The Aging Eye:
Normal Changes, Age-Related Diseases and Sight-Saving Approaches
About ORSF

The mission of the Ocular Research Symposia Foundation (ORSF) is to accelerate the pace of discovery in diseases of the eye by sharing information, ideas and findings and promoting the translation of these discoveries into preventions, treatments and cures for blinding ocular diseases.

ORSF is a nonprofit organization founded in 2011 and based in Los Angeles. It has emerged from a series of seven symposia bringing together nationally and internationally esteemed physicians and researchers to identify and evaluate new directions for developing treatments and finding cures for various diseases of the eye. The 2002-2009 symposia, funded by the Drabkin Foundation, were presented biannually through The Washington Advisory Group, located in Washington, DC. When The Washington Advisory Group closed its offices, ORSF was formed to continue the catalytic role of the symposia in the field.

The ORSF would like to thank Bausch & Lomb for their support in the publishing of this supplement on the Aging Eye.
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All articles in this Special Issue were peer reviewed prior to being scientifically accepted for publication.
Preface: The Aging Eye: Normal Changes, Age-Related Diseases, and Sight-Saving Approaches

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This volume presents articles based on a workshop held June 14 to 16, 2013 in Rancho Palos Verde, CA sponsored by the Ocular Research Symposia Foundation (ORSF). The mission of the ORSF is to focus attention on unmet needs and current research opportunities in eye research with the objective of accelerating translation of research findings to effective clinical care. In this workshop, the subject of the “The Aging Eye” was addressed, including the prevalence of eye diseases in aging and the economic burden imposed by these diseases. New research work was highlighted on the genetics, biology, biochemistry, neurochemistry, and the impact of nutrition and the environment on function in the older eye. By identifying “low-hanging fruit” (i.e., the best opportunities for successful transition of laboratory research for the prevention of and new treatments and cures for ocular diseases), we seek to spur funding at both the basic research and clinical levels, resulting in sight-saving and sight-restoration measures in the near future.

Keywords: aging, nutrition, eye

THE UNITED STATES AND THE WORLD: AN AGING POPULATION

The United States and other industrialized nations are aging societies with rapidly increasing percentages of populations over the age of 65, and this is the fastest growing segment of society in many countries. In the United States, the number of seniors is projected to more than double from approximately 40 million now to approximately 90 million by 2050. It is everyone’s hope to age gracefully and without impairment, but at present this is rarely possible. Most of the major eye diseases are age-related, in that the prevalence of these sight-threatening diseases dramatically increases above 75 years of age. If we look at world estimates overall, there are 285 million people who have some visual impairment, 256 million with low vision, and about 40 million who are blind or have significant visual impairment. Tellingly, 65% of those with visual impairment and 82% of those who are blind are over 50 years of age. In the United States, there are 4.2 million who are blind or have a significant visual impairment, which is up by almost 30% in the last decade.¹ By 2015, it is thought that over 10 million Americans will be blind or have a significant visual impairment. These numbers are staggering in their effects on individuals and on our society in both the costs of healthcare and in lost productivity. As just one example, over 10 million Americans have been diagnosed with some form of retinal degeneration. These currently have poor treatment prospects, yet cost estimates for available treatments are huge, with direct medical costs of retinal disorders in 2013 of approximately $8.7 billion. Even for treatable disorders such as cataract and refractive errors annual costs in the United States are $10.7 and $16.1 billion, respectively. The total annual burden for visual disorders in the United States is estimated to be $139 billion (http://costofvision.preventblindness.org/costs/direct-costs/medical-costs-by-disorder). More specific data for both the prevalence and the economics of age-related eye diseases are given in the individual articles of this volume.

The eye is an amazing organ with the only two clear tissues in the body (Fig.). Its function is to receive and focus light and then transform that photic energy to chemical and electrical signals that are sent to the brain. There, they are recoded into the images that we describe when we talk about our sense of sight and seeing. There are several critical tissues that are directly involved in the visual process and many others that indirectly support this function. Initially, light enters the transparent cornea. From the back of the cornea, it passes through the aqueous humor, the fluid that feeds the lens, and on through the transparent lens. Both the cornea and lens are critical to focusing light on its final destination, the central foveal area of the retina, also called the macula. It is in the retina that the light is converted into chemical and then electrical impulses that are sent down the optic nerve to the brain. Together, the retina and brain constitute our central nervous system.

Time takes its toll on all the tissues of the eye. Common age-related problems at the eye surface include dry eye, and the major age-related disease in the lens is cataract. In the retina, aging is frequently accompanied by macular degeneration. These are discussed below and, in more detail, in the accompanying articles in this issue of Investigative Ophthalmology & Visual Science.

There are many other age-related problems that afflict the eye. With age, for example, the jelly-like vitreous body that fills
Figure. A schematic view of the tissues of the eye. Light passes through the transparent cornea and the opening in the center of the iris called the pupil. Then, it passes through the clear lens and the vitreous body, which fills the central cavity of the eye. When the optical properties of the cornea and lens are normal, the light is focused on the foveal (macula) area of the neural retina, and is captured by the retinal photoreceptor cells where it is converted into an electrical signal. The electrical signal is processed by other retinal cells and transmitted down the optic nerve to specific brain areas. These areas do the final conversion of the signals into a visual image.

The central cavity of the eye liquefies and is able to pull away from its natural attachments to the neural retina. This can lead to the presence of annoying floaters, but is also associated with sight-threatening retinal detachment. Preshypoxia is another example of natural aging changes that lead to a diminished ability to focus on near objects. Although usually correctable with eyeglasses, the cumulative optometric costs are high. Significant, age-related cell death in tissues, such as the cornea and retina, can lead to vision loss but, more importantly, set the stage for the onset of age-associated diseases. These are described individually below. Many of these deprivities have a genetic component, but they are also induced by environmental factors (e.g., smoking). Some are of unknown etiology. However, they are particularly insidious because they are generally painless in their earlier stages, and thus tend to remain unnoticed and untreated until it is often too late to institute an effective therapy. The National Eye Institute classifies glaucoma, AMD, and diabetic retinopathy in this category of usually asymptomatic, sight-threatening diseases.

