Philip L. Penfold
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Editors

Macular Degeneration
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

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September 2004
1 Organization of the Adult Primate Fovea

Anita Hendrickson

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