leakage component measured was due to fluorescein leaking out of the choroid and diffusing into the optic nerve. However, abnormal leakage into the ON tissue could be demonstrated in glaucoma. We could also extract the component of leakage of fluorescein from the choroid into the fovea centralis (Riva, Ben-Sira, Feke, Exp Eye Res, 1977) and showed abnormal early leakage in some retinal pathologies.
It was under a particular circumstance that I met Prof. G Benedek. GB was giving a seminar at Brandeis University on laser light mixing spectroscopy for measuring the diffusion of micro-particles. At the end of the talk, I mentioned to him that this technique might be a way to measure the speed of red blood cells in the retinal vessels. He liked the idea and we met the next day in his MIT office to discuss this possibility, upon which he offered me a spot in his lab to test the concept. This was the beginning of a long-term collaboration with Prof. Benedek and my wife and I were quite happy to host him in our house here in Switzerland some years later.

The figure shows the setup used to measure the velocity of particles through a 200 μιχρονο διαμετρο glass capillary tube (short explanation).
After about 3 months of unsuccessful attempts, I obtained on the 24th of December 1971 Doppler spectra of the velocity of the particles in water. At first, we did not fully understand the shape of these spectra, but then it became clear that the square spectrum corresponded to the parabolic distribution of the velocities and the cutoff frequency corresponded to the maximum or centerline blood velocity, Vmax.

Left: Spectrum of 0.5 mm Polystyrene spheres in water; Recording time: about 2 min
Middle: Spectrum of whole blood;
Right: Spectrum of a rabbit retinal artery.

The first measurement of blood velocity in a volunteer was obtained by Tanaka, Riva and Ben-Sira. These authors used a correlator developed by L. Hocker of MIT. This instrument allowed much faster measurements than the spectrum analyzer. The paper reporting the data in humans was published in Science in 1974.
With Dr Gilbert Feke joining the Physics department in 1976, the technique was extended to humans. Using a fast spectrum analyzer, we showed in particular that:
1. Short recording times of the Doppler spectra improved the detection of the cut-off frequency (i.e. Vmax);
2. The pulsatile nature of Vmax in retinal arteries; and
3. Developed the bi-directional LDV technique to obtain absolute measurements of Vmax in retinal vessels, a technique now implemented in various OCT LDV systems, such as that of the University of Vienna and Duke University groups.
In the RF library, I came across a 40-page paper written in German in 1924, about “Blutbewegung im Auge”, i.e. “Blood motion in the eye”. Scherrer, the author, described the blue field entoptic phenomenon by which one can perceive cell-like particles moving in the capillaries of the macular retina. Using a narrow-band optical filter at 430 nm instead of the blue filter used by Scherrer in 1920, I obtained a marked improvement in the perception of the particles. An entoptoscope was then built and made commercially available. Drs Loebl and Sinclair performed a number of clinical studies with this instrument, in particular the testing of the vision behind a cataract or in the case of eye trauma. Cataracts do not prevent the vision of the particles, which are the leukocytes moving in the capillaries of the macula. (such as see refs). We also demonstrated for the first time in humans the presence of retinal autoregulation in response to increases in IOP.
In the late 1970s, I got to know Dr Alan Laties, research director at the Scheie Eye Institute. We met a few times in Boston and at some point he suggested that I move to the Scheie Eye Institute of the U-Penn. I had obtained a “Carrier Development Award” from NIH and was also interested in the possibility of teaching, which I did not have at the ERI. Dr Laties’s proposal seemed to offer what I wanted and I moved to Philadelphia in 1979 as a tenured-track Associate Prof. of biophysics. Soon after, Dr Grunwald and Petrig joined me. Dr Grunwald had done his residency under Prof. Ben-Sira in Israël.
I had met Dr Petrig during a sabbatical period at the ETH in Zürich, where he was completing his PhD on binocular vision using random dots stereograms. His experience proved to be highly valuable for simulating the blue field phenomenon and advance the LDV technique.

Instrumental advances at that time included:

LDV/LDF: Fundus camera bidirectional LDV, on-line computerized analysis of Doppler spectra, near-ir and eye-tracking LDVs, optic nerve and subfoveal choroidal LDF

BFS: Simulation. Scheiner et al., demonstrated for the first time the time course of the increase in macular capillary blood flow induced by flickering light.

Grunwald et al., showed loss of autoregulation of macular blood flow in response to increase in IOP in glaucoma.

Phosphorescence Quenching by O2: Shonat et al. determined the PO₂ in the retinal vasculature and demonstrated in cats the autoregulation of this PO₂.
Investigations demonstrated the regulation of ONH, retinal and choroidal blood flows in animals and humans in response to \(O_2\) breathing, to increases and decreases of the ocular perfusion pressure, to flicker stimulation and to various pharmacological agents.

**Examples:** Response of RBF to hyperoxia, increases in OPP and RBF to flicker.

Regarding flicker, the investigations in the cat eye of Vo Van Toi and Riva demonstrated that the ONH and retinal blood flow changes induced by flicker were due to the activity of the ganglion cells. *J. Physiology, 1995.*

Buerk, Riva and Cranstoun studied the mechanisms of the flicker-induced blood flow response in the cat ONH and showed the role of NO, potassium ion and adenosine in this response.
Our laboratory was fortunate to have from its start in 1979 the full-time contribution of Juan Grunwald, who conducted a number of basic investigations of ocular blood flow and, after 1984 did extensive clinical investigations of retinal blood flow in diabetes. Using LDF, he has since 1994 measured subfoveal choroidal blood flow under various conditions (aging, AMD, etc) using a choroidal Doppler blood flowmeter developed in our lab at Scheie Eye Institute.
25 years ago, the Canton of Valais in the Southern part of Switzerland undertook a program to attract scientists and engineers to work in this rather beautiful alpine and wine region. Part of this program was to establish laboratories connected to the University of Lausanne. Prof Gailloud, from Jules Gonin had proposed to the authorities of the Canton to set-up a research laboratory in the field of ophthalmology and Vision and was looking for someone to direct this laboratory. Having spent a large part of my military service and many summers in the mountains there, I decided to give a try and in 1994 moved to Sion. Soon Dr Petrig joined me in this adventure.
Soon the group expanded and we benefitted from a number of collaborations with various researchers and visiting scientists. Among the projects and achievements in the field of ocular circulation, I would like to mention (see slide):

This led to a number of publications summarized in various chapters:

Describe findings

In 2003, I had to take mandatory retirement from the IRO and the University of Lausanne. On the suggestion of Prof. Emilio Campos, I moved part of the Lab to The Eye Clinic of the University of Bologna and was able to continue some of the instrumental work in collaboration with Prof Rovati from the Engineering department of the University of Modena and perform some clinical studies with the Eye Clinic of the University of Bologna.
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- Thanks also to my 4 sons. Although they were often puzzled by what I was doing and why I was doing it, they were always ready to come to the lab and volunteer for experiments.

- Last but not least: my wife, Liselotte, for her constant support, patience and tolerance. In many circumstances she shared my concerns and provided me with the most pertinent pieces of advice.