The relaxed confocal scanning laser ophthalmoscope

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ABSTRACT

The development of the Scanning Laser Ophthalmoscope is reviewed from a historical perspective. Since a flying-spot scanning principle for an electro-optical ophthalmoscope was first disclosed in 1950, enabling milestones have included the introduction of the laser and inversion of the usual Gullstrand's configuration of optical pupils in 1977, and the application of the optical principle of confocality by means of double or de-scanning in 1983. As a result, high resolution and high contrast confocal infra-red ophthalmoscopy with a 790 nm diode laser, at video rates, is a major novel imaging modality when compared to traditional optical techniques. This imaging mode is ideal to provide the necessary fiducial landmarks for microperimetry, therapeutic laser and SD-OCT based optical sectioning of the retina. DPSS or He-Ne lasers emitting at 532, 543, 561 or 575 nm are used for complimentary red-free fundus imaging. The diode 790 nm and DPSS 490 nm lasers are also used for fluorescence excitation.

KEYWORDS

Scanning laser ophthalmoscope, SLO, confocality, infra-red, retina, imaging

RÉSUMÉ

Le développement de l'Ophtalmoscope à Balayage Laser est revu sur le plan de son historique. Depuis la première présentation du principe d'exploration par point lumineux servant pour un ophtalmoscope électro-optique en 1950, le modèle de base a évolué vers l'introduction du laser et l'inversion de la configuration de Gullstrand usuelle pour les pupilles optiques en 1977, et vers l'application du principe optique de confocalité au moyen du double balayage ou du dé-balayage en 1983. Par conséquent, l'ophtalmoscopie à haute résolution et à haut contraste confocal par infra-rouge avec un laser diode de 790 nm, à des fréquences vidéo, représente une nouvelle modalité majeure en imagerie en comparaison avec les techniques optiques traditionnelles. Cette méthode d'imagerie est idéale pour fournir les repères de cadre nécessaires pour la micropérimétrie, laser thérapeutique et le sectionnement optique de la rétine basé sur le modèle SD-OCT. Les lasers DPSS ou He-Ne émettant à 532, 543, 561 ou 575 nm sont utilisés pour l'imagerie complémentaire du fond de l'œil en lumière anérythre. Les lasers diode de 790 nm et DPSS de 490 nm sont également utilisés pour l'excitation de fluorescence.

MOTS-CLÉS

Ophtalmoscope à balayage laser, SLO, confocalité, infra-rouge, rétine, imagerie

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INTRODUCTION

In 1951, coincidentally at the time of the 100th anniversary of the use of the optical ophthalmoscope by Herman von Helmholtz,[1,17-19,41,60] Harold Ridley [42,44] reported on a method to build an electronic version of this instrument by two of his collaborators at St. Thomas' Hospital in London, England. The flying spot from a cathode ray monitor with an appropriate fast and strong phosphor would be used for its projection onto the retina in a raster like fashion. The returning light was collected by a sensitive photocell and after amplification and conditioning this signal was to be displayed on a television monitor (Fig. 1). It did not work, though a related optical instrument invented by Young and Roberts in 1951,[65] the flying-spot microscope, was operational.[45] The insurmountable problem in the case of the ophthalmoscope was that conventional thermal light sources, however powerful and regardless of the ingenuity of the optical projector, cannot concentrate enough light power onto a small enough spot size on the retina to generate enough backscattered light to reach the photo detector in a very small amount of time (Fig. 2). The microscope can use a thermal light source to generate enough power in the spot because it can scan at much lower speeds with a large lens aperture. Unavoidable eye movements are a reason why a high scanning speed is necessary in ophthalmoscopy. Also the relatively small optical aperture of the anatomical pupil is a second factor limiting available power density. The advent of the laser and mechanical scanning devices such as the galvanometer and polygon mirror would in time solve this problem. In 1958 Schawlow and Townes formulated a method to extend the action of the maser into the optical spectrum of wavelengths.[47-48] But the first practical laser which had a ruby crystal medium and emitted pulsed radiation at 694 nm arrived only in 1961.[27] The He-Ne, krypton and argon gas lasers radiating continuously at better visible wavelengths, and infra-red solid state lasers would follow even later. By then, Harold Ridley and his collaborators had already stopped working on their project.

