MECHANISMS OF THE GLAUCOMAS

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MECHANISMS OF THE GLAUCOMAS

Disease Processes and Therapeutic Modalities

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Who contributed to this book and, as a true clinician-scientist, made major contributions to our understanding of glaucoma
In the year 2000, as we crossed the millennium into the twenty-first century, it was tempting to look back and consider what might have been the greatest achievements of the past century. In the field of glaucoma, there were many candidates.

For more than half of the twentieth century, glaucoma was felt by most investigators and physicians to be synonymous with elevated intraocular pressure. If the pressure was above the statistical norm of about 21 mmHg, the patient was considered to have glaucoma, and if the pressure could be lowered below that value, the glaucoma was believed to be controlled. With the seminal importance of intraocular pressure, therefore, one might argue that applanation tonometry—introduced by Goldmann (1) in the 1950s and still the gold standard by which other tonometers are compared—was the greatest contribution in glaucoma during the twentieth century.

But, in the latter half of the century, it became increasingly clear that the diagnosis and management of glaucoma was not so simple. Not all patients with elevated intraocular pressure acquired glaucomatous optic nerve damage and visual field loss, and some patients with normal pressures did develop glaucomatous damage. Today, a commonly accepted definition of glaucoma is “a group of optic neuropathies in which a level of intraocular pressure is an important causative risk factor.” Consequently, it might be argued that diagnostic instruments, which quantify glaucomatous damage, were the most important contributions in glaucoma. During the second half of the twentieth century, perimetry evolved from the manual, bowl perimeter—again a contribution of Goldmann—to the computer-driven perimeters of today, while laser and computer technologies were being applied to image analysis of the optic nerve head.

Although sophisticated diagnostic instruments are clearly important in the prevention of blindness from glaucoma, others might argue that the greater contributions were the advances in the treatment of glaucoma. When we entered the twentieth century, the only available drugs for glaucoma were pilocarpine and other cholinergic agents. By the end of the century, at least four additional classes of drugs—prostaglandins, beta blockers, adrenergic agonists, and carbonic anhydrase inhibitors—were available, and the medical management of glaucoma had changed dramatically. But medications are not effective or tolerated in all glaucoma patients, and many would undoubtedly lose their sight were it not for surgical interventions.

Arguably, one of the greatest contributions in many fields of surgery was the introduction and application of laser technology in the second half of the twentieth century. Ophthalmology was among the first disciplines to develop this technology, initially in the treatment of retinal disorders. In glaucoma, the replacement of incisional iridectomy by laser iridotomy has had a profound effect on our management of angle-closure glaucoma, and cyclophotocoagulation has a role in some patients with advanced, intractable glaucoma. For chronic forms of open-angle glaucoma, laser trabeculoplasty
has become an important part of our treatment plan, although the magnitude and
duration of intraocular pressure reduction is limited, and a high percentage of patients
eventually require the more definitive filtering or drainage implant surgery.

Filtering surgery is truly a product of the twentieth century, having been introduced
around 1906. The technique evolved throughout the century, with the transition from
full-thickness fistulas to the guarded trabeculectomy, the application of microsurgical
techniques, and the adjunctive use of antifibrotic agents. However, the operation is
still limited by a significant rate of failures and complications, which prompted the
development during the second half of the century of drainage implant devices as an
alternative to glaucoma filtering surgery. While both of these commonly used surgical
techniques have serious shortcomings—and the quest goes on for better glaucoma
operations—they have undoubtedly saved the sight of countless thousands of patients
with glaucoma.

So, what was the greatest contribution to glaucoma in the twentieth century? Was
it the ability to accurately measure the intraocular pressure or to document the extent
of the visual field loss or to analyze the status of the optic nerve head? Or, was it the
dramatic advances in glaucoma pharmacology or the application of laser technology or
the incisional surgical procedures, when the former treatments were ineffective? While
all of these diagnostic and therapeutic advances have undoubtedly been critical in the
prevention of blindness from glaucoma, a careful analysis of the bigger picture leads
to the conclusion that the greatest contribution to glaucoma in the twentieth century
was none of the above.

