Glaucoma: Macrocosp to Microcosm
The Friedenwald Lecture

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 Jonas Stein Friedenwald, the son and grandson of ophthalmologists, was born in Baltimore in 1897. He attended Johns Hopkins Medical School, graduating in 1920. After medical internship, he spent 1 year studying ophthalmic pathology with Fredrich Verhoeff (Harvard), had a 1-year preceptorship with George de Schweinitz (Philadelphia), and then began practice without further training. He seemed not to need it.

He was in charge of “Ophthalmic Pathology... and directed the lion’s share of research activities of the Wilmer Institute” from 1923 to his death in 1955.1(p24) He excelled at the correlation of clinical and pathologic findings, as continued by A. Edward Maumenee and W. Richard Green at Wilmer after him. He was described as a “many faceted genius,” accomplished in physics, mathematics, chemistry, and ophthalmology. In his 1949 Proctor Lecture,2 he summarized evidence that the formation of aqueous humor was an energy-dependent, enzyme-driven process. These ideas led to the development of carbonic anhydrase inhibitors for glaucoma treatment. He placed the calibration of the Schiotz tonometer on an experimental, scientific footing and studied “ocular rigidity”—an area engaging the glaucoma field at present in the interaction between cornea and tonometry. 5

He wrote on the relation between art and vision mechanisms and detailed legal theory with his friend, Supreme Court Justice Felix Frankfurter. Norman Ashton wrote of Jonas: “His intellectual grasp of scientific problems and his remarkable knowledge of many widely different fields of art and learning made him a quite exceptional person by any standards.”4(p58) He was instrumental in the development of Hadassah Hebrew University Medical Center in Israel, visiting in 1936 and 1945 and lecturing in Hebrew.

Robert Moses, his student and colleague, wrote: “He applied physics in his studies on tonometry, chemistry to his work on aqueous secretion. . . . and optics in his design of an advanced ophthalmoscope. . . . If a given problem needed knowledge he did not possess, he simply got some recent books on the subject, sat down and studied.”4(p58) Wilmer Chairperson Alan C. Woods stated: “When the pathogenesis of chronic glaucoma is finally resolved and understood, I am confident that the solution will rest largely on the foundations laid down by Jonas Friedenwald.”1(p26)

During his 32 years of scientific work, he “devoted himself tirelessly to a large practice. He was never too busy or too tired to give his skill, his attention and his time to any needy or ill patient.”1(p27) Thus, Jonas Friedenwald was the epitome of an ophthalmic clinician scientist. He is a role model to whom all of us can aspire. As I walk the halls of Wilmer, caring for glaucoma patients and chasing the mysteries of this disease, I have often felt the presence of this gentleman giant whose portrait gazes at us from the wall of the Friedenwald Library. I could not hope for a greater honor than to receive an award in his name.

The Setting

I had the good fortune to work as a student in the laboratories of Nobelist George Wald and past ARVO awardees Jay Enoch and John Dowling. I was first intrigued by glaucoma in 1973, challenged by friend and teacher Irvin Pollack and by my ophthalmic father Ed Maumenee. At that time, angle closure and open-angle glaucoma (OAG) had been conclusively distinguished by gonioscopy, while optic disc photography and Goldmann perimetry produced standardized evaluations of nerve damage, and eye drop therapy was becoming somewhat more acceptable. Laser iridotomy was in its infancy, and laser angle treatment was 5 years off. We did the first trabeculectomy at Wilmer that year.

But, OAG was then considered a disease of “elevated” intraocular pressure (IOP). We were puzzled by the occurrence of high IOP in many persons with no disease, while some OAG sufferers had normal IOP. Epidemiology had scarcely been applied to determine the prevalence of OAG (except by Mansour Armaly3 and Fred Hollows (Hollows and Graham5)), nor were its risk factors clear. Clinical changes observed in the optic disc were not understood histopathologically. Fields seemed to remain “normal” while the disc increasingly “cupped,” then function rapidly worsened, confounding our understanding of the rate of progression. It was often said that OAG was a disease that couldn’t be diagnosed properly and for which treatment wasn’t proven to work.

In this report, I will describe aspects of OAG that we now understand better, focusing on subjects that I have studied in collaboration with many colleagues. In each area, the remaining challenges will be highlighted.

