

Philip L. Penfold

Jan M. Provis

Editors

**Macular Degeneration**



Philip L. Penfold

Jan M. Provis

Editors

# Macular Degeneration

With 70 Figures in 193 Separate Illustrations  
and 14 Tables

**Dr. Philip L. Penfold**

Chief Scientist  
Regenera Limited  
PO Box 9  
2 Brindabella Circuit  
Canberra Airport  
ACT 2609  
Australia

**Dr. Jan M. Provis**

Research School of Biological Sciences  
The Australian National University  
GPO Box 475  
Canberra  
ACT 2601  
Australia

Library of Congress Control Number: 2004105923

ISBN 3-540-20058-4 Springer Berlin Heidelberg New York

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilm or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer. Violations are liable to prosecution under the German Copyright Law.

**Springer is a part of Springer Science+Business Media**

springeronline.com

© Springer-Verlag Berlin Heidelberg 2005

Printed in Germany

The use of general descriptive names, registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Product liability: the publishers cannot guarantee the accuracy of any information about dosage and application contained in this book. In every individual case the user must check such information by consulting the relevant literature.

Editor: Marion Philipp, Heidelberg, Germany  
Desk Editor: Martina Humberger, Heidelberg, Germany  
Production: ProEdit GmbH, 69126 Heidelberg, Germany  
Cover: E. Kirchner, Heidelberg, Germany  
Typesetting: K. Detzner, 67346 Speyer, Germany

Printed on acid-free paper 24/3150 ML 5 4 3 2 1 0

## Preface

This book provides a unique overview of current thinking on the pathogenesis, incidence and treatment of age-related macular degeneration (AMD). It includes, for the first time, a synthesis of the views of the world's leading scientists and clinical practitioners regarding retinal biology and the basic mechanisms, clinical and pathogenetic processes and rational approaches to the treatment of AMD.

Although the fovea is less than a millimetre in diameter, disorders of the fovea and its immediately surrounding area (the *macula*) are responsible for the majority of cases of untreatable blindness in the developed world. The basis for the vulnerability of the macula region in these degenerative changes is beginning to emerge. The fovea has a number of features that distinguish it from other parts of the retina and reflect its specialization for high visual acuity, principally a high density of photoreceptors and a lack of retinal vessels. Chapter 1, written by Anita Hendrickson, provides an overview of the anatomy of the primate macula. The fovea is a characteristic feature of the primate retina, lies on the temporal side of the optic disc and regards the central visual field. A sound understanding of macular anatomy is essential for understanding the impact of AMD on the patient.

In Chap. 2, we summarise the evidence suggesting a critical dependence of the central retina on vascular supply. The interrelationships between the physiological and immunological function of the blood-retinal barrier and the consequences of barrier breakdown are described. Increasing evidence is presented for the involvement of both resident microglia and choroidal leukocytes. New observations concerning the significance of drusen, the involvement of the retinal vasculature and the measurement of inflammation in AMD are presented for the first time. Taken together, the data lead to the conclusion that immunity plays both a primary and secondary role in the pathogenesis of AMD.

The link between photoreceptor dysfunction and the risk of neovascularization in Bruch's membrane is explored by Jackson and colleagues in Chap. 3. Because the RPE is polarized, problems pertaining to the re-supply of photoreceptors on the apical aspect of the RPE (leading to photoreceptor death) should be conceptually separated from problems pertaining to waste removal on the basal aspect of the RPE (leading to Bruch's membrane damage and neovascularization), at least for the purposes of designing mechanistic experiments. These processes are governed by different proteins and pathways at the cellular level and will be reflected in different risk factors and genetic predispositions at the population level. A rigorous test of a nutrient-deficiency hypothesis of AMD-associated photoreceptor death awaits more information about normal nutrient delivery mechanisms across the RPE/Bruch's membrane complex, intra-retinal contributions to photoreceptor nutrition,

changes in these mechanisms with age and pathology, and differential effects on rods and cones.

In Chap. 4, AMD is considered as a complex genetic disease in which environmental risk factors impact on a genetic background. Finding the genes that determine susceptibility or modify the disease process is one of today's challenges, but also offers a chance for understanding underlying disease processes and for the development of preventive strategies and treatments. This chapter explores our current knowledge about the genetic influences on AMD and indicates possible directions for future study.