All of these advances in glaucoma represent technologies, which will one day be
replaced by newer and better technologies. What will not be replaced, and what was
undoubtedly the most important contribution to glaucoma in the twentieth century, is
the knowledge that was gained through scientific investigation, on which all future
understanding of the mechanisms of glaucoma and of its management will be based.

At the beginning of the twentieth century, our understanding of the ocular mecha-
nisms related to glaucoma was extremely limited. We knew almost nothing about
aqueous humor dynamics; indeed, we did not even know whether aqueous humor
was dynamic. We did not know the difference between open-angle and closed-angle
glaucoma. We did not know whether elevated intraocular pressure in the various forms
of glaucoma was because of reduced outflow or increased inflow. And we knew
virtually nothing about the mechanism of glaucomatous optic neuropathy.

During the first half of the twentieth century, there was controversy as to whether
aqueous humor was stagnant with general metabolic exchange throughout the ocular
tissues or whether there was continuous gross circulation within the anterior ocular
segment. It was not until 1941, when Ascher (2) described aqueous veins draining
aqueous from the anterior chamber into the venous system, that the theory of continuous
circulation was confirmed. Many investigators have subsequently contributed to our
current understanding of the anatomy and physiology of aqueous humor production by
the ciliary body, the circulation and metabolic activity of aqueous in the anterior ocular
segment, and its outflow primarily through the trabecular and uveoscleral pathways.

The mechanisms of the various forms of glaucoma were unknown at the outset of
the twentieth century. We did not even know the difference between open-angle and
closed-angle mechanisms of glaucoma, and it was the gonioscopic studies of Barkan (3) in 1938 that clarified this fundamental classification of the glaucomas and provided a rational basis for their treatment. In 1950, using his concept of tonography to noninvasively estimate the facility of aqueous outflow, Grant (4) showed that in virtually all forms of glaucoma, the mechanism of elevated intraocular pressure is increased resistance to outflow. Many investigators have contributed to our understanding of the specific mechanisms that lead to the increased outflow resistance in the various glaucomas, again providing a more rational approach to management.

Late in the twentieth century, two nascent areas of research were beginning to provide glimpses of what the twenty-first century held in store for the future of glaucoma: the mechanisms of glaucomatous optic neuropathy and the molecular basis of the glaucomas. Several investigators began to disclose pieces of the complex pathways that lead to apoptosis of the retinal ganglion cells in glaucoma, and this information was being applied to the evaluation of pressure-independent neuroprotective agents. Other scientists were reporting preliminary findings in gene-linkage studies for specific forms of glaucoma. These two areas of glaucoma research will likely be the most important as we move farther into the twenty-first century and promise major changes in our understanding and management of glaucoma.

Whatever the future holds for glaucoma research and management, it is clear that the advances will be based on the knowledge that has been gained from the work of basic and clinician scientists over the past decades. The purpose of this book is to review that knowledge. The intent of the book is not primarily to describe the clinical appearances of the glaucomas nor how to manage them. Rather, it is to provide basic scientists, who are working in the field of glaucoma, with a current understanding of the clinical aspects of glaucoma and to provide clinician scientists with the basic knowledge, as they attempt to translate it into rational treatments for glaucoma.

To achieve the goal for this book, we have invited leaders in the various fields to review our current understanding of glaucoma from epidemiology and genetics, through molecular, cellular, and tissue responses, to the mechanisms of the glaucomas and the mechanisms by which we manage them. We are grateful to all the contributors of the book and hope that the contents will be of value to the reader, as we work together to prevent the blindness of glaucoma.