The Macrocosp

OAG Defined

OAG is now defined as a disease of retinal ganglion cells (RGCs), characterized by structural change in the optic disc that is best described as excavation, and by a typical, slowly progressive loss of function that begins in the midperipheral field and expands both toward the center and peripherally. There is considerable variation in the normal appearance of the optic disc7–9 and in the number of RGCs from one person to...
Incidence and Progression

To analyze how OAG affects populations, I estimated its incidence—the number of new cases per year at each age. While this might be calculated by serial examinations of large groups over extended periods, Leske, Edener, and Podgor suggested that incidence could be inferred from age-specific prevalence of OAG. This results from two key features of OAG: once present, it does not go away; and persons with OAG do not die of OAG. This results from two key features of OAG: once present, it does not go away; and persons with OAG do not die of OAG. This results from two key features of OAG: once present, it does not go away; and persons with OAG do not die of OAG.

It is now clear that OAG incidence increases with age, so that there is a more than linear increase in prevalence from younger age groups to older ones. Using this approach, Susan Vitale and I estimated OAG incidence for European- and African-derived persons. Direct estimates by follow-up examinations have corroborated our measures. It is now clear that OAG incidence increases with age, so that there is a more than linear increase in prevalence from younger age groups to older ones. Using this approach, Susan Vitale and I estimated OAG incidence for European- and African-derived persons. Direct estimates by follow-up examinations have corroborated our measures. It is now clear that OAG incidence increases with age, so that there is a more than linear increase in prevalence from younger age groups to older ones.

The progression rate for OAG with and without therapy has been studied recently. It was widely believed that many persons with glaucoma lose useful vision. On the contrary, population studies document that fewer than 10% of those with OAG become bilaterally blind. Some clinic-based data appeared to show worse outcomes, but those in the care system typically have more severe disease. To estimate progression rate, we used a similar method to that for estimating incidence from prevalence—namely, we calculated mean damage in younger compared with older OAG patients. The resultant slow progression estimated by this method was confirmed in clinical trials, as well as in our own longitudinal studies. Approximately 4% of those with OAG have progressive field loss each year of treated follow-up. With an average length of disease of 15 years, only 60% would be expected to have any progression, and most do not become significantly impaired.

Some have (wrongly) concluded from this finding that “OAG isn’t that bad.” OAG blinds a modest proportion of those with the disease, but since it is a highly prevalent disorder, this small proportion is a large absolute number. Furthermore, our estimates are the mean worsening rate—there are some persons who are injured much more quickly than average. Those who develop OAG early in life are exposed to the risk of progression for longer times. It is vital that we develop better methods to measure progression so that aggressive treatment can be offered to these individuals at greater risk, while preventing those with a more benign course from suffering the side effects of therapy.

It can be estimated that 1.3 million ocular hypertensive (OH) OAG suspects are receiving topical preventive therapy in the United States. If the life-table model is applied, it is estimated that the average OH lives 25.5 years from onset to death, with nearly 50% moving from OH to OAG status in their lives (2% per year). Treatment is estimated to cut this conversion rate in half, sparing 325,000 persons (25% of the total) from OAG. Conservatively, the unilateral blindness rate from treated OAG is 20%; hence, 65,000 eyes per year are likely to be saved from blindness by OH treatment. Annual prostaglandin therapy costs over $800 per year. Thus, with 25 years of therapy in 2004 dollars ($26 billion), the cost is $400,000 per eye saved from blindness. It is important that we evaluate both the individual and the public health consequences of our therapies.

Case Identification (Screening)

The identification of OAG cases in a population is more challenging than the screening for cataract. For adequate predictive power, we must combine two methods of examination: one for disc structure, one for visual function. However, screening is performed in various contexts, each with a different, optimal approach. Community screening programs in the United States have, unfortunately, a low yield at high cost. In the developing world, case identification is even more challenging and is impractical for most countries, though it can be accomplished with extraordinary effort for demonstration or research studies.

In medical care offices, screening with expensive technology may be practical, but this has not yet been applied in an effective way. Too often, a promising set of data generated in one group of patients is not generalizable to other groups. It is hoped that laser-based imaging devices can be tested in nonophthalmic care delivery offices with a national, central reading system to sort suspects from the population at risk.

Risk Factors for OAG Prevalence

To improve case identification, as well as to understand the causes of OAG, it is important to define its risk factors. Diseases rarely have only one “cause”; rather, they have groups of...
necessary and contributing factors that differ among persons with identical phenotypes. A necessary factor in one person (higher than normal IOP) may be merely contributing in another and not at all present in others. Some risk factor analyses have dramatically changed our ideas about OAG.