Until recently, most of the information about the natural history of AMD has come from clinical and histopathological studies. Most such studies have previously been of short duration involving select groups of patients attending ophthalmology clinics or participating in trials in which severe disease may be overrepresented. In the past 15 years data from population-based studies have resulted in a better understanding of the epidemiology of this disease. Chapter 5 examines the epidemiology of AMD, focusing on data from several recent population-based studies.

In Chap. 6, the racial/ethnic differences in the incidence and prevalence of AMD in China are examined. In China AMD is considered one of the most important causes of blindness in those over the age of 50. With improvement of economic conditions in China, the most common causes of blindness such as cataract, corneal diseases, trachoma and glaucoma have been largely brought under control, while AMD has increased in prevalence, now fourth on the list of causes of blindness in the age group of those 60 years and over. Considering the large population of China, it has been estimated that AMD currently affects at least 20 million individuals.

Experimental models of age-related macular degeneration capture only selected features of the human disease. Animal models that encompass both atrophic and exudative aspects of retinal degenerations are needed to better understand disease progression and to predict and assess potential therapeutic approaches. Recent insights into the pathogenesis of macular degeneration, along with the combination of rapid screening techniques with transgenic and other methods, are giving rise to several promising experimental systems outlined by Ray Gariano in Chap. 7.

Normal function is dependent upon a balance between the generation of free radicals and oxidative species and the availability of antioxidants and free radical scavengers. David Pow and colleagues investigate the role of transporters and oxidative stress in AMD in Chap. 8. In Chap. 9, Jonathan Stone and colleagues describe a widespread degenerative phenomena observed at the edge of the 'normal' retina. The observations suggest that the edge of the retina is subject to localized stress throughout life, inducing a progressive degenerative process. These edge-specific changes are part of the life history of the normal retina and form part of the baseline against which retinal degeneration takes place.

In the final chapter Scott Cousins and colleagues address – in the context of the scientific information described in the other sections – current clinical research strategies to provide a concept-based overview of the status of current and future treatments for AMD. A brief review of key scientific definitions and pathogenic theories is followed by the rationale for current treatments and ongoing trials. Space is also set aside for a bit of “educated speculation” about the potential future directions of clinical research based upon scientific discoveries described in other chapters.

## Acknowledgments

We are indebted to the contributing authors and many other colleagues for their help in preparing this book. Special thanks are due to Emily Bell for her assistance in formatting the initial submissions and to Diana van Driel, both for her contributions as an author and fellow electron microscopist and for her diligence as proof-reader *par excellence*.

**Philip L. Penfold, MPhil., PhD.**

**Jan M. Provis, PhD.**

Australian National University  
Canberra, Australia

September 2004





# Contents

<b>1</b>	<b>Organization of the Adult Primate Fovea</b> . . . . .	<b>1</b>
	Anita Hendrickson	
1.1	<b>Anatomy of the Human Fovea</b> . . . . .	<b>1</b>
1.1.1	General Anatomy . . . . .	1
1.1.2	Photoreceptor Distribution, Types, and Numbers in the Human Retina . . . . .	3
1.1.3	Inner Retinal Neurons Associated with Cones in Central Primate Retina . . . . .	9
1.1.4	Vascular and Glial Specializations of the Fovea . . . . .	12
1.1.5	Pigment Epithelium Numerical Relationships with Foveal Photoreceptors . . . . .	13
1.2	<b>Anatomy of the Old and New World Monkey Fovea: What Are the Differences with Human Foveas?</b> . . . . .	<b>14</b>
1.3	<b>What Are the Anatomical Requirements to Create a Fovea?</b> . . . . .	<b>17</b>
1.3.1	Midget Ganglion Cells . . . . .	17
1.3.2	High Cone Density and Types of Foveal Cones . . . . .	18
1.3.3	Absence of Rods . . . . .	18
1.3.4	Striate Cortex Expansion . . . . .	19
1.3.5	Vascular Specializations . . . . .	19
	<b>References</b> . . . . .	<b>20</b>
<b>2</b>	<b>Immunology and Age-Related Macular Degeneration</b> . . . . .	<b>25</b>
	Philip L. Penfold, James Wong, Diana van Driel, Jan M. Provis, Michele C. Madigan	
2.1	<b>Introduction: Why the Macula?</b> . . . . .	<b>25</b>
2.2	<b>The Immune Status of the Retina</b> . . . . .	<b>26</b>
2.2.1	The Blood-Retinal Barrier . . . . .	26
2.2.2	Microglia . . . . .	29
2.3	<b>Immune Mechanisms in AMD</b> . . . . .	<b>30</b>
2.3.1	Blood-Retinal Barrier Breakdown . . . . .	30