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REFERENCES
Contents

Preface ................................................................. vii
Contributors .......................................................... xv
Companion CD ........................................................ xix

Part I Epidemiology of Glaucoma

1 Age and Racial Variation in the Prevalence of Open-Angle Glaucoma in the USA
   Joshua D. Stein and Paul P. Lee ............................. 3

2 Epidemiology of and Risk Factors for Primary Open-Angle Glaucoma
   Paulus T. V. M. de Jong, Nomdo M. Jansonius,
   Roger C. W. Wolfs, and Richard H. C. Zegers .............. 19

3 The Reykjavik Eye Study on Prevalence of Glaucoma in Iceland and Identified Risk Factors
   Fridbert Jonasson, Arsaell Arnarsson, and Thor Eysteinsson ........ 35

4 Defined Glaucoma in Chinese Population
   Chun Zhang, Ningli Wang, and Wei Wang .................... 49

5 The Wroclaw Epidemiological Study
   Screening Possibilities of Glaucoma Detection
   Radoslaw Kaczmarek and Maria H. Nizankowska ............. 63

Part II Mechanisms of Intraocular Pressure Elevation in the Glaucomas

6 Pretrabecular Mechanisms of Intraocular Pressure Elevation
   Sarwat Salim and M. Bruce Shields ........................... 83

7 Glaucomatous Changes in the Trabecular Meshwork
   Douglas H. Johnson and Elke Lutjen-Drecoll ................ 99

8 Trabecular Mechanisms of Intraocular Pressure Elevation
   Pseudoexfoliation Syndrome
   Ursula Schlötzer-Schrehardt and Gottfried O. H. Naumann .... 117
Contents

9 Post-Trabecular Glaucomas with Elevated Episcleral Venous Pressure

Augusto Paranhos, Jr, João Antonio Prata, Jr, Paulo Augusto de Arruda Mello, and Felício Aristóteles da Silva

10 Angle-Closure Glaucomas

Anterior (Pulling) Mechanisms

Malik Y. Kahook and Joel S. Schuman

11 Angle-Closure Glaucomas

Posterior (Pushing) Mechanisms with Pupillary Block

Takashi Kanamoto and Hiromu K. Mishima

12 Angle-Closure Glaucomas

Posterior (Pushing) Mechanisms Without Pupillary Block

Yaniv Barkana, Clement C. Tham, Syril K. Dorairaj, and Robert Ritch

Part III Genetics of Glaucoma

13 Genetics and Glaucoma Susceptibility

Karim F. Damji and R. Rand Allingham

14 Myocilin Mutations and Their Role in Open-Angle Glaucoma

Paul N. Baird

15 The Functional Role of Myocilin in Glaucoma

Ernst R. Tamm

16 Roles of CYP1B1, Optineurin, and WDR36 Gene Mutations in Glaucoma

Mansoor Sarfarazi, Sharareh Monemi, Dharamainder Choudhary, Tayebeh Rezaie, and John B. Schenkman

17 Genetic Association in the Open-Angle Glaucomas

Hui-Ju Lin and Fuu-Jen Tsai

18 ApoE Polymorphisms and Severity of Open-Angle Glaucoma

Chi Pui Pang, Clement C. Tham, and Dennis Shun Chiu Lam

Part IV Molecular and Cellular Responses in the Eye to Glaucoma

19 Changes in Aqueous Humor Dynamics with Age and Glaucoma


20 Mechanosensitive Genes in the Trabecular Meshwork at Homeostasis

Elevated Intraocular Pressure and Stretch

Teresa Borrás
21 Reactive Astrocytes in the Glaucomatous Optic Nerve Head
   Protective and Destructive Mechanisms ....................... 363
   M. Rosario Hernandez and Bin Liu

22 Optic Neuropathy and Ganglion Cell Degeneration
   in Glaucoma
   Mechanisms and Therapeutic Strategies ....................... 393
   Dong Feng Chen and Kin-Sang Cho

23 Proteomics in Defining Pathogenic Processes Involved in
   Glaucomatous Neurondegeneration .......................... 425
   Gülgün Tezel

24 Proteomic Advances Toward Understanding Mechanisms of
   Glaucoma Pathology ........................................ 443
   Sanjoy K. Bhattacharya and John W. Crabb