THE ECONOMICS OF VISION LOSS

Although the present costs associated with visual impairment are approximately $139 billion/year in the United States (see above), worldwide, the International Federation on Aging predicts the cost of vision loss by 2020 will reach an alarming $2.8 trillion with indirect costs adding another $760 billion (http://www.ifa-fiv.org/ifa-publication/demographics/the-high-cost-of-low-vision-the-evidence) (see article by Rein in this volume for additional breakdown of costs associated with specific age-related eye deprivities). In the United States, the numbers are not strictly proportional with those worldwide and vary somewhat as to the particular eye disease as compiled by the American Academy of Ophthalmology in 2011. Although not the major blinding disease in the United States or much of the developed countries, cataract is the major cause of blindness in lesser developed countries where surgical options are limited. Additionally, risk is different for different age groups. Cataract, for example, affects about 22 million Americans age 40 and older. For those 80 years and above, more than half are affected with cataract, and the other major ocular diseases as considered individually in the next section.

Besides direct medical costs, there is a huge cost to society from related factors, such as the loss of independence, medical costs of secondary sequelae (falls, etc.), the loss of work productivity, and the ability to earn a living. A new analysis shows that indirect costs, such as productivity loss and long-term care “actually exceed direct costs for eye and vision problems.” Additional analyses place the costs at orders of greater magnitude; thus, delay of vision loss, improved low vision, or restoration of functional vision to those already blind could have an enormous impact, decreasing the costs of institutionalization and increasing personal productivity and revenue generation. Encouragingly, it is thought that just delaying cataract by only 10 years could eliminate the need for half of the cataractous-lens extractions, and markedly diminish the costs that are associated with the surgery and the loss of vision due to cataract.

MAJOR UNMET NEEDS FOR PREVENTION AND TREATMENT: INDIVIDUAL EYE CONDITIONS

1. Dry Eye: This age-related condition is estimated to affect 5 million persons in the United States or the age of 50. About twice as many women are affected with dry eye as men. It is estimated that 70% of Americans over the age of 60 have dysfunction of their meibomian glands, the glands of the eyelid responsible for production of the protective, oily components of tears. The condition is associated with discomfort and pain and may affect vision. Although some short-term treatments are available (eye drops, etc.), there are significant new opportunities here for prevention and better modes of treatment. This is also true in addressing other serious ocular surface problems such as bullous keratopathy, a condition caused by an age-related disease called Fuch’s dystrophy that can necessitate a costly corneal transplant. In all of this, there is the potential for significant cost savings with even only modest improvements in current modes of treatment.

2. Cataract: It is estimated that cataract affects almost 22 million Americans over the age of 40 and nearly half of US citizens over the age of 80.2 Direct costs for treatment are estimated at $10.7 billion/year. Indirect costs must be added on to this figure, but would be substantially decreased if cataract development could be delayed even a decade or two, or if cataract-induced vision loss could be more fully obviated through other means such as improved surgery, new drugs, optimized nutrition, and so forth. In many developing countries where cataract is more frequent at even earlier ages, the impact would be even greater.

3. Glaucoma: Glaucoma is a complex disease with vision loss due to pathologic changes of the neural retina, optic nerve, and brain but also with associated changes in areas of the anterior segment (i.e., the front portion of the eye). The most common forms of primary glaucoma can best be described as age related, possibly even as a disease of premature cellular senescence. There are
approximately 2.3 million Americans over the age of 40 with glaucoma 2 with a total estimate of 3.4 million by 2030. Unfortunately, an equal number have glaucoma without realizing it or it being diagnosed. Available treatments only slow disease progression toward severe vision loss and blindness; even the direct costs of glaucoma treatment were estimated to be $5.8 billion in the United States in 2013. (http://costofvision. preventblindness.org/costs/direct-costs/medical-costs-by-disorder). Treatment costs also include the rising costs of required surgery, in some cases, and the cost of visual disability. This will be an increasingly heavy economic burden on American healthcare as our population ages. Recently pinpointed opportunities for novel treatment (including gene therapy and stem cell therapy) could substantially bring down long-term care costs and the costs to society of visual disability due to glaucoma;

4. **Age-Related Macular Degeneration**: Age-Related Macular Degeneration, as the name implies, is an age-related disease most common in those over age 65. It is a complex disease in that has both genetic and environmental components (e.g., long-term smoking substantially increased the risk of developing AMD as it does for cataract). Today, more than 2 million Americans have significant vision loss due to AMD, 3 with up to 8 million more having earlier signs of the disease. In the 40- to 50-year-old age bracket, the prevalence of AMD is around 2% but, startlingly, over 80, it rises to 35%. Overall, AMD is the leading cause of blindness in industrialized nations like the United States. In 2010, the AMD Allian

5. **Diabetic Eye Complications**: Diabetes can lead to damage of many tissues, including many parts of the eye. Commonly, the retinal blood vessels are damaged, leading to subsequent vision loss and blindness. Diabetic retinopathy affects almost 4.5 million Americans over the age of 40, and is estimated to cost the US $500 million annually for its management. Diabetes also markedly increases the risk for cataract and diabetic cataracts develop at earlier ages than in nondiabetics. People with diabetes also have twice the risk of developing glaucoma, relative to nondiabetic persons. Sight-imparing problems with the cornea can also develop. In the retina, macular edema is a major complication of diabetes. Existing and new, abnormal retinal vessels may leak and fluid accumulates in the central macular region of the retina causing swelling and blurred vision. It has been estimated that up to 1 million Americans have macular edema with accompanying significant vision loss. As we now know, improvement in clinical healthcare as well as better education, including early diagnosis can substantially cut down on all the ocular problems of diabetes. Nevertheless, in part because of the obesity epidemic, the prevalence of diabetes is expected to rise along with the eye problems that are associated with diabetes (i.e., a high risk of severe vision loss). This requires urgent attention as it is an increasing global problem; and

6. **Low Vision**: Low vision is a condition in which a person’s vision is poor even with eyeglasses that afford the best correction possible. Low vision may be observed already in early childhood but increases dramatically with aging, mainly due to the eye diseases cited above. It has been estimated that there are 3.6 million Americans aged 40 and above, who are visually impaired with eyeglasses at 20/40 or worse even after correction. 2 Lighthouse International estimates that, because of the rapidly increasing numbers of baby boomers, 61 million Americans are now at risk of serious vision loss due to developing these age-related eye conditions.

**OPPORTUNITIES FOR PREVENTION AND TREATMENT**

As noted earlier, Prevent Blindness America recently estimated that our national financial burden for eye diseases is $139 billion annually. 2 They conclude that “eye disorders and vision loss are among the costliest conditions to the US economy and, based on ever-increasing healthcare costs and an aging population, this cost is set to continue to grow.” 2 On the other hand, it has been recently estimated that 80% of vision loss is preventable and that “vision loss is no longer an inevitable part of the aging process.”