2.3.2	Pigmentary Disturbance . . . . .	30
2.3.3	Drusen . . . . .	31
2.3.4	Cell-Mediated Immunity and Inflammation . . . . .	33
2.3.5	Humoral Immunity . . . . .	35
2.4	Clinical Significance of Drusen . . . . .	37
2.5	Atrophic (“Dry”) Macular Degeneration . . . . .	37
2.6	Neovascular (“Wet”) Macular Degeneration . . . . .	37
2.7	Involvement of the Retinal Vasculature in AMD . . . . .	38
2.8	Leucocyte Common Antigen (CD45) Expression in AMD: A Measure of Inflammation . . . . .	40
2.9	Conclusion . . . . .	41
	References . . . . .	41
<b>3</b>	<b>Photoreceptor Degeneration in Aging and Age-Related Maculopathy . . . . .</b>	<b>45</b>
	Gregory R. Jackson, Christine A. Curcio, Kenneth R. Sloan, Cynthia Owsley	
3.1	Introduction to Age-Related Maculopathy . . . . .	45
3.2	Photoreceptor Loss . . . . .	47
3.3	Photoreceptor Dysfunction . . . . .	51
3.3.1	Topography of Loss and Dysfunction . . . . .	52
3.4	Photoreceptor Function as a Bioassay of RPE and Bruch’s Membrane Health . . . . .	54
3.5	Impairment of Transport Between RPE and Photoreceptors . . . . .	56
3.6	Summary . . . . .	57
	References . . . . .	58
<b>4</b>	<b>Genes and Age-Related Macular Degeneration . . . . .</b>	<b>63</b>
	Robyn H. Guymer, Niro Narendran, Paul N. Baird	
4.1	Age-Related Macular Degeneration, a Complex Genetic Disease . . . . .	63
4.2	Genetic Basis of Disease . . . . .	64
4.2.1	Family Studies . . . . .	64
4.2.2	Sibling Studies . . . . .	64
4.2.3	Twin Studies . . . . .	65
4.3	Approaches to Genetic Investigation of AMD . . . . .	65
4.3.1	Linkage Analysis . . . . .	65
4.3.2	Candidate-Gene Screening . . . . .	67

<b>4.4</b>	<b>Future Directions</b>	73
4.4.1	Single-Nucleotide Polymorphisms	73
4.4.2	Microarrays	73
4.4.3	Proteomics	74
<b>4.5</b>	<b>Conclusions</b>	74
	References	75
<b>5</b>	<b>Epidemiology of Age-Related Macular Degeneration</b>	79
	Ronald Klein	
<b>5.1</b>	<b>Prevalence and Incidence of Age-Related Macular Degeneration</b>	79
5.1.1	Introduction	79
5.1.2	Prevalence of Age-Related Macular Degeneration	80
5.1.3	Prevalence: Race/Ethnicity	81
5.1.4	Incidence of Age-Related Macular Degeneration	82
<b>5.2</b>	<b>Risk Factors for Age-Related Macular Degeneration</b>	82
5.2.1	Introduction	82
5.2.2	Familial Factors	83
5.2.3	Systemic Factors	83
5.2.4	Lifestyle Behavior	87
5.2.5	Environmental Factors	89
5.2.6	Ocular Factors	90
5.2.7	Socioeconomic Factors and Work Exposures	92
<b>5.3</b>	<b>Age-Related Macular Degeneration and Survival</b>	93
<b>5.4</b>	<b>Public Health Issues</b>	93
<b>5.5</b>	<b>Conclusions</b>	93
	References	94
<b>6</b>	<b>Prevalence and Risk Factors for Age-Related Macular Degeneration in China</b>	103
	Zheng Qin Yin, Meidong Zhu, Wen Shan Jiang	
<b>6.1</b>	<b>Introduction</b>	103
<b>6.2</b>	<b>Regional Prevalence and Relationship of Morbidity to Age and Gender</b>	104
6.2.1	Population-Based Studies	105
6.2.2	Clinical Review Studies	106
6.2.3	The Relationship of Morbidity to Age and Gender	107
<b>6.3</b>	<b>Prevalence of ‘Wet’ and ‘Dry’ AMD</b>	107
<b>6.4</b>	<b>Visual Acuity in AMD</b>	107