Although the efforts to build an electronic or flying spot ophthalmoscope failed, Harold Ridley experimented more successfully with television ophthalmoscopy,[43] in which an optical front-end camera was coupled to a vidicon television tube. These two distinct endeavors have sometimes been confused in the literature. Harold Ridley and Charles Schepens shared many research interests and facts of life, both died at the age of 94 shortly after having received a major governmental award, the Knighthood of the British Empire for Harold Ridley, The Legion of Honor for Charles Schepens.[2]

THE RELAXED CONFOCAL SCANNING LASER OPHTHALMOSCOPE

Pomerantzeff's principle

In 1977, shortly after working on the equator-plus wide-angle fundus camera, Oleg Pomerantzeff realized that it should be possible to invert the optical principle of the fundus camera and use the central portion of the anatomical pupil of the eye for illumination of the retina, and all of the larger surrounding area of the pupil for light collection from the retina. A major motivation for his idea was the potential for reducing the intensity of the illuminating light source. Part of his handwritten recollection of the invention is reproduced in the editorial. His approach would require scanning a thin pencil of laser light around a pivot point situated in the anterior segment of the eye. Such an instrument was built over a period of three years by his collaborators Robert Webb and George Hughes.[38,64] In 1980 a graduate student, Ulrich Klingbeil, and his collaborators working in the laboratory of Joseph Bille at Heidelberg University, reported on a similar concept [21-23,33-34] and he completed a thesis project on the scanning laser ophthalmoscope in 1982.[20]

Largely dependent on wavelength of illumination and pigmentation factors within the eye,[3,8,39] about 2 to 4 % of incident light is returned from the fundus. The anterior corneal surface is also

reflecting about 2 % of this light. Hence a fundamental problem in ophthalmoscopy to separate these two sources of reflection. Gullstrand's principle not only requires that the optical pupil(s) of observation and the illumination pupil are distinct in the plane of the anatomical pupil of the eye, but also spatially separated as much as possible, not just to eliminate the specular reflections from the cornea of the powerful light source - something already done since the time of Helmholtz, but also to avoid stray scattered light generated mostly in the cornea and lens, which upon returning to the observer would reduce significantly the contrast of the retinal image.[15-16] Inverting or rearranging the Gullstrand configuration as it is practiced in indirect ophthalmoscopy and the fundus camera was exactly what Oleg Pomerantzeff had in mind. This rearrangement is called Pomerantzeff's principle by Charles L. Schepens.[49] It is important to realize that a separation of optical pupils still exists, requiring dilation of the anatomical pupil and the insertion of an effective optical stop in a pupillary conjugate plane within the instrument. This type of optical configuration has therefore also been called co-pupillary (Fig. 3).

In this early co-pupillary configuration, a typical entrance laser beam diameter of about 1.0 mm is used. The Gaussian beam profile of the gas lasers permits diffraction limited focusing on the retina. The location of the scanning pivot point - or rather volume - is manually positioned and optimized within the anatomical pupil. All of the returning light through the pupil, minus the stopped reflections, is detected with a photomultiplier tube and amplified into a standard video signal. This video signal is displayed on a TV monitor, synchronously with the original scanning. Various visible krypton (568.2 nm), argon (488 nm, 514 nm) and He-Ne (632.8 nm) wavelengths or a combination of these were used for obtaining monochromatic red-free images, fluorescein angiographic video and color images, but no infra-red was experimented with at the time, probably because the results had been disappointing with this wavelength in optical fundus imaging. Images were expected to be, and effectively looked similar to, ones taken with a classic fundus camera. Thus, the main advantages of the instrument so far were a significant light saving and real-time video capability. A retinal irradiance of about 50 μwatt/cm^2 or less at 632.8 nm compares favorably with peak power densities used in fundus photography. But being equivalent to 25,000 trolands, it is still capable of bleaching half of the photo pigment concentration in a matter of minutes.

In addition, graphics could also be projected onto the retina. At first by positioning a perforated neutral density filter at a retinal conjugate plane within the instrument, reminiscent of a technique developed by Trantas for the direct optical ophthalmoscope. Then shortly after by elegantly modulating the scanning laser beam with the help of an acousto-optic modulator [61-62] under video control.