How do we control these costs while alleviating the physical and societal problems of the individual suffering from vision loss and blindness, especially in an aging population at much greater risk of eye disabilities? One major step would be to convince governments, healthcare providers, and the general public that many eye diseases can, in fact, be managed or even obviated with early diagnosis. Programs that create early awareness and detection are key elements here with probable and quick success in substantially lowering the vision loss in our country and around the world. Another way is to take advantage of the recent increase in knowledge in understanding the basic biology of these eye diseases, and also new opportunities in translating this knowledge into meaningful preventions, treatments, and cures. Even a decade ago, these pathways to treatment were unknown or unrecognized. Now, they are becoming clearer and better defined, for instance, the “low-hanging fruit” alluded to at the beginning of this introduction. In this issue, readers will find articles that define the problems we currently face as we search for treatments for age-related eye diseases and also opportunities to alleviate these blinding conditions for the sake of both the individual and for our society.

**Acknowledgments**

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References


The Prevalence of Age-Related Eye Diseases and Visual Impairment in Aging: Current Estimates

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Purpose. To examine prevalence of five age-related eye conditions (age-related cataract, AMD, open-angle glaucoma, diabetic retinopathy [DR], and visual impairment) in the United States.

Methods. Review of published scientific articles and unpublished research findings.

Results. Cataract, AMD, open-angle glaucoma, DR, and visual impairment prevalences are high in four different studies of these conditions, especially in people over 75 years of age. There are disparities among racial/ethnic groups with higher age-specific prevalence of DR, open-angle glaucoma, and visual impairment in Hispanics and blacks compared with whites, higher prevalence of age-related cataract in whites compared with blacks, and higher prevalence of late AMD in whites compared with Hispanics and blacks. The estimates are based on old data and do not reflect recent changes in the distribution of age and race/ethnicity in the United States population. There are no epidemiologic estimates of prevalence for many visually-impairing conditions.

Conclusions. Ongoing prevalence surveys designed to provide reliable estimates of visual impairment, AMD, age-related cataract, open-angle glaucoma, and DR are needed. It is important to collect objective data on these and other conditions that affect vision and quality of life in order to plan for health care needs and identify areas for further research.

Keywords: age-related eye diseases, age-related macular degeneration, cataract, diabetic retinopathy, glaucoma, prevalence, review, visual impairment

Prevalence estimates indicate the burden of a condition (e.g., visual impairment) at a defined location at a point or period in time. Accurate prevalence estimates are needed to plan for availability of health care services, associated monetary costs, and quality of life connected with having the condition. Such data are also of importance in planning future studies, such as controlled clinical trials of prevention and treatment of the disease. Periodic estimates of prevalence enable the tracking of temporal trends; this is important especially in situations where new, costly interventions are being introduced. Prevalence estimates reflect disparities in vision loss and vision-threatening conditions among racial/ethnic groups as well as age, income, and education groups, as well as between the sexes. In addition to these characteristics, nutritional and environmental exposures may affect prevalences or disparities among groups. Aside from true disparities, apparent differences may be related to differences in case definition. For eye conditions this may rely upon self-reported history of a condition, findings at a clinical exam, or imaging (e.g., digital fundus photography, film fundus photography, optical coherence tomography). Variations in diagnostic procedures to define conditions (phenotypes) may further confound the ability to estimate prevalence as well as to identify temporal trends and cohort effects.

Definitional differences of conditions frequently occur among different groups of investigators, even when attempts are made to use the same characteristics and standardized protocols to classify subjects. For example, estimates of the prevalence of AMD may vary depending on whether size, type, and/or area of drusen or presence of retinal abnormalities are used to define its presence. This occurred among three population-based cohorts that used the Wisconsin Age-Related Maculopathy Grading System to classify and grade AMD lesions. Each group made modifications to the protocol. These modifications led to several systematic differences in grading fundus photographs that exaggerated differences in the prevalence of early AMD among the studies. Harmonization was required to achieve a uniform definition of early AMD to facilitate meta-analyses. Similar problems affect other conditions (e.g., open-angle glaucoma and cataract) because definitions and methods used to assess the conditions vary among studies.

Despite these problems, estimates, even if imperfect, are needed to describe public health and clinical burden as well as to plan for future needs. We describe estimates of prevalence of age-related cataract, open-angle glaucoma, AMD, diabetic retinopathy (DR), and visual impairment using data from several sources. We also highlight current needs in an effort to obtain data that will be used to successfully prevent visual loss due to these conditions.

Methods

Data are derived from the Eye Diseases Prevalence Research Group (EDPRG), the National Health and Nutrition Examination Survey (NHANES) III, the NHANES 1999 to 2008, and the National Health Interview Survey (NHIS). Other sources of data include local population-based studies (the Los Angeles Latino Eye Study [LALES]). Wisconsin Epidemiolog-
The EDPRG was a collaborative effort that combined data from up to 10 different studies of mostly European-derived populations, but including cohorts with persons of African or Mexican heritage: the Baltimore Eye Survey, the Barbados Eye Study, the BDES, the Blue Mountains Eye Study, Proyecto Vision Evaluation and Research, the Rotterdam Study, the Salisbury Eye Evaluation Project, the San Antonio Heart Study, the San Luis Valley Diabetes Study, and the Melbourne Visual Impairment Project. The number of studies contributing data depended upon each study’s availability of information on...
Blindness by WHO definition†

<table>
<thead>
<tr>
<th>Age, y</th>
<th>White Persons</th>
<th>Black Persons</th>
<th>Hispanic Persons</th>
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Blindness by US definition‡

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<td>70–74</td>
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Low vision§

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<td>10.84 (5.89–19.11)</td>
<td>17.72 (13.02–23.66)</td>
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* All estimates are based on the 2000 US Census population.
† Blindness as defined by the WHO standard is the best-corrected visual acuity of less than 6/120 (<20/400) in the better-seeing eye.
‡ Blindness as defined by the US definition is the best-corrected visual acuity of 6/60 or worse (<20/200) in the better-seeing eye.
§ Low vision is defined as the best-corrected visual acuity less than 6/12 (<20/40) in the better-seeing eye (excluding those who were categorized as being blind by the US definition).

