The Essentials in Ophthalmology series represents an unique updating publication on the progress in all subspecialties of ophthalmology.

In a quarterly rhythm, eight issues are published covering clinically relevant achievements in the whole field of ophthalmology. This timely transfer of advancements for the best possible care of our eye patients has proven to be effective. The initial working hypothesis of providing new knowledge immediately following publication in the peer-reviewed journal and not waiting for the textbook appears to be highly workable.

We are now entering the third cycle of the Essentials in Ophthalmology series, having been encouraged by readership acceptance of the first two series, each of eight volumes. This is a success that was made possible predominantly by the numerous opinion-leading authors and the outstanding section editors, as well as with the constructive support of the publisher. There are many good reasons to continue and still improve the dissemination of this didactic and clinically relevant information.

G.K. Krieglstein  
R.N. Weinreb  
Series Editors  
September 2008
This third volume in the series, *Essentials of Ophthalmology*, just like the first, seeks to bring the ophthalmic practitioner up to date in the important new advances or changes in glaucoma diagnosis or management that have occurred over the last ten years. The last decade has seen significant changes in our understanding of the pathophysiology of some glaucomas, in our diagnostic approaches and in our management of them. Toward the goal of providing the most up-to-date information in a readable fashion, we have asked some of the world’s experts to discuss areas to which they have contributed in a way that will be useful for the practicing doctor. For example, one of the pioneers in the imaging of live ganglion cells is Dr. Francesca Cordeiro. Her studies could lead to a potentially significant breakthrough as, in the future, clinicians may be able to determine the health and number of ganglion cells in the retina as both a diagnostic and monitoring test. As the prevalence of glaucoma increases in our aging population, epidemiology has become more important as a methodology to identify risk factors; Drs. Giangiacomo and Coleman discuss what we have recently learned that is relevant to our clinical understanding of glaucoma. Drs. Doshi, Weinreb and colleagues describe the diurnal fluctuation of intraocular pressure, how those fluctuations impact on glaucoma, the relationship of postural change to that fluctuation, and what it means for managing glaucoma. Detecting progression of glaucoma can be tricky. Imaging techniques may be helpful. Strouthidis and Garway-Heath tell us how. Our concepts of and terminology for angle-closure glaucoma have undergone major changes over the last few years. Sharma, Low and Foster describe these changes and introduce the new—now internationally agreed upon—terminology. The association of uveitis and glaucoma has been known and has frustrated those caring for patients with these two concurrent conditions for many years; Drs. Nagpal and Acharya discuss the interrelationship between uveitis and glaucoma, what the doctor should look for, and how to manage these difficult patients. New approaches to glaucoma surgery have been described recently. Drs. Mendrinos and Shaarawy describe the techniques and results of nonpenetrating glaucoma surgery. Drs. Tam and Ahmed describe and discuss several new approaches to glaucoma surgery using special shunts that have appeared in the past few years. As electronic medical record systems gain popularity around the world, Drs. Schargus and Grehn describe the European Glaucoma Society’s electronic glaucoma record and their agreement on what is important to include in such a system. We hope that all the topics and authors that we have selected are helpful in improving the understanding of the many faces of glaucoma and, ultimately, will contribute to reduced visual loss and better care for our patients.

Franz Grehn
Robert L. Stamper
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Chapter 1

Imaging Individual Ganglion Cells in the Human Retina

Nicholas E.H. Nick Wood, Li Guo, M. Francesca Cordeiro

1.1 Introduction

Glaucoma is a leading cause of blindness worldwide [1] and it is expected that the number of people with the disease will rise dramatically by 2020 [2]. Diagnosis is traditionally from changes in the optic nerve head (ONH) and visual field loss, but these can only detect the disease after significant (25–40%) loss of retinal ganglion cells (RGCs), the key cell implicated in this process [3, 4].

The inner retinal layers, being optical media that are therefore transparent to visible-frequency light, are inherently low contrast. This presents a significant challenge for traditional imaging such as fundus imaging. Modern technologies now use many different properties of light to differentiate between the retinal structures and these technologies are enabling us to observe fine detail, such as the photoreceptor layers, in vivo [5].

Recent advances have allowed unprecedented access to the retinal layers, creating the possibility of potentially visualizing ganglion cells in order to provide a new and early clinical parameter for glaucomatous injury. This chapter aims to cover the current research achievements in RGC imaging and the promising directions they are taking visual science.