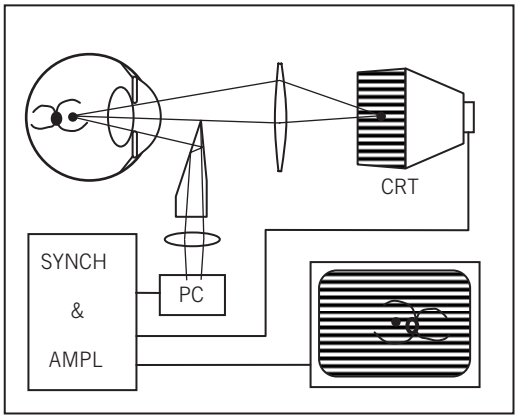

Fig. 1. The "Ridley era" design

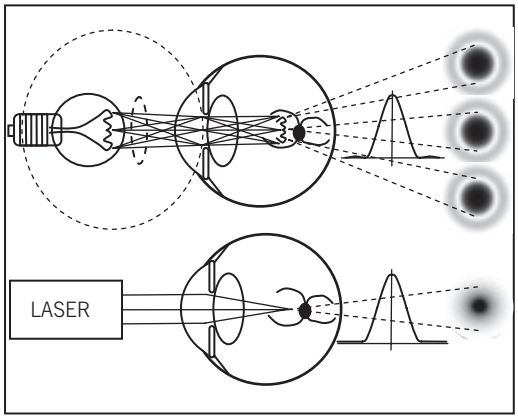

Fig. 2. Coherent vs non-coherent light

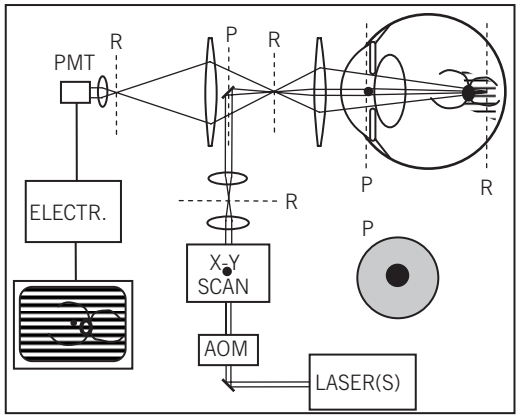

Fig. 3. Pomerantzeff's priciple

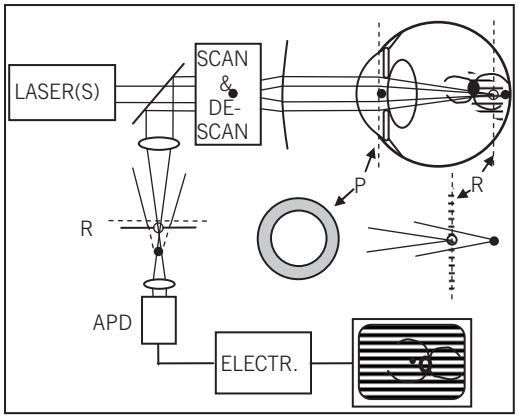

Fig. 4. Minsky's concept applied

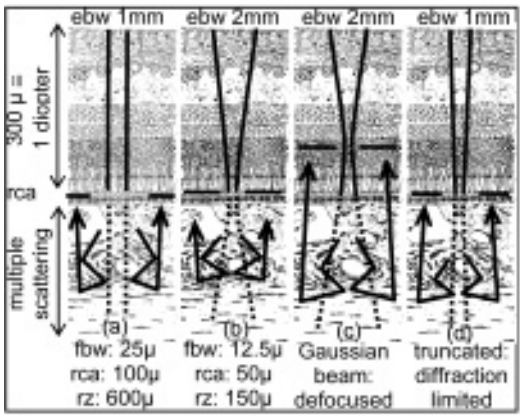

Fig. 5. Beam profiles and confocality

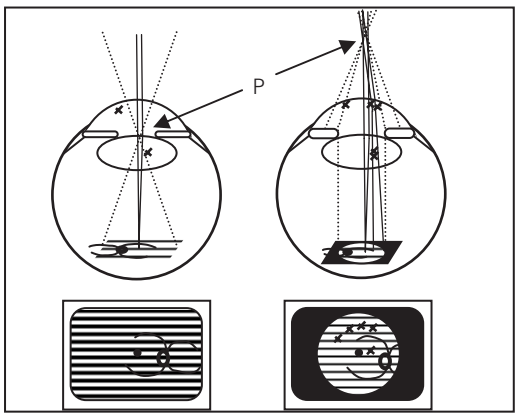

Fig. 6. Maxwellian illumination view

THE CONFOCAL OR DOUBLE SCANNING PRINCIPLE

In 1957 Marvin Minsky, then and now still at MIT,[31] made a fundamental contribution to microscopy by inventing the confocal imaging concept based on a double scanning method.[29-30] He also moved the object on a translational stage, permitting a stationary light source to be used. Both a transmissive and a reflective configuration were realized. Minsky was interested in visualizing brain cells with his microscope. In brief, a point-like source of light was focused to a similarly small spot inside biological tissue. This was accomplished with a large aperture focusing lens. The same aperture served for light collection and a beam splitter directed the backscattered light onto a pinhole of similar dimensions as the illuminating spot. In this fashion, multiply scattered light that was coming from other layers or adjacent spots within the tissue was stopped by this confocal aperture. The detector behind the aperture turned the light intensity into a video signal suitable for display on a TV monitor, synchronously with the movement of the translation stage. In this optical configuration Gullstrand's principle is no longer necessary. Therefore, the same entrance and exit pupil can be used by the light.

In 1983 Cohen-Saban and his collaborators at the Institut d'Optique de Paris used this optical construction for modifying the scanning laser ophthalmoscope of Pomerantzeff and Webb (Fig. 4). By means of de-scanning, the laser light source became again stationary as in Minsky's original

application. The collimated laser source could then use a fairly large anatomical pupil for both illumination and detection purposes. Thus, a confocal scanning laser ophthalmoscope was realized for the first time.[5-7] As an advantage, the relatively large diameter of the collimated laser beam could focus to a very small spot. In addition, their catadioptric design neutralized some spurious reflections from lenses in the original co-pupillary dioptric configuration.

Webb and Hughes realized a catadioptric confocal instrument based on back-scanning in 1987.[61,63] Instead of a beam splitter, they used an equivalent pinhole configuration to separate the retinal backscattered light from a smaller diameter incident laser beam. A non-polarizing beam splitter would waste a lot of the laser beam energy in this situation.