Given disease or visual function. The purpose of this collaborative effort was to estimate prevalence in the year 2000 of visual impairment and of five specific eye conditions (refractive error, cataract, open-angle glaucoma, DR, and AMD) in people 40 years of age or older and to project prevalence estimates to the year 2020. The data in these studies were collected from as early as 1980 to as recently as 2000. An attempt was made to standardize diagnostic criteria among the studies. The EDPRG’s findings were presented in an issue of the Archives of Ophthalmology in 2004 and included tables and figures showing the prevalence of the specific condition by age, sex, and race/ethnicity for each study and combined estimates of prevalence and total numbers of persons of each condition in the United States (US) by age, sex, and race/ethnicity. These papers, along with their tables and figures, are available electronically.9,11,12,22,23

The NHANES was conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention.9,11,12,22,23 A stratified four-stage area probability sampling procedure was used to obtain a cross-sectional representative sample of the US civilian noninstitutionalized population aged 13 years and older for the NHANES III. It provided estimates of the prevalence of AMD and DR based on gradings of fundus photographs between 1988 and 1994 (one 45° nonstereoscopic field centered on the optic nerve head). In the 2005 to 2008 survey, two 45° nonstereoscopic fields, one centered on the optic nerve head and the other on the fovea of both eyes, were taken of people 40 years of age and older. In the 1999 to 2004 and 2005 to 2008 NHANES, the best-corrected visual acuity was measured and prevalence estimates of visual impairment were reported.11,13,24,25

The NHIS Vision Health supplement published in 2002 provides data based on self-reported diagnosed eye conditions (Table 1).14 The survey, involving 31,044 persons aged 18 years and older, was conducted by the US Census Bureau through in-person household interviews. The household response rate for the NHIS was 89.5%.

In the current paper, we include data from the LALES because of the limited amount of data on Hispanics, especially for cataract status.15 The study involved examination of 6357 Latinos 40 years and older living in six census tracts in Los Angeles, California. It included standard protocols to measure visual acuity and the grading of lens for identification of presence and severity of cataract at the slit lamp using the Lens...
Opacity Classification System II and fundus and optic disc photography; the Wisconsin Age-Related Maculopathy Grading System and the Airlie House classification scheme for DR were used in the grading of these photographs. The main outcomes included the prevalence and incidence of visual impairment, blindness, cataract, glaucoma, DR, and AMD. More detailed information is presented elsewhere.15

RESULTS

Estimated age-specific prevalence and number of people with the condition in the year 2000 from the EDPRG appear in Table 2.4–6 Estimates vary from a prevalence of 0.8% for geographic atrophy to 17.2% for cataract. Most estimates of eye disease prevalence increase with age. The heaviest burden of age-related eye disease was in those 80 years of age or older who had one-third of all cases of cataract, open-angle glaucoma, and early AMD and two-thirds of persons with late AMD.

Visual Impairment

In the EDPRG, the estimated number of persons with low vision (best-corrected visual acuity of <20/40 in the better seeing eye) and severe visual impairment (best-corrected visual acuity of <20/200 in the better seeing eye) for persons 40 years of age and older in the year 2000 was estimated to be 2,400,000 and 937,000, respectively.3 Visual impairment and severe visual impairment increased with age and age-specific prevalence were higher in blacks and Hispanics than whites (Table 3). Specific causes of blindness and visual impairment in the EDPRG vary by race/ethnicity.3 Severe visual impairment was most commonly attributed to cataract in blacks (56.8%) and in Hispanics (28.6%), and to AMD in whites (54.4%, Figure). The second most common cause of blindness was glaucoma in blacks (26.0%), AMD, cataract, and DR (14.3% for each) in Hispanics, and cataract in non-Hispanic whites (8.7%).

In the NHIS there were 19.1 million civilian, noninstitutionalized adults who reported some visual impairment by answering affirmatively the question: "Do you have any trouble seeing even when wearing glasses or contact lenses?" of whom 0.7 million reported being blind by answering affirmatively the question: "Are you blind or unable to see at all?" Self-reported visual impairment was 9.3% and increased with age, from 5.7% among people 18 to 44 years of age to 21.1% among people 75 years of age or older. Visual impairment was more frequent among women than among men and was inversely associated with education and income (Table 4). The prevalence of visual impairment was higher in non-Hispanic blacks than in non-Hispanic whites and Hispanics. In 2002, 30.6% of visually impaired people reported having 1 or more of 4 eye diseases in the past 12 months; the prevalence of cataract, glaucoma, AMD, and DR among people with visual impairment was 19.4%, 6.1%, 6.0%, and 3.4%, respectively. The prevalence of blindness among US adults was 0.3%, rose with age and was similar between men and women. The prevalence of blindness was higher in those aged 75 years.
Cataract

It was estimated by the EDPRG that there were 20.5 million persons older than 40 years of age in the United States with cataract (Table 2) and 6.1 million persons with aphakia/pseudophakia in the year 2000. The prevalence was 17.2% for cataract and 5.1% for aphakia/pseudophakia. The prevalence of cataract increased with age and for each specific age was higher in females than males and higher in whites than blacks (Table 5). Data were not available for cataract prevalence in Hispanics in the EDPRG. Data from the LALES, not included in the EDPRG, provided estimates of cataract prevalence based on slit-lamp evaluation using the Lens Opacity Classification System II (Table 6). 15,16

In the NHIS, the lifetime prevalence for self-reported diagnosed cataract was 8.6% (Table 1). Prevalence of diagnosed cataract increased with age, with the highest self-reported prevalence in persons 75 years and older (55%). Whites were more likely to report being diagnosed with cataract than black or Hispanic adults. These associations were similar to those reported in the EDPRG. There was no information on cataract prevalence in the NHANES because the study did not measure this endpoint.

Open-Angle Glaucoma

In the EDPRG, open-angle glaucoma was estimated to be present in 2,218,000 persons in the United States, a prevalence of 2%. 6 Open-angle glaucoma increased with age and was highest in blacks and lowest in whites, with Hispanics between whites and blacks (Table 7). Age-specific prevalence was higher in younger women than in younger men and was similar between men and women after age 70 years. In the 2002 NHIS, in persons aged 18 years and older, the lifetime prevalence for self-reported diagnosed glaucoma was 2% (Table 1), 14 Blacks were twice as likely as whites and Hispanics to have glaucoma, and more education and higher income were associated with lower prevalence of glaucoma. Data from the LALES for age-specific prevalence of glaucoma are presented in Table 6. 15,17 The prevalence in Mexican Americans was higher than in whites.