1.2 Description of the Imaging Techniques

- **Scanning laser polarimetry (SLP):** A confocal imaging system with a polarimeter to measure the birefringence caused by the retinal nerve fibre layer (RNFL)
- **High-resolution reflectance imaging:** Based around a fundus camera with a high-quality CCD camera, this system can take a sequence of rapid images which can measure wavelength-dependent reflectance changes with very high temporal resolution
- **Optical coherence tomography (OCT):** A low-coherence interferometry-based imaging system where changes in reflectivity are measured in a volume of the retina with very high axial resolution
Confocal scanning laser ophthalmoscopy (cSLO): A confocal imaging system which uses a fine confocal aperture to limit the light detected to that from the focal plane, and therefore achieves high lateral resolutions.

Adaptive optics (AO): An adaption which uses a patterned guide laser to sense errors in the optics of the eye and a deformable mirror to correct for them in real time.

Retrograde labelling of RGCs via direct application of dyes has enabled the analysis of ganglion cell number and morphology in numerous studies with animal models.

RGC-specific fluorescent protein expression has been developed in a number of mouse lines to enable RGC identification and subtype study.

The detection of apoptosing retinal cells (DARC) uses an injection of fluorescently labelled annexin-5 which binds to the membrane of apoptosing cells to act as a marker for RGC disease.

Summary for the Clinician

- Glaucoma is the leading cause of irreversible blindness if left untreated, and current methods will only detect it when significant damage has already been done.
- RGCs are the key cells implicated, and observing them could lead to effective treatment and monitoring regimens.

1.3 The Imaging Techniques

The imaging of cells in living systems poses numerous problems, as (unlike histology) it involves direct exposure of living tissue, and even relatively innocuous staining compounds bind to cell constituents and therefore may interfere with cellular function. Intrinsic cellular properties are therefore sought that allow them to be resolved from the surroundings. The RGCs in particular have proven a challenge to image, but modern techniques taken from other fields such as cell biology and cosmology are beginning to yield some insight into their morphology and behaviour in vivo.

Many techniques have recently been developed to assess the RNFL thickness, as its thinning is associated with glaucomatous progression [10]. In real terms, this thinning process represents the large-scale loss of the RGC axons. However, higher resolutions are needed to gain access to individual cell bodies, and here we discuss the most current methods and some of the promising directions the research is taking.

1.3.1 Scanning Laser Polarimetry

First reported by Weinreb et al. in 1990 [11], the basic layout of this can be seen in Fig. 1.1. This is based on the linear relationship between the birefringence and thickness of the RNFL. Birefringence is a quality of highly ordered optical media such that they exhibit polarising properties and refractive indices that are dependent on the polarisation of the incident light. This can be detected by a system with polarisation-sensitive detectors. The parallel microtubule structures in the RNFL cause birefringence and the degree of birefringence is dependent on the tissue thickness. This measure has been shown to be sensitive and specific and, unlike the cSLO technology (Heidelberg Retinal Tomography (HRTIII), Heidelberg Engineering Vista, CA, USA), it has the advantage of not requiring the operator to provide reference points [12]. The cornea had previously been a problem in SLP imaging, as it also has a degree of birefringence. The current incarnations of the commercially available machine (the GDx, Carl Zeiss Meditec, Inc., Dublin, CA, USA) have overcome this [13] with a variable corneal compensator (VCC-SLP) which uses the macular as a reference point non-birefringent to gain a measure of the corneal birefringence. This was followed by the enhanced variable compensator (ECC-SLP), which avoids problems with low-quality images [14] by using software correction. The machine is still limited to measuring the RNFL thickness though, and is therefore not as versatile as the other devices in terms of RGC cell body assessment.

Summary for the Clinician

- SLP uses the polarisation change imparted on incident light by the RNFL to measure its thickness.
- VCC and ECC have been developed to counter problems with corneal birefringence.
- The machine is limited to RNFL thickness analysis.

1.3.2 High-Resolution Reflectance Imaging

This uses a high-quality, high-speed CCD attached to a fundus camera with a method for the illumination of the retina in time with image detection. The sensitivity of the camera allows for very accurate measurement of reflectivity changes. The stimulation of nervous tissue has been shown to cause reflectivity changes [15–17]. Such changes are most likely due to changes in membrane reflective index or morphology and can be detected with the sensitive camera to give an indication...