It was discovered that the virtual confocal pinhole could not match the theoretical size of the focused laser spot within the retina as in a scanning laser microscope, but had to be much larger when scanning at high video rates within the eye. A true tight confocal aperture would render the instrument again light starved. This fact explains our usage of the word ''relaxed'' as an adjective to the word ''confocal''. Also, infra-red laser sources had by then become readily available and the clinicians wanted to use these to avoid the need for a medical dilation of the anatomical pupil, taking further advantage of the possibility to use the optical entrance pupil also as the exit pupil (Fig. 5).

Infra-red light penetrates more easily through the optical media and has a reduced absorption both by melanin and the hemoglobins when compared to wavelengths shorter than 585 nm.[3,8,9,39] As a result, the backscattering of the strongly increased diffuse and lateral multiple scattering of the infra-red light in the choroid reduces very significantly the contrast in conventional optical infra-red fundus images (Fig. 8) - and the same phenomenon would occur in a co-pupillary SLO design. The relaxed confocal aperture fortuitously blocks this particular backscattering just enough. Therefore infra-red relaxed confocal images preserve the look and feel of monochromatic images taken with either the scanning or optical ophthalmoscope in the visible wavelength range, except for variations due to the absorption characteristics of the yellow pigment, hemoglobins and melanin. Compared to figure 8, figures 7 and 11 are a high contrast representation of the fundus using infra-red illumination and such confocal detection. A complimentary Tyndall or indirect viewing modality in which the confocal aperture is replaced by a central stop will collect only the multiple scattered light.[63] Atypical ''glowing'' images of drusen and pigment epithelium detachments have thus been obtained,[52,57] sometimes leading to a pseudo stereoscopic appearance of irregularities of Bruch's membrane.[40]

Interestingly, in their original patent Pomerantzeff and Webb discussed the possibility of confocality to limit the detection of light to the vicinity of the illuminated fundus surface. For this purpose they proposed using a low resolution spatial detector at a retinal conjugate plane, essentially the equivalent of scanning a single element detector.[38]

In 1989, Plesch and Klingbeil who was then also a visiting scientist at Schepens, reported on a similar confocal scanning laser ophthalmoscope that was commercialized by the Rodenstock company. It used argon 488 nm and 514 nm, He-Ne 632 nm and a diode 790 nm laser sources, equipped with an acousto-optic modulator for the He-Ne laser and two interchangeable small or large fields of view with different magnification.[35-36] For this last feature, a reversible ''Campini-Herschel'' telescopic mirror arrangement [14,28,32] was inserted between the galvanometer mirror and polygon scanning elements. This construction adjusted optically the Gaussian beam diameter and horizontal angle of scanning. The vertical angle of scanning was as before controlled by varying the angular amplitude of the galvanometer mirror. Using 488 nm laser light, excellent high resolution and high contrast fluorescein angiographic transits could be video recorded (Fig. 9). Similarly, the 790 nm light source has been used for obtaining indocyanin green angiograms.