OAG prevalence increases with age, with startlingly high rates of disease in the very elderly found by David Friedman in the Salisbury Eye Evaluation OAG study (Friedman DF, personal communication, December 2004). Since RGCs die during aging, OAG can be thought of as accentuated neuronal aging, associated with a sagging optic nerve head. Rohit Varma34 found that the nerve rim area of the optic disc was related to IOP level—higher IOP was associated with fewer nerve fibers among normal persons. Possibly, the level of IOP affects the age-related loss of RGC. Of course, aging could affect other potentiators of OAG progression. Furthermore, age is a surrogate for duration of exposure to the other risk factors for OAG.

The most fundamental change in our view of OAG and IOP came from clinical observations of Stephen Drance40 and epidemiologic analyses by Al Sommer55 in the Baltimore Survey. The IOP levels of those with OAG overlapped with the normal population distribution, though, on average, OAG cases had a higher mean IOP. While OAG was more common at higher IOP, it occurred nearly as often at normal IOP. Since there were so many more persons in a population with lower IOP, the prevalence of OAG at lower IOP was substantial. Thus, there was no reason to differentiate between the mythical “low-tension” and “high-tension” OAG, except artificially.

Indeed, analyses of OAG that dichotomize using the ancient “magic number” 21 mm Hg do themselves a disservice. By looking only at those with IOP lower or higher than an arbitrary criterion value, they reduce study sample size and the statistical power to assess risk. In addition, they probably miss associations that occur in the “other” half of the IOP distribution. IOP should be treated as a parameter, not a cutoff criterion, in order better to understand and study OAG. In OAG treatment, IOP-lowering is now known to work in lower56 and higher57 IOP ranges, and we individualize the therapeutic approach by establishing baseline and target pressures for each patient, as described by Henry Jampel.40

OAG has a familial occurrence,41 but persons are more likely to report a positive family history if they have been previously diagnosed. deJong (Wolfs et al.15) examined all available family members of a population-based OAG cohort, estimating 10 times greater risk for first-degree family members. I suggest that targeted projects to increase surveillance among first-degree relatives would be more highly productive than random screening. The exciting era of specific OAG genes began with the discovery of myocilin by Stone, Finnert, and Alward,52 but we must heed the lesson of other disorders in which mutations in different genes are associated with similar phenotype, mutations in a single gene that cause different clinical pictures, and large numbers of persons with normal alleles have indistinguishable OAG from those with mutations. We will learn much from glaucoma’s genetic elements, but they will not solve everything.

High blood pressure (HBP) has been considered an OAG risk factor, but the Baltimore Survey45 found a more complex relationship. Younger persons with HBP are less likely to have OAG than young normotensives, while older persons with HBP are at greater risk for OAG. We speculated that the vascular perfusion of the RGC layer was higher in young eyes with HBP and that their vessels had not yet undergone chronic damage, leading to a protective effect. The elderly with HBP, on the other hand, had vessel damage from prolonged disease, and their RGCs had poorer nutrition as a result. In addition, lower BP combined with higher IOP (low perfusion) was a much more serious risk factor than HBP overall. When the difference between diastolic BP and IOP is below 50 mm Hg, the risk of OAG goes up by four times or more. We must investigate the autoregulation of retinal and optic nerve blood flow in vivo to elucidate this risk area, and prospective studies in this area are needed.

While diabetes mellitus was traditionally considered to be an OAG risk factor, Tielsch et al.43 found no such association, and other population-based surveys have found no consistent relationship.45–48 This is intriguing, since diabetics have higher IOP than nondiabetics in every survey. Could diabetics, at least before overt retinopathy, have protective effects that counterbalance the higher IOP? This speculation was supported by the Ocular Hypertension Treatment Study (OHTS)49 and Early Manifest Glaucoma Trial (EMGT) surveys, in which diabetes was protective against progressive disease in OH and early OAG. We typically ignore findings that are dissonant with established dogma, but I suggest that the vascular permeability defects in early diabetes may provide protective, serum-derived growth factors to the RGCs.

Optic disc diameter varies widely in normal subjects, leading to OAG misdiagnosis in large discs with large cup-disc ratios. Two population studies50,51 show a slightly greater OAG risk in eyes with larger disc diameter. Caprioli (Caprioli and Miller52) had shown that larger discs have more nerve fibers. Biomechanically, a bigger hole in the eyeball would more poorly resist deformation, suggesting that RGC axons might die faster in a big disc. This detrimental effect would be balanced by inherently greater reserve in RGC numbers in big disc eyes.