Age-Related Macular Degeneration

For AMD, estimates in the EDPRG were made only for blacks and non-Hispanic whites. There was an estimated 1.75 million persons with advanced AMD in at least one eye and 7.3 million with large drusen, a measure used to define early AMD, in the

---

**Table 4.** Prevalence of Visual Impairment and Blindness Among US Adults 18 Years and Older: National Health Interview Survey, 2002

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>Total</th>
<th>% (95% CI)</th>
<th>Blindness, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>18-44</td>
<td>5.7 (5.2, 6.2)</td>
<td>0.2 (0.1, 0.2)</td>
</tr>
<tr>
<td></td>
<td>45-54</td>
<td>11.5 (10.5, 12.5)</td>
<td>0.3 (0.2, 0.5)</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>10.4 (9.3, 11.4)</td>
<td>0.3 (0.1, 0.5)</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>14.5 (13.0, 16.0)</td>
<td>0.5 (0.3, 0.8)</td>
</tr>
<tr>
<td></td>
<td>≥75</td>
<td>21.1 (19.4, 22.8)</td>
<td>1.5 (1.0, 2.0)</td>
</tr>
<tr>
<td>Women</td>
<td>18-44</td>
<td>7.8 (7.3, 8.4)</td>
<td>0.3 (0.2, 0.5)</td>
</tr>
<tr>
<td></td>
<td>45-54</td>
<td>10.6 (10.0, 11.1)</td>
<td>0.3 (0.3, 0.4)</td>
</tr>
<tr>
<td>Race/ethnicity†</td>
<td>Non-Hispanic</td>
<td>11.7 (10.5, 13.0)</td>
<td>0.5 (0.2, 0.7)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>9.0 (7.9, 10.1)</td>
<td>0.4 (0.2, 0.7)</td>
</tr>
<tr>
<td>Income level‡</td>
<td>Below 200% of FPL</td>
<td>13.5 (12.5, 14.2)</td>
<td>0.7 (0.5, 0.9)</td>
</tr>
<tr>
<td></td>
<td>Above 200% of FPL</td>
<td>7.9 (7.4, 8.5)</td>
<td>0.2 (0.2, 0.3)</td>
</tr>
<tr>
<td>Education level†</td>
<td>Less than high school</td>
<td>14.4 (13.2, 15.5)</td>
<td>0.6 (0.4, 0.8)</td>
</tr>
<tr>
<td></td>
<td>High school graduate</td>
<td>10.2 (9.4, 11.0)</td>
<td>0.4 (0.2, 0.6)</td>
</tr>
<tr>
<td></td>
<td>Some college or associate’s degree</td>
<td>9.9 (9.1, 10.7)</td>
<td>0.3 (0.2, 0.4)</td>
</tr>
<tr>
<td></td>
<td>Bachelor’s degree or higher</td>
<td>7.4 (6.6, 8.2)</td>
<td>0.3 (0.1, 0.4)</td>
</tr>
<tr>
<td>Diagnosed diabetes‡</td>
<td>Persons with diabetes</td>
<td>18.4 (15.4, 21.3)</td>
<td>0.9 (0.3, 1.4)</td>
</tr>
<tr>
<td></td>
<td>Persons without diabetes</td>
<td>8.6 (8.2, 9.0)</td>
<td>0.3 (0.2, 0.4)</td>
</tr>
<tr>
<td>Total†</td>
<td>9.3 (8.9, 9.7)</td>
<td>0.4 (0.3, 0.4)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 5.** Prevalence of Cataract by Age, Sex, and Race/Ethnicity

<table>
<thead>
<tr>
<th>Sex/Age, y</th>
<th>White Persons</th>
<th>Black Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence per 100 Individuals (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>1.9 (1.2–2.8)</td>
<td>2.2 (1.4–3.5)</td>
</tr>
<tr>
<td>50–54</td>
<td>5.0 (4.0–6.2)</td>
<td>7.5 (5.7–9.3)</td>
</tr>
<tr>
<td>55–59</td>
<td>9.4 (7.7–11.5)</td>
<td>12.8 (10.2–16.0)</td>
</tr>
<tr>
<td>60–64</td>
<td>16.9 (14.1–20.0)</td>
<td>20.1 (16.4–24.2)</td>
</tr>
<tr>
<td>65–69</td>
<td>27.7 (24.1–31.6)</td>
<td>28.5 (24.3–33.1)</td>
</tr>
<tr>
<td>70–74</td>
<td>41.0 (36.9–45.1)</td>
<td>37.4 (32.6–42.5)</td>
</tr>
<tr>
<td>75–79</td>
<td>54.7 (50.2–59.1)</td>
<td>46.1 (40.1–52.2)</td>
</tr>
<tr>
<td>≥80</td>
<td>76.6 (71.2–81.2)</td>
<td>60.9 (51.0–69.9)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>2.8 (2.1–3.7)</td>
<td>1.7 (1.1–2.5)</td>
</tr>
<tr>
<td>50–54</td>
<td>4.9 (4.2–5.7)</td>
<td>4.5 (3.6–5.6)</td>
</tr>
<tr>
<td>55–59</td>
<td>8.2 (7.0–9.5)</td>
<td>7.6 (6.2–9.3)</td>
</tr>
<tr>
<td>60–64</td>
<td>13.8 (12.1–15.7)</td>
<td>11.9 (9.9–14.2)</td>
</tr>
<tr>
<td>65–69</td>
<td>22.4 (20.1–24.8)</td>
<td>17.5 (15.0–20.3)</td>
</tr>
<tr>
<td>70–74</td>
<td>33.9 (31.2–36.8)</td>
<td>24.1 (21.0–27.5)</td>
</tr>
<tr>
<td>75–79</td>
<td>47.2 (43.9–50.4)</td>
<td>31.3 (27.1–36.0)</td>
</tr>
<tr>
<td>≥80</td>
<td>71.3 (67.0–75.2)</td>
<td>46.2 (37.9–54.6)</td>
</tr>
</tbody>
</table>


* Includes blindness.
† Adjusted for age.
‡ Persons of Hispanic origin may be of any race.
§ Estimates are considered unreliable. Relative standard error is greater than 30%.
The prevalence of advanced AMD was 1.5%, with neovascular AMD estimated to be present in 1%, while pure geographic atrophy was estimated to be present in 0.8% (Table 2). The prevalence of early AMD, defined by the presence of at least one large druse (≥125 μm in diameter) in at least one eye, was 6% (Table 2). In the LALES, for Mexican Americans, the age-specific prevalence increased with age for signs of both early and late AMD (Table 6). In the NHIS, the prevalence of AMD was 1% and rose with age (Table 1). Diagnosed AMD was twice as prevalent among whites as among blacks.

Overall, the prevalence of any AMD in the 2005 to 2008 NHANES was 6.5%. This was lower than the 9.4% prevalence reported in the 1988 to 1994 NHANES III. This finding might be explained, in part, by possible methodological differences and differences in race/ethnicity distributions between the surveys. The lower overall prevalence of AMD in the more recent NHANES is consistent with a decreasing incidence of AMD in whites reported in the BDES and it has important public health care implications. It suggests that there may be fewer people with early AMD than expected based on projections that assumed that the prevalence would not change.