A characteristic of the optical zoom is that compared to the original electronic zoom of the laser raster the focused laser spot size will vary relative to the laser raster dimensions. Figure 5 b demonstrates that a wider e.g. double-sized diameter Gaussian entrance beam will result in a smaller half-sized spot diameter and a 4 times smaller depth of focus or Rayleigh zone. This

gives rise to a depth resolution that may be used for tomographic purposes, though an optical coherence based technique (OCT) would be much better suited for this purpose (Fig. 7).
New compact and powerful solid state lasers of different wavelengths may have an output profile that is non-Gaussian and less than optimal. In practice this problem is addressed by a spatial filtering and truncating of the original beam. The resulting beam profile will be neither completely smooth nor a pure Gaussian or top-hat. By changing the truncation ratio, it is possible to reduce the collimated illuminating beam diameter - an advantage - and still obtain a small enough diffraction limited spot on the retina, though there will be a loss of laser efficiency. Also, the depth of focus will become somewhat larger (Fig. 5 d).[46]
In preparation of figure 5 showing the laser scanning beam traversing the retina, the following assumptions were relied upon. Because the backfocal length of the eye (22.72 mm) is much smaller than the depth of focus (Rayleigh zone) of the collimated entrance laser beam (0.5 m), Gaussian beam formulas can be reduced to the expressions in references 46 and 56. Then the eye-focused Gaussian beam waist is located at the focal plane of the eye optics, and so is the virtual confocal aperture. The retina is considered to be transparent; specular reflexes from its surface are ignored. A variable patterned absorption by melanin and the hemoglobins occurs at the level of the retinal pigment epithelium and choroid; the remainder of the light is then multiply scattered in all directions and depolarized. While the laser beam waist is scanning to the next distinct picture element, it should not cause overlapping when in focus (at least considering a FWHM defined diameter). But the multiply scattered light ultimately returned from the eye will still originate from largely overlapping volume elements, even in the presence of a smallest possible confocal aperture.
The spatial intensity distribution of the focused laser spot at the retina (Fig. 2 b) - and consequently the resolution and contrast of the retinal image - not only depends on the previously discussed beam characteristics, but also on the refractive state of the eye and any scattering or deflection by the optical media. The pivot point of the scanning laser beam can be optimally positioned within the anatomical pupil of the eye to minimize aberrations. The Maxwellian view illumination used by the SLO allows the positioning of the scanning pivot point in front of the anatomical pupil of the eye. It is then possible to evenly transilluminate the optical media as illustrated in figure 6. Pathology such as corneal changes, floaters and cataracts can cause a deflection and scattering of the illuminating laser beam. As a result, less light is returned through the confocal aperture and this darkens the retinal background image in certain areas [56] - as would defocus (Fig. 5 c). Without confocal detection this qualitative representation of the optical quality of the eye would not be possible. As an example, figure 10 shows the impact of a too small optical zone after excimer ablation of the cornea. Because of the video capabilities of the SLO, the dynamics of floaters can also be documented in a similar fashion.[58-59]
The instrument can focus on the anterior segment as well, bypassing the eye optics. Since the infra-red laser that is used for imaging elicits no pupillary constriction response, an additional variable intensity visible laser scanning source can be used to cause pupillary constriction. Pupil dynamics are thus recordable (Fig. 12).
Diode pulsed solid state (DPSS) or He-Ne lasers emitting at 532, 543, 561 or 575 nm [50] are used for complimentary red-free fundus imaging. As mentioned, wavelengths shorter than about 590 nm will cause the SLO image to look and feel like a classic optical fundus image, largely independent of confocality. Some subtle differences between the above mentioned green-yellow wavelengths with regard to the absorption by either melanin or the hemoglobins merits citation.[3,8-9,39]
All avoid absorption and masking of retinal details by the xanthophyll pigment. The longer the wavelength, the less absorption by melanin and more light should therefore be available for backscattering from the eye. With shorter wavelengths, the relative proportion of the specular component from superficial retinal layers and epiretinal membranes should be increased. The predominant oxyhemoglobin has two closely spaced absorption peaks respectively near the 532 nm and 575 nm wavelengths. The wavelengths of 543 nm and 561 nm fall slightly on either side of the single intermediate peak of hemoglobin absorption. It thus appears that for maximum