The fact that high refractive error is also associated with greater OAG risk may relate to features of the eyeball size, thickness, and configuration. Differences in disc anatomy may play a role in greater OAG risk among African-derived persons, since their discs are larger but have fewer RGC axons for the size. Age and race are not risk factors. When a risk factor study finds a lack of association, we tend to stop thinking about that factor. Why isn’t cigarette smoking a factor in OAG (as it is for cataract and macular degeneration)? Does this suggest that its detrimental effects on oxygenation, vascular perfusion, and free radical generation are not relevant in OAG?

**Ethnic Differences in OAG**

The Baltimore Survey53 found greater OAG risk for African-derived than European-derived persons. Since higher OAG prevalence is also true of African-derived persons in Tanzania54 and Barbados,55 this risk crosses large differences in culture, economy, diet, and health delivery among these populations. Yet, no genes have been identified among African-derived persons—an area demanding investigation. We must be cautious about ascribing a disease association to gene effects when the result may be socioculturally derived. Even the designations of ethnicity (“race”) are challenging on scientific grounds. Ethnic differences in risk may be partly explained by lack of access to care, differential response to therapy, cultural attitudes that inhibit compliance, and the many consequences of lower economic status. Compared to European-derived persons, OAG prevalence is higher in U.S. Hispanics,40 and in
Indians, but is similar in prevalence among Chinese. Paul Foster and coworkers report that tonometric IOP in Asians may read differently from Europeans. Whether this is a tonometric artifact or an important pathophysiological difference in ocular biomechanics remains to be investigated.

**CLINICAL OAG DAMAGE**

**Optic Disc**

The most fundamental difference between OAG and other optic neuropathies is the physical excavation of the disc. Douglas Anderson and Anita Hendrickson demonstrated that acute IOP elevation in monkeys produces axonal transport obstruction at the nerve head, and I had the joy of working for 2 years in Doug’s laboratory, detailing how this block was localized to the portion of the nerve head at the level of the sclera, reversed after short IOP elevations, and correlated with RGC death after chronic blockade.

In human OAG eyes, clinical-pathologic correlation shows that the connective tissue of the lamina cribrosa stretches backward, collapses its successive plates, and rotates outward on its scleral insertion to give the typical excavated appearance. This does not happen in ischemic optic neuropathy, in which RGC death follows a similar distribution, nor in primary atrophy after optic nerve transection. The connective tissue alteration underlaying excavation can be produced in monkey eyes that have high IOP, as demonstrated by John Morrison in human OAG, whether IOP is high or not, implying that biomechanical effects on nerve head tissue underlie the clinical uniqueness of OAG and its pathophysiology. The fact that excavation occurs in eyes with OAG at normal IOP suggests that their lamina cribrosa stretches under forces that do not distort normal nerve heads and that require higher IOPs to produce in many eyes. Hence, abnormal connective tissue response is a likely factor in those with OAG at normal IOP. Connective tissue structural genes would be good candidates for study in persons with OAG at lower IOP.

The regional architecture of normal nerve heads explains, in part, why RGCs whose axons pass through the upper and lower disc die first in OAG. The connective tissue in the nerve head polar regions is quantitatively thinner, providing less resistance to deformation and contributing to RGC death in an hourglass pattern. This is the only known feature of ocular anatomy or physiology that corresponds to the OAG pattern of RGC loss; the pattern differs in ischemic or compressive optic neuropathy. It is important to see whether new methods of blood flow measurement in regions of the nerve head can detect regional differences linked either to connective tissue movement or axon loss. Point-in-time studies will never solve etiological issues in OAG, as we know that blood vessels and flow decrease simply as an effect of RGC loss.

**Nerve Fiber Layer**

Hoyt et al. recognized that nerve fiber layer (NFL) atrophy in OAG was visible ophthalmoscopically in green light. Neil Miller (Sommer et al.) brought the method to Wilmer, where Al Sommer (Quigley et al.) led our efforts to show that detectable NFL damage predicted future OAG visual field loss. With disc rim change and disc hemorrhage, NFL examination remains one of the few prospectively documented predictors of functional OAG damage. Through clinical–pathologic comparisons in human OAG eyes and monkeys, NFL thickness was shown to be useful in detecting and monitoring OAG damage, especially when implemented in laser imaging devices. The digital imagers may soon show prospective predictive power. Part of our difficulty in implementing new technology is the tendency to force machines to duplicate what humans do best. Disc imaging devices can be forced to yield a cup-disc ratio, but they detect and follow damage much better by use of parameters like cup shape measure, neural network analysis, and average change in superpixel zone topography. What the human eye does well should be complemented by what machines can uniquely do better.