### Diabetic Retinopathy

Diabetic retinopathy is an important cause of severe visual impairment in persons 25 to 64 years of age. Its prevalence has been changing as a result of marked improvements in management of blood sugar, dyslipidemia, and blood pressure, as well as the development of new technology and medications to monitor blood sugar and treat high lipid and blood pressure levels.

The EDPRG estimated DR to be present in 4 million persons, of whom 900,000 were estimated to have vision-threatening diabetic retinopathy (VTDR) defined as the presence of severe non-proliferative DR or worse, or presence of macular edema. The prevalence was 40% and 8% for any DR and VTDR, respectively. In the NHANES 2005 to 2008, the prevalence of VTDR varied from 9.3% in non-Hispanic blacks and 7.3% in Mexican Americans to 3.2% in non-Hispanic whites (Table 8) and was lower than the EDPRG estimates. In the NHIS in 2000, the estimated prevalence of diagnosed diabetes among adults was 6.5%, or 13.4 million people; the estimated prevalence of DR among adults was 0.7%, or 1.3 million people; and the prevalence of DR among those with diagnosed diabetes was 9.9% (Table 9).

### Table 6. Estimated Prevalence of Eye Conditions in the Los Angeles Latino Eye Study

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Cataract, %</th>
<th>Open-Angle Glaucoma, %</th>
<th>Large Drusen ≥125-μm Diameter, %</th>
<th>Late AMD, %</th>
<th>Any Visual Impairment, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSC</td>
<td>NSC</td>
<td>Cortical</td>
<td>1.3</td>
<td>8.5</td>
</tr>
<tr>
<td>40–49</td>
<td>0.6</td>
<td>0.6</td>
<td>2.0</td>
<td>8.5</td>
<td>0</td>
</tr>
<tr>
<td>50–59</td>
<td>1.4</td>
<td>2.2</td>
<td>8.0</td>
<td>2.9</td>
<td>13.6</td>
</tr>
<tr>
<td>60–69</td>
<td>5.7</td>
<td>15.1</td>
<td>27.8</td>
<td>7.4</td>
<td>19.3</td>
</tr>
<tr>
<td>70–79</td>
<td>10.4</td>
<td>44.5</td>
<td>45.6</td>
<td>14.7</td>
<td>26.3</td>
</tr>
<tr>
<td>≥80</td>
<td>28.4</td>
<td>76.9</td>
<td>60.2</td>
<td>21.8</td>
<td>45.3</td>
</tr>
</tbody>
</table>

NSC, nuclear sclerotic cataract; PSC, posterior subcapsular cataract.

### Table 7. Prevalence of Open-Angle Glaucoma by Age, Sex, and Race/Ethnicity

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Prevalence per 100 Persons (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White Subjects</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>0.83 (0.65–1.06)</td>
</tr>
<tr>
<td>50–54</td>
<td>0.89 (0.78–1.02)</td>
</tr>
<tr>
<td>55–59</td>
<td>1.02 (0.89–1.16)</td>
</tr>
<tr>
<td>60–64</td>
<td>1.23 (1.07–1.41)</td>
</tr>
<tr>
<td>65–69</td>
<td>1.58 (1.37–1.82)</td>
</tr>
<tr>
<td>70–74</td>
<td>2.16 (1.87–2.49)</td>
</tr>
<tr>
<td>75–79</td>
<td>3.12 (2.68–3.63)</td>
</tr>
<tr>
<td>≥80</td>
<td>6.94 (5.40–8.88)</td>
</tr>
</tbody>
</table>

Men

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Prevalence per 100 Persons (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>0.36 (0.27–0.47)</td>
</tr>
<tr>
<td>50–54</td>
<td>0.61 (0.50–0.74)</td>
</tr>
<tr>
<td>55–59</td>
<td>0.85 (0.72–1.00)</td>
</tr>
<tr>
<td>60–64</td>
<td>1.18 (1.02–1.37)</td>
</tr>
<tr>
<td>65–69</td>
<td>1.64 (1.40–1.91)</td>
</tr>
<tr>
<td>70–74</td>
<td>2.27 (1.90–2.72)</td>
</tr>
<tr>
<td>75–79</td>
<td>3.14 (2.53–3.90)</td>
</tr>
<tr>
<td>≥80</td>
<td>5.58 (4.15–7.47)</td>
</tr>
</tbody>
</table>

Prevalence of DR appears to be declining. In the 8 years between the beginning of the WESDR and the beginning of the BDES, the prevalence of any DR in persons with type 2 diabetes fell by 30% (from 50% in the WESDR in 1980–1982 to 35% in the BDES in 1988–1990) and prevalence of VTDR fell by 70% (from 10% in the WESDR in 1980–1982 to 3% in the BDES in 1988–1990).

**DISCUSSION**

We have presented national estimates of the prevalence of visual impairment, cataract, open-angle glaucoma, AMD, and DR showing that they increase with age, and may vary by race/ethnicity and sex. Differences among studies regarding the age-specific prevalences of these conditions may be due to methodological issues (e.g., ophthalmoscopy versus grading of fundus photos) and differences in the definitions used. The prevalence estimates are largely from data collected mostly in the 1980s and 1990s, 25 to 30 years ago. There are no national data estimates for most corneal diseases, conditions affecting the optic nerve, and less common retinal conditions.

The following needs were identified:

1. Ongoing surveillance, through national surveys (e.g., the NHANES); objectively measuring the presence and severity of common conditions (e.g., age-related cataract, AMD, DR, and open-angle glaucoma); and those conditions not routinely measured in population-based studies (e.g., Fuchs’ dystrophy, ischemic optic neuropathy, macular hole, and dry eye);
2. Standardize protocols to be used in the field to assess each condition and establish consensus on how to define the conditions being studied;
3. Incorporate into classification schemes and validate new technologies (e.g., spectral domain optical coherence tomography) used to define the presence and severity of disease;
4. Identify cost-effective methods to measure phenotypes;
5. Incorporate economic analyses and quality of life measures in epidemiologic cohort studies;
6. Train clinicians in understanding and interpreting epidemiologic data; and
7. Educate the public and Congress on why collecting epidemiologic data is important.