---

<b>6.5</b>	<b>Risk Factors of AMD in China</b>	107
6.5.1	Race/Ethnicity	109
6.5.2	Light Exposures/Occupation	109
6.5.3	Smoking	109
6.5.4	Drinking	110
6.5.5	Systemic Diseases	111
<b>6.6</b>	<b>Conclusions</b>	111
	<b>References</b>	111
<b>7</b>	<b>Experimental Models of Macular Degeneration</b>	113
	Ray F. Gariano	
<b>7.1</b>	<b>Introduction</b>	113
<b>7.2</b>	<b>Aging</b>	113
<b>7.3</b>	<b>Laser-Induced CNV</b>	114
<b>7.4</b>	<b>Growth Factor-Induced CNV</b>	114
<b>7.5</b>	<b>Genetically Defined Animal Models</b>	116
<b>7.6</b>	<b>Conclusions</b>	118
	<b>References</b>	118
<b>8</b>	<b>Transporters and Oxidative Stress in AMD</b>	123
	David V. Pow, Robert K.P. Sullivan, Susan M. Williams, Elizabeth WoldeMussie	
<b>8.1</b>	<b>Redox Reactions, Health, Oxidative Damage and Disease</b>	123
<b>8.2</b>	<b>Does Epidemiology Support a Role for Oxidation in AMD?</b>	124
<b>8.3</b>	<b>Exogenous Factors Influencing AMD Incidence</b>	125
<b>8.4</b>	<b>Hallmark Features of Oxidative Damage and Free Radical Damage</b>	125
8.4.1	Oxidized Proteins	125
8.4.2	Oxidized Lipids	125
8.4.3	DNA Damage	125
<b>8.5</b>	<b>Oxidative Challenges in the Eye</b>	125
8.5.1	Endogenous Antioxidants, Enzymes and Related Molecules in the Retina	126
8.5.2	Classes of Antioxidants	128
8.5.3	The Glutathione System	128
8.5.4	GSH in the Retina: Intrinsic Synthesis and Possible Interplay with the RPE	128
8.5.5	Synthesis of GSH	128