**Visual Field**

We strengthened the concept that structural alteration in the disc and NFL precedes functional abnormality by showing in human OAG eyes that a substantial minority of RGCs die before manual or automated perimetric defect. This should not necessarily be used as evidence that all OAG suspects should be treated, rather it may stimulate the search for more sensitive and reliable signs of early injury. In early or moderate damage, we found that OAG causes selectively greater loss of larger-diameter RGCs with larger axon diameters projecting to the magnocellular lateral geniculate body. The anatomic facts supporting this finding have been confirmed in other laboratories in rats, cats, and monkeys with experimental glaucoma, as well as in human OAG. If we accept that there is selective death of larger RGCs, its pathophysiological basis deserves further investigation.

As stated by Robert Shaffer, OAG patients don’t care what their eye pressure is, they care if they can see. It has been of great interest to us to test how visual field damage (the ophthalmologist’s view of OAG injury) affects persons with the disease. Quality-of-life questionnaires describe how persons report the effects of OAG on their functionality. Alternatively, one can test the actual tasks such as reading, face recognition, mobility, and automobile driving. We know little about whether it is functionally better to have one normal eye and one severely damaged eye, or, to have two moderately damaged eyes. More studies are needed on the functional effects of OAG.

**THE MICROSCOSM**

**Who Dies in OAG Damage?**

It was formerly common to see debates pitting simplistic “mechanical” or “vascular” theories of OAG against one another. With present sophistication, we realize that many factors can be contributory and that both biomechanics and vascular nutrition are contributing issues in damage. But, newer, basic knowledge of neuronal death processes has touched OAG research. While a study of secondary glaucoma offered evidence for photoreceptor loss, we found that photoreceptors and other retinal layers are generally intact in primary human OAG and only RGCs die. What do we know about RGC death and what is the next step in research?

**How Do RGCs Die?**

Clearly, one site of injury is the RGC axon at the level of the nerve head where orthograde and retrograde axonal transport are blocked. In 1994, we found that apoptotic RGC death occurs in experimental monkey and human OAG as well as in other optic neuropathies (a line of research suggested by Robert Nickells [Quigley et al.] and Don Zack [Kerrigan et al.]). While many disorders have been reported to be somehow associated with apoptosis, in OAG a logical theory that links known events and apoptotic cell death suggested itself. RGCs receive protein signals (neurotrophins) from target neurons in the brain that support their survival. In embryologic life, RGCs that grow an axon to the proper target receive brain-derived neurotrophic factor (BDNF) and live, while mistargeted RGCs die by turning on their apoptotic, pro-
grammed death genetic sequence. This parsimonious system prunes two of three early RGCs that would represent excess retinal baggage.

**Gene Therapy for RGCs**

If BDNF dependence continues during adult life, the blockade of axonal transport in OAG would cut off the supply coming from the brain, possibly reactivating the cell death program. In this scenario, pathology recapitulates ontogeny. Mary Ellen Pease, who has headed our laboratory efforts so capably, showed that BDNF is blocked from entry into the eye by experimental glaucoma (Quigley et al.93), as is the transport molecule on which it travels.34 To prove this theory directly, Hani Levkovitch-Verbin95 generated a reproducible model of IOP elevation in the rat, to allow large-scale, therapeutic studies. Keith Martin96 produced an adeno-associated viral vector that expressed the human BDNF gene in the inner retina. Replacement of BDNF in the rat glaucoma model salvaged that expressed the human BDNF gene in the inner retina. Replacement of BDNF in the rat glaucoma model salvaged nearly 40% of RGC that would otherwise have died.