**TABLE 8.** Estimated Prevalence of Diabetic Retinopathy and Vision-Threatening Diabetic Retinopathy in Individuals With Diabetes Aged 40 Years and Older and in the Adult US Population, by Age, Sex, and Race/Ethnicity: NHANES 2005 to 2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.*</th>
<th>No.†</th>
<th>Weighted Size, in Thousands‡</th>
<th>Diabetes Population</th>
<th>US Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>Crude prevalence of DR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1006</td>
<td>324</td>
<td>4202</td>
<td>28.5 (24.9–32.5)</td>
<td>3.8 (3.2–4.5)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–64</td>
<td>575</td>
<td>189</td>
<td>2588</td>
<td>28.0 (23.5–33.6)</td>
<td>0.64</td>
</tr>
<tr>
<td>≥ 65</td>
<td>431</td>
<td>135</td>
<td>1613</td>
<td>29.5 (25.4–33.9)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>504</td>
<td>173</td>
<td>2257</td>
<td>31.6 (26.8–36.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Female</td>
<td>502</td>
<td>151</td>
<td>1944</td>
<td>25.7 (21.7–30.1)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>396</td>
<td>107</td>
<td>2507</td>
<td>26.4 (21.4–32.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>306</td>
<td>119</td>
<td>1006</td>
<td>38.8 (31.9–46.1)</td>
<td></td>
</tr>
<tr>
<td>Mexican American</td>
<td>197</td>
<td>70</td>
<td>401</td>
<td>34.0 (26.7–42.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>107</td>
<td>28</td>
<td>286</td>
<td>19.7 (12.5–29.7)</td>
<td></td>
</tr>
<tr>
<td>Crude prevalence of vision-threatening DR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1006</td>
<td>62</td>
<td>655</td>
<td>4.4 (3.5–5.7)</td>
<td>0.6 (0.5–0.8)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–64</td>
<td>575</td>
<td>36</td>
<td>376</td>
<td>4.1 (2.8–5.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>≥ 65</td>
<td>431</td>
<td>26</td>
<td>278</td>
<td>5.1 (3.5–7.3)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>504</td>
<td>24</td>
<td>298</td>
<td>4.2 (2.8–6.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Female</td>
<td>502</td>
<td>38</td>
<td>356</td>
<td>4.7 (3.2–6.9)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>396</td>
<td>13</td>
<td>304</td>
<td>3.2 (2.0–5.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>306</td>
<td>28</td>
<td>241</td>
<td>9.3 (5.9–14.4)</td>
<td></td>
</tr>
<tr>
<td>Mexican American</td>
<td>197</td>
<td>16</td>
<td>85</td>
<td>7.3 (3.9–13.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>107</td>
<td>5</td>
<td>22</td>
<td>1.6 (0.6–5.8)§</td>
<td></td>
</tr>
</tbody>
</table>


* Number of participants with diabetes in NHANES 2005–2008.
† Number of participants with diabetes who had DR or VTDR in NHANES 2005–2008.
‡ Weighted total number of US adult population who had DR or VTDR.
§ Estimate is considered unreliable because relative standard error is greater than 30%.
Prevalences of Age-Related Eye Diseases


<table>
<thead>
<tr>
<th></th>
<th>Diabetest, % (95% CI)</th>
<th>DR, % (95% CI)</th>
<th>DR Among Adults With Diabetes, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>6.5 (6.2, 6.8)</td>
<td>0.7 (0.5, 0.9)</td>
<td>9.9 (8.5, 11.4)</td>
</tr>
<tr>
<td><strong>Age group, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–44</td>
<td>1.9 (1.7, 2.2)</td>
<td>0.2 (0.1, 0.2)</td>
<td>8.0 (5.0, 11.1)</td>
</tr>
<tr>
<td>45–54</td>
<td>7.4 (6.6, 8.2)</td>
<td>0.8 (0.5, 1.1)</td>
<td>9.8 (6.0, 13.6)</td>
</tr>
<tr>
<td>55–64</td>
<td>12.6 (11.4, 13.9)</td>
<td>1.3 (0.9, 1.6)</td>
<td>9.5 (6.7, 12.2)</td>
</tr>
<tr>
<td>65–74</td>
<td>17.3 (15.8, 18.7)</td>
<td>2.4 (1.7, 3.1)</td>
<td>12.4 (9.1, 15.8)</td>
</tr>
<tr>
<td>≥75</td>
<td>14.9 (13.4, 16.4)</td>
<td>1.5 (1.1, 2.0)</td>
<td>9.2 (6.3, 12.2)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7.3 (6.8, 7.8)</td>
<td>0.7 (0.6, 0.9)</td>
<td>8.0 (5.4, 10.5)</td>
</tr>
<tr>
<td>Female</td>
<td>6.1 (5.7, 6.5)</td>
<td>0.7 (0.6, 0.9)</td>
<td>8.1 (6.4, 9.9)</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>10.1 (9.1, 11.1)</td>
<td>1.2 (0.8, 1.6)</td>
<td>8.6 (5.5, 11.7)</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>5.8 (5.6, 6.1)</td>
<td>0.6 (0.3, 0.7)</td>
<td>7.3 (5.4, 9.2)</td>
</tr>
<tr>
<td>Hispanic†</td>
<td>9.3 (8.2, 10.4)</td>
<td>1.3 (0.8, 1.8)</td>
<td>10.6 (6.2, 14.9)</td>
</tr>
<tr>
<td><strong>Income level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 200% of FPL</td>
<td>9.0 (8.2, 9.7)</td>
<td>1.1 (0.9, 1.4)</td>
<td>9.0 (6.5, 11.5)</td>
</tr>
<tr>
<td>Above 200% of FPL</td>
<td>5.7 (5.4, 6.1)</td>
<td>0.6 (0.5, 0.7)</td>
<td>7.3 (5.4, 9.2)</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>11.3 (10.2, 12.3)</td>
<td>1.5 (1.1, 1.9)</td>
<td>10.4 (6.5, 14.2)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>7.8 (7.2, 8.5)</td>
<td>0.7 (0.5, 1.0)</td>
<td>7.1 (4.5, 9.7)</td>
</tr>
<tr>
<td>Some college or associate's degree</td>
<td>7.2 (6.5, 7.9)</td>
<td>0.9 (0.6, 1.1)</td>
<td>10.0 (7.0, 13.0)</td>
</tr>
<tr>
<td>Bachelor's degree or higher</td>
<td>4.8 (4.2, 5.4)</td>
<td>0.5 (0.3, 0.7)</td>
<td>10.7 (5.0, 16.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6.6 (6.3, 6.9)</td>
<td>0.7 (0.6, 0.8)</td>
<td>8.0 (6.5, 9.4)</td>
</tr>
</tbody>
</table>


* Adjusted for age.
† Persons of Hispanic origin may be of any race/ethnicity.