25 Molecular and Cellular Responses in the Eye
   to Glaucoma
   Ocular Gene Expression in Experimental Glaucoma ........ 459
   Tomonari Ojima and Nagahisa Yoshimura

Part V Ocular Tissue and Psychophysiological Responses
   in Glaucoma

26 Ocular Biomechanics in Glaucoma ............................. 471
   C. Ross Ethier, Victor H. Barocas, and J. Crawford Downs

27 Intraocular Pressure, Perfusion Pressure, and Optic Nerve
   Energy Metabolism ........................................... 491
   Einar Stefánsson

28 Optic Nerve
   Physiology and Mechanisms of Glaucomatous Atrophy .... 517
   Makoto Aihara and Goji Tomita

29 Psychophysiology of Glaucoma
   From Form to Function ....................................... 527
   Chris A. Johnson and Shaban Demirel

Part VI Models of Glaucoma

30 The Primate Model of Experimental Glaucoma ............... 551
   Arthur J. Weber and Suresh Viswanathan

31 Involvement of Inflammation in a Mouse Model of Inherited
   Pigmentary Glaucoma ........................................ 579
   Wei Cao

32 Use of Purified Retinal Ganglion Cells for an In Vitro Model
   to Study Glaucoma ........................................... 601
   Yasumasa Otori
## Part VII Therapeutic Modalities

33 Pharmacological Therapies for Managing Glaucoma .......... 611  
*Jess T. Whitson and Nalini K. Aggarwal*

34 Redox-Based Therapies for Neuroprotection ............... 645  
*Leonard A. Levin*

35 Neuroprotective Signaling Pathways in Glaucoma .......... 657  
*Frédéric Lebrun-Julien and Adriana Di Polo*

36 Role of Selective Laser Trabeculoplasty in the Management of Glaucoma ............................... 683  
*Mark A. Latina, Navin Prasad, and Jorge A. Alvarado*

37 Mechanisms and Mechanics of Incisional Surgery for Glaucoma .................................. 693  
*Robert D. Fechtner and Albert S. Khouri*

38 Aqueous Shunts ............................................. 715  
*D. S. Minckler and S. Mosaed*

39 New Approaches to the Surgical Management of the Glaucomas .................................. 739  
*Carl B. Camras and M. Bruce Shields*

Index ........................................................................ 753
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Companion CD

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Chapter 1, Fig. 4, p. 14
Chapter 4, Fig. 1, p. 53
Chapter 6, Figs. 1A, 1B, 1C, 2–7, p. 86, 87, 90, 91
Chapter 7, Figs. 1, 6, 7, 10 p. 101, 103, 104, 106
Chapter 8, Fig. 4 p. 125
Chapter 9, Fig. 1 p. 140
Chapter 11, Figs. 2, 4, 6 p. 169, 171, 172
Chapter 12, Figs. 3, 6, 7 p. 177, 180, 181
Chapter 13, Figs. 2, 3 p. 198, 199
Chapter 15, Fig. 1 p. 224
Chapter 20, Figs. 1–3 p. 331, 335, 336
Chapter 21, Figs. 2, 5, 7, 9, 10, 11 p. 368, 372, 377, 380, 381, 382
Chapter 24, Fig. 1 p. 446
Chapter 25, Figs. 1, 2 p. 460, 462
Chapter 26, Fig. 5 p. 482
Chapter 27, Figs. 4, 5, 10, 11, 12, 14, 15, 17, 18 p. 496, 497, 500, 505, 506, 507, 508, 509, 509
Chapter 29, Figs. 1, 2, 3, 4, 7, 10 p. 529, 531, 532, 533, 538, 543
Chapter 33, Fig. 1 p. 623
Chapter 34, Fig. 1 p. 651
Chapter 36, Figs. 1A, 1B, 02, 03, 04 p. 684, 684, 685, 686, 687
Chapter 38, Figs. 1, 2, 3, 4 p. 717, 726, 729, 730