contrast in visualizing blood or pigment in dark individuals one would tend to use the higher wavelengths, and if superficial retinal detail is to be seen in lightly pigmented persons one would choose the shorter wavelengths. For economical reasons, at present 532 nm would be more than acceptable for all variations of purpose and pigmentation, especially if combined with a 635 nm for further distinction between melanin or hemoglobins. Stereoscopic clues of depth location might also be helpful in this respect. Both 532 nm and 635 to 660 nm happen to be also complimentary for scotopic and photopic microperimetry.

DPSS lasers and He-Ne lasers have a much better circular Gaussian beam shape compared to the natural astigmatic and elliptic output of diode lasers used for IR imaging. Verification of a clean focusing capability with the help of a beam profiler is necessary to ensure that the fundamental prerequisite for scanning laser ophthalmoscopy, i.e. the capability of focusing enough light on a small enough spot, is met. Often this advice is unheeded in the construction of scanning laser ophthalmoscopes with a drastic reduction in the MTF as a result. Also, the peak to peak noise level of the CW lasers has to be less than 5 percent with an even better RMS value, otherwise this noise will appear in the signal from the photodetector.

Tight confocality aiming at tomographical sectioning of the retina was further pursued in the laboratory of Bille in Heidelberg,[4,10-11,25-26] where Liang used adaptive optics for the first time. However, scanning laser ophthalmoscopy is not the ideal approach for tomography due to the fairly large depth of focus, the Rayleigh zone, of the laser (Fig. 5). Optical coherence techniques are far better suited for this purpose and several methods will be further discussed in this volume by de Boer and Podoleanu. An adaptive optics capable scanning laser ophthalmoscope is however still necessary if one wants to further reduce the lateral ''x-y'' resolution of the instrument. Such an endeavor is reported upon in this volume by Roorda.

Polarization of light is an important issue in ophthalmoscopy since the cornea and nerve fiber layer are birefringent, and polarized light will become unpolarized in tissue when multiply scattered. Polarization sensitive scanning laser ophthalmoscopes where constructed early-on [12-13] and the current state of the art is discussed in this volume by Zhou and Huang.

Pomerantzeff and Webb also proposed using their instrument as a photocoagulator.[38] Their approach of using the same scanning laser for imaging and therapy was not pursued, but we used part of the high resolution and high contrast infra-red video images of a confocal instrument to serve as a fiducial landmark, while coupling the instrument experimentally with various external light sources by means of a beam splitter. These external light sources can include lasers for PDT, TTT and microphotocoagulation,[51-55] and may involve the use of an external liquid crystal on silicon (LCOS) chip for graphics projection or the combination with a scanning beam for spectral domain OCT (SD-OCT) purpose.