8.5.6	The GSH-GSSG Cycle . . . . .	129
8.5.7	Elimination of Superoxides by Superoxide Dismutases . . . . .	131
8.5.8	Ascorbic Acid . . . . .	132
8.5.9	Vitamin E . . . . .	132
8.5.10	Taurine . . . . .	133
8.5.11	Metallothionein . . . . .	136
8.5.12	Zinc, Copper, Selenium and Manganese . . . . .	136
8.5.13	Selenium Compounds . . . . .	137
8.5.14	Manganese . . . . .	137
8.5.15	Macular Pigments . . . . .	138
8.5.16	Ascorbate and Recycling of Carotenoids . . . . .	138
8.5.17	A Summary of Mechanisms for Antioxidant Protection . . . . .	138
<b>8.6</b>	<b>Cellular Interactions and Photoreceptor Death . . . . .</b>	<b>138</b>
8.6.1	Light-Mediated Damage: Experimental Lesions and AMD . . . . .	139
8.6.2	Mechanisms of Cell Death . . . . .	140
8.6.3	Cell Death in Response to Oxidative Damage . . . . .	140
<b>8.7</b>	<b>A Role for Glial cells in AMD? . . . . .</b>	<b>141</b>
8.7.1	Metabolic Functions of Müller Cells in the AMD Retina . . . . .	141
8.7.2	Cell Death and Glutamate Toxicity . . . . .	144
<b>8.8</b>	<b>Conclusions . . . . .</b>	<b>144</b>
	<b>References . . . . .</b>	<b>145</b>
<b>9</b>	<b>Photoreceptor Stability and Degeneration in Mammalian Retina: Lessons from the Edge . . . . .</b>	<b>149</b>
	Jonathan Stone, Kyle Mervin, Natalie Walsh, Krisztina Valter, Jan M. Provis, Philip L. Penfold	
<b>9.1</b>	<b>Introduction . . . . .</b>	<b>149</b>
<b>9.2</b>	<b>Approach . . . . .</b>	<b>150</b>
<b>9.3</b>	<b>Stages in Photoreceptor Degeneration at the Edge of the Retina . . . . .</b>	<b>150</b>
9.3.1	Postnatal Development of the Edge: Site of Early Stress and Degeneration . . . . .	150
9.3.2	The Edge of the Retina Is Functionally Degraded . . . . .	154
9.3.3	The Edge of the Retina Is Highly Stable in the Face of Acute Stress . . . . .	155
9.3.4	The Adult Retina Aged 2 Years: Observations in the Marmoset . . . . .	155
9.3.5	The Adult Retina Aged 20 Years: Observations in the Baboon . . . . .	155
9.3.6	The Adult Retina Aged 30–70 Years: Observations in the Human . . . . .	158
9.3.7	Evidence of Progression in Edge Degeneration in Humans . . . . .	161
<b>9.4</b>	<b>Discussion . . . . .</b>	<b>161</b>
9.4.1	The Edge of the Retina as a Model of Retinal Degeneration . . . . .	162
9.4.2	Why Is the Protection of Photoreceptors Stress-Inducible? . . . . .	162

9.4.3 Vulnerability to Oxidative Stress in Mice and Humans . . . . . 163  
 9.4.4 The Link to AMD . . . . . 163  
 References . . . . . 164

**10 Clinical Strategies for Diagnosis and Treatment of AMD:  
 Implications from Research . . . . . 167**

Scott W. Cousins, Karl G. Csaky, Diego G. Espinosa-Heidmann

**10.1 Dry AMD . . . . . 167**  
 10.1.1 Definition of Dry AMD . . . . . 167  
 10.1.2 Pathogenic Mechanisms for Drusen Formation . . . . . 168  
 10.1.3 Established or Evaluated Treatments . . . . . 170  
 10.1.4 Ongoing Trials: Multicenter Investigation of Rheopheresis  
 for AMD (MIRA-1) Study Group . . . . . 172  
 10.1.5 Future Research . . . . . 172  
**10.2 Wet AMD . . . . . 178**  
 10.2.1 Definition of Neovascular AMD . . . . . 178  
 10.2.2 Pathogenic Mechanisms for CNV Formation . . . . . 180  
 10.2.3 Established or Evaluated Treatments for Neovascular AMD . . . . . 184  
 10.2.4 Therapies Currently in Clinical Trial . . . . . 185  
 10.2.5 Future Research . . . . . 189  
 References . . . . . 191

**Subject Index . . . . . 201**

# List of Contributors

## Chapter 1

### **Anita Hendrickson**

Department of Biological Structure, University of Washington,  
1959 NE Pacific Street, Box 357420, Seattle, WA 98195-7420, USA

Department of Ophthalmology, University of Washington, 1959 NE Pacific Street,  
Box 357420, Seattle, WA 98195-7420, USA

e-mail: anitah@u.washington.edu, Tel.: +1-206-6852273, Fax: +1-206-5431524

## Chapter 2

### **Philip L. Penfold, James Wong, Diana van Driel, Jan M. Provis, Michele C. Madigan**

Save Sight Institute, University of Sydney, GPO 4337 Sydney 2001, NSW, Australia

### **Jan M. Provis**

Department of Anatomy and Histology, University of Sydney 2006, NSW, Australia

*Current address:* Philip L. Penfold, Jan M. Provis, Research School of Biological  
Sciences, The Australian National University, GPO Box 475, Canberra, ACT 2601,  
ACT, Australia