The hypothesis that neurotrophin withdrawal leads to RGC death suggests that cell death follows by pathways of intracellular alteration that have been delineated in other cell types. Stuart McKinnon97 found that cysteine proteases were activated in the rat glaucoma model. This pathway leads to cell death by digestion of nuclear DNA. This idea led to another successful gene therapy experiment that preserved RGC in rat glaucoma by blocking the activation of caspase enzymes.98

**Upstream Inhibition of Injury**

While these experiments suggest new therapeutic avenues for OAG, we should be asking how the earliest injury to RGC might be avoided. If we wait until RGCs are in extremis, it is more difficult to avoid ultimate neuronal death than if we stopped the process “upstream.” Since change in lamina cribrosa connective tissue is the keystone of clinical glaucoma detection and since regional laminar architecture is the explanation of typical field loss pattern, we infer that change in connective tissue is important in OAG injury. The lamina is heavily invested with elastin that helps it stand up to 85 years of ocular pulsation without irreversible stretching. In the OAG nerve head studies, the number of elastin molecules is unchanged (as reported by Erica Quigley), but their appearance suggests that they are disconnected from the remainder of the extracellular matrix.99–102 Burgoyne103 found a loss of elastic compliance of the nerve head in acute and chronic IOP elevation experiments in monkeys. The elastin gene or those of associated extracellular fibrils would be fine choices as candidate OAG genes.

How do RGC axons sense that their environment has changed, leading to blocked axonal transport? There are pressure-sensitive channels in axonal membranes that may respond to deformation caused by lamina cribrosa strain. These TRAAK channels are linked to intracellular actin and microtubular networks. External compression and/or disturbed energy metabolism could block transport by affecting key motor proteins, kinesin in the direction toward the brain (orthograde for RGCs) and dynein for transport toward the RGCs (retrograde). We have found that experimental glaucoma alters dynein, perhaps affecting neurotrophin transport toward the cell body along tubulin tracks using ATP power. Protection of this transport system may represent an important new therapeutic direction for OAG.

Dynein-mediated transport runs on ATP energy, and so poor autoregulation of nutritional blood flow may participate in ultimate RGC death at this site. In our studies of nerve head blood flow in chronic monkey glaucoma, axons died without any detectable decrease in flow or loss of capillary structure.104–107 This shows that RGCs can be injured in normal monkeys without altering blood vessels or flow (i.e., other factors are sufficient). The monkey experiments do not negate the high likelihood that poor autoregulation of flow may be a contributing feature of OAG damage in some elderly humans.

**Other Factors Implicated in Damage to RGCs**

A variety of other mechanisms have been implicated in OAG damage. How some of these relate to other risk factors for glaucoma is, as yet, unclear. For example, glutamate neurotoxicity has been proposed as a mechanism in OAG injury. We detected disequilibrium responses in the number of glutamate transporters in experimental glaucoma,108 others report possible therapeutic success in blocking glutamate excitotoxicity experimentally.109 Human clinical trials are now ongoing. But, it is unclear why excess glutamate would be present to injure RGCs in OAG. Perhaps it results from the same neurotrophin signal failure and is a midlevel step in damage. If it results from already ongoing damage or death of RGCs, then it would be a secondary degeneration event. It may be more useful to augment glutamate transport (sequestration) than to block its receptors.

Oxidative free radicals are implicated in many neuronal disorders, and there are several reports of possible involvement in OAG. Typically, oxidative damage occurs in the penumbra of major vascular injury as a secondary feature. Recent study of gene expression patterns with microarray analysis by Ron Farkas et al.110 have shown that experimental glaucoma and human OAG are associated with increased expression of iron-regulating genes that are intended to block free radical damage. Again, this mechanism may play a role in secondary damage, but how it becomes activated by the early events of OAG is unknown at this time.

The 2002 Friedenwald awardee Michal Schwartz111 suggested that immune-mediated phenomena may play a role in causing or preventing optic nerve damage. The beneficial effects of Copaxone immune therapy show promise, but it also may block only secondary damage events. To study secondary degeneration in isolation, we devised a model of partial transection of the optic nerve.112–113 Primary injury to upper retinal RGCs is caused by transection, while injury in the inferior retina occurs only if secondary excitotoxic or immune-mediated events are the basis for RGC death. We hope to use this model to dissect in greater detail the events of primary compared to secondary RGC injury.

**Acknowledgments**

The names of many colleagues, teachers, and friends have appeared here to highlight who truly did the work involved. Two of my coworkers were my children, David and Erica, others are my surrogate children, and all comprise a research family that has hopefully had fun in the objective enterprise of generating a few new facts about a complex disease that is rapidly opening its petals to our poking. Thanks to Cristina for her love and support and to ARVO for this high honor.

**References**