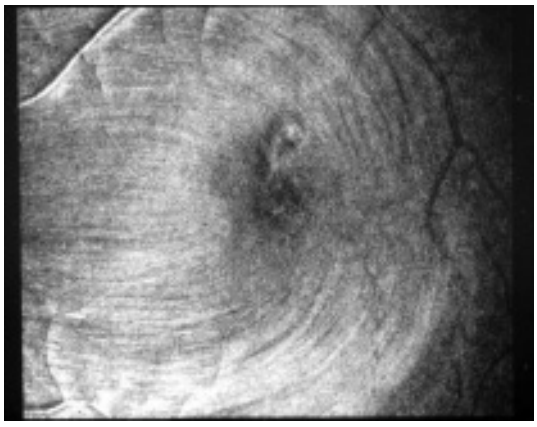

Fig. 7. IR SLO nerve fiber layer

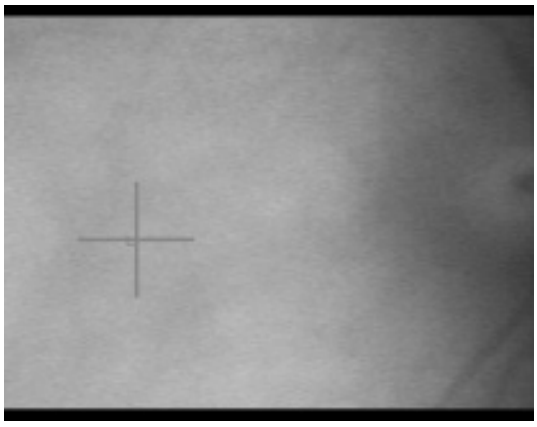

Fig. 8. IR optical fundus image

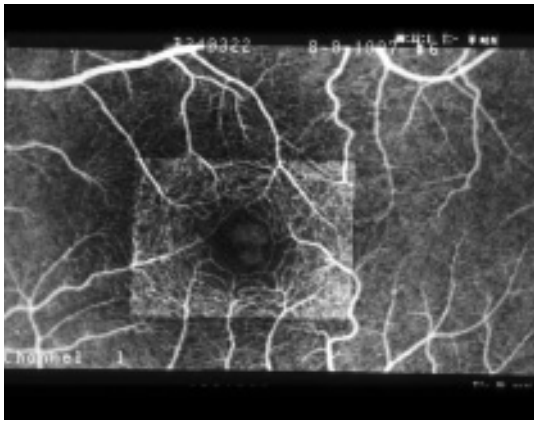

Fig. 9. SLO fluorescein transit macula

Fig. 10. SLO overview of optical media

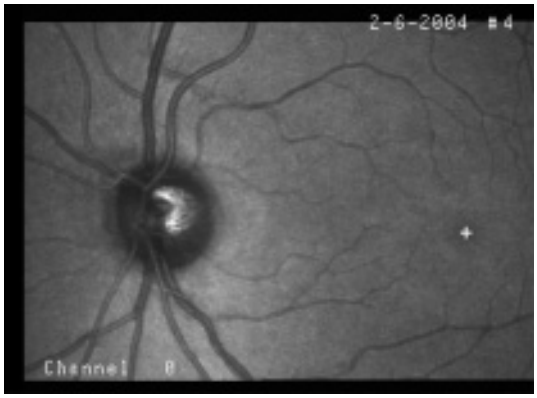

Fig. 11. IR SLO overview - optics disc

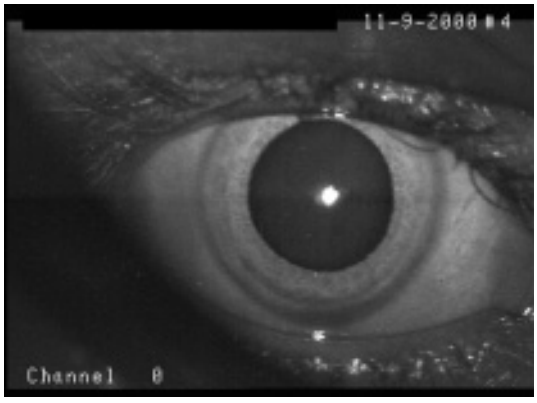

Fig 12. IR SLO - dynamic pupil study

CONCLUSION

From a clinical relevance point of view SLO imaging is unique and useful in many respects. Relaxed confocal high contrast and detailed infra-red fundus still images and video have ample specular content capable of visualizing the nerve fiber layer (Fig. 7). They also reveal subtle pigment variations of the retinal pigment epithelium within the macular area, unimpeded by the xanthophyll yellow pigment (Fig. 7). The transmission and backscattering of infra-red light through the optical media is higher than with any other visible wavelength. We also found that subtle variations in water content of the retina or subretinal space, caused by edema, are easy to observe. We can see well through the retina from the nerve fiber layer into the suprachoroidal space due to a large depth of focus, and thus we obtain a comprehensive image that the clinician is so much accustomed to in traditional ophthalmoscopy. Spatial variations in optical quality of the media of the eye can be evaluated. The invisibility of the infra-red light offers many advantages. Additional wavelengths within the instrument are used for microperimetry (discussed later in this volume), video fluorescein angiography and red-free imaging thereby providing the same or more clinical information than color fundus photography alone would do.

At this point, it would be a natural extension of the SLO to be capable as well of a simple slit lamp like biomicroscopic sectioning of the retina and RPE-choriocapillary layer complex: when an abnormality is detected by the clinician in the ''x-y'' plane, it should be straightforward to obtain a relevant precision reflectivity profile or ''cut'' in the ''z''-direction not hindered by eye

movements or the lack of fiduciary landmarks. These drawbacks are still present in all current TD-OCT systems that use an optical image for anatomical referencing. To accomplish this goal we are currently developing an SLO not only with microperimetry but with concurrent real-time video rate SD-OCT capabilities as well.

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