e-mail: philip.penfold@regenera.com.au, Tel.: +61-2-62574155, Fax: +61-2-62574355

e-mail: jan.provis@anu.edu.au, Tel.: +61-2-61254242, Fax: +61-2-61250758

## Chapter 3

### **Gregory R. Jackson, Christine A. Curcio, Cynthia Owsley**

Department of Ophthalmology, University of Alabama School of Medicine,  
Birmingham, AL 35294-0009, USA

e-mail: jackson@uab.edu, Tel.: +1-205-325-8674, Fax: +1-205-325-8692

### **Kenneth R. Sloan**

Department of Computer and Information Sciences, University of Alabama at  
Birmingham, AL, USA

## Chapter 4

### **Robyn H. Guymer, Paul N. Baird**

Department of Ophthalmology, University of Melbourne, 1<sup>st</sup> Floor Royal Victorian Eye and Ear Hospital, 32 Gisborne Street. East Melbourne 3002  
e-mail: rhg@unimelb.edu.au, Tel.: +613 9929-8360, Fax: +613-9662-3859

### **Robyn H. Guymer, Niro Narendran, Paul N. Baird**

Centre For Eye Research Australia, University of Melbourne,  
1<sup>st</sup> Floor Royal Victorian Eye and Ear Hospital, 32 Gisborne Street,  
East Melbourne 3002, Australia

## Chapter 5

### **Ronald Klein**

Department of Ophthalmology and Visual Sciences,  
University of Wisconsin Medical School, Madison, WI, USA  
e-mail: kleinr@epi.ophth.wisc.edu, Tel.: +1-608-263-0280, Fax: +1-608-263-0279

## Chapter 6

### **Zheng Qin Yin, Meidong Zhu, Wen Shan Jiang**

Southwest Eye Hospital, Southwest Hospital, Third Military Medical University,  
40038, Chongqing, Peoples Republic of China

### **Meidong Zhu**

Save Sight Institute, University of Sydney, NSW 2006, Sydney, Australia  
e-mail: zqyin@mail.tmmu.com.cn, Tel.: +86-23-6875-4401, Fax: +86-23-6875-3686

## Chapter 7

### **Ray F. Gariano**

Department of Ophthalmology, Stanford University School of Medicine  
330 Pasteur Dr., Palo Alto, CA 94305, USA

Santa Clara Valley Medical Center, Santa Clara, CA, USA  
e-mail: Ray.Gariano@hhs.co.santa-clara.ca.us, Tel.: +1-408-885-6775,  
Fax: +1-408-885-7166

## Chapter 8

### **David V. Pow, Robert K.P. Sullivan, Susan M. Williams**

School of Biomedical Sciences, University of Queensland, Australia  
e-mail: d.pow@mailbox.uq.edu.au, Tel.: +7-33654086, Fax: +7-33651766

### **Elizabeth WoldeMussie**

Department of Biological Sciences, Allergan Inc., Irvine, CA, USA



**Chapter 9****Jonathan Stone, Krisztina Valter, Jan Provis, Philip Penfold**

Biological Sciences, Australian National University, Canberra, Australia  
e-mail: stone@rsbs.anu.edu.au, Tel.: +61-26125-3841, Fax: +61-26125-0758

**Jonathan Stone, Kyle Mervin, Natalie Walsh, Krisztina Valter, Jan Provis**

Department of Anatomy and Histology and Institute for Biomedical Research,  
University of Sydney, Australia

**Jan Provis, Philip Penfold**

Save Sight Institute, Department of Clinical Ophthalmology, University of Sydney

**Chapter 10****Scott W. Cousins, Diego G. Espinosa-Heidmann**

Department of Ophthalmology, Bascom Palmer Eye Institute,  
University of Miami School of Medicine, Miami, FL, USA

**Karl G. Csaky**

National Eye Institute, National Institutes of Health, Bethesda, MD, USA  
e-mail: scousins@med.miami.edu, despinosa@med.miami.edu,  
Tel.: +1-305-326-6329, Fax: +1-305-326-6536