**Acknowledgments**

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Disclosure: R. Klein, None; B.E.K. Klein, None

**References**

Projected Prevalences of Age-Related Eye Diseases

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Purpose. To examine projections of age-related eye diseases in the United States for health care planning.

Methods. Review of published scientific articles, census data, and unpublished research findings.

Results. The numbers of cases of all age-related eye diseases are expected to rise in the coming years. These projections are primarily based upon population projections, but give little consideration to changes in health behaviors, racial/ethnic differences, environmental exposures, and changes in health care practices that may influence estimates of costs of actual health care burden.

Conclusions. Ongoing monitoring of trends in eye disease distribution is needed rather than projections based on old data that may be inadequate for generating reliable prediction models. There is a perpetual need to train new researchers with expertise in epidemiology, as the exigency for current prevalence estimates is crucial to maximize optimal visual health in the population.

Keywords: age-related eye diseases, prevalence, review

The prevalence of most eye diseases increases with age in virtually all populations. The Eye Diseases Prevalence Research Group (EDPRG) reported on data from ten different prevalence studies to estimate the prevalence of visual impairment and several specific eye diseases in persons 40 years of age or older to estimate the burden of these conditions in the United States (US) in 2000.1–6 These data and information from the National Health and Nutrition Examination Survey (NHANES) and other sources are compiled in another publication in this volume. In order to plan for future eye healthcare needs, projections for the future are desirable. It is the purpose of this paper to briefly describe current projections and potential limitations thereof.

Materials and Methods

Study Population

Population projections to the year 2020 are from published projections from the EDPRG. For POAG, the projections are supplemented by information from 2011.7

Measurements

Estimates of prevalence were based on protocols that varied among the studies. Errors and systematic differences among studies are incorporated in the projections because there were no attempts to adjust prevalence data to uniform criteria for diagnostic labeling.

An example of the varying criteria for diagnostic labeling was given for glaucoma. In the EDPRG, six different sets of criteria were given for the studies.5 Some included disc photography, cutpoints varied for cup/disc diagnostic criteria, some studies included a cutpoint for IOP, each used different techniques to assess visual fields, and some studies had subjective evaluation of components of glaucoma-related abnormalities, while others used a uniform set of criteria.

Statistical Analysis

The projected estimates from the EDPRG of the numbers and percentages of persons with the conditions were generated by applying the age, sex, and race/ethnicity of the prevalence data estimated for 2000 to projected middle series population projections for 2020.1–6 For the POAG estimates, Vajaranant and colleagues used prevalence estimates from the Baltimore Eye Survey, the Los Angeles Latino Eye Study, and the Tanjong Pagar Survey and applied these to the US Census population projections from 2011 to 2050 using middle series.7 Census population projections for 2000 to 2050 as well as methods for the 2012 updated projections were obtained from the US Census Bureau.8,9 Figures in this paper are reproduced from reports from the US Census Bureau;10 the Table is a summary of projections that appeared in papers from the EDPRG.1–6

Results

Predictions of disease prevalence depend upon projections of population changes by age and sex to the same date as the predictions aim for. For example, Figure 1 describes the middle series projections of the population by age and sex for 2012 to 2060 as calculated by the US Census Bureau.

The EDPRG projected prevalences of age-related eye diseases and visual functions from the year 2000 to 2020 based on projections of the US population to 2020 (Table). The estimated number of cases of each disorder was projected to increase over the 20-year period. They made the
assumption that prevalence would remain the same; the projected increase in number is a reflection of the increase in the population size. However, projections should also account for shifting demographics of the population, as these may affect disease estimates. The US Census Bureau provided estimates by region of origin of foreign-born immigrants (Fig. 2).

The US Census Bureau projected that the non-Hispanic, white population will peak in 2024 and then fall by nearly 20.6 million to approximately 179 million by 2060, while the Hispanic population will increase to approximately 128.8 million, the black population will increase to approximately 61.8 million, and the Asian population will increase to approximately 34.4 million. Members of other racial/ethnic groups including American Indians, Alaskan Natives, Native Hawaiians, and other Pacific Islanders as well as those who identify themselves as being of two or more races/ethnicities will also increase. The older population will still be primarily non-Hispanic white in 2060 but this will change in subsequent years as the increasing numbers of persons of other races/ethnicities age.

Attempting to adjust for racial/ethnic shifts in demography, Vajaranant and colleagues projected the burden of POAG in 2050 based on the estimated prevalence in 2011. Their assumption was that more recent population projections accounting for shifts in race/ethnicity, especially for Hispanics and Asians, would improve upon the estimates made by the EDPRG. They estimated that there were 2.71 million persons with POAG in 2011 and that this number would increase to 7.32 million by 2050. However, population projections tend to be imperfect and the longer the time period in the forecast, the less accurate it tends to be. A comparison of US population projections made in 2008 and again in 2012 to the year 2050 illustrates this problem (Fig. 3). The estimated population projections differ by nearly 10%. Those data will be reflected in different predictions of estimates of disease prevalence.

There are other factors that predictions based solely on projected differences in population by demographic changes do not account for. There are temporal changes in the distribution of risk factors (e.g., changes in care of persons with diabetes, increasingly frequent cataract surgery, changes in socioeconomic status, access to care, and changes in environmental exposures, such as exposure to UV-B light). In addition, there appear to be temporal patterns in disease incidence, which are also likely to affect prevalence in

TABLE. Eye Diseases Prevalence Research Group Estimates of Age-Related Eye Disease Prevalences in 2000 and Projections to 2020 in Persons Aged 40 Years and Older

<table>
<thead>
<tr>
<th>Eye Disease</th>
<th>2000 N in Millions (%)</th>
<th>2020 N in Millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract*</td>
<td>20.5 (17.2)</td>
<td>30.1</td>
</tr>
<tr>
<td>Pseudophakia†</td>
<td>6.1 (5.1)</td>
<td>9.5</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>4.1 (3.4)</td>
<td>6.1</td>
</tr>
<tr>
<td>Vision-threatening diabetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>retinopathy</td>
<td>0.9 (0.8)</td>
<td>1.4</td>
</tr>
<tr>
<td>Open-angle glaucoma</td>
<td>2.2 (1.9)</td>
<td>3.4</td>
</tr>
<tr>
<td>Late age-related macular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>degeneration</td>
<td>1.8 (1.5)</td>
<td>3.0</td>
</tr>
<tr>
<td>Large drusen</td>
<td>7.3 (6.1)</td>
<td>13.7</td>
</tr>
<tr>
<td>Blindness</td>
<td>0.9 (0.8)</td>
<td>1.6</td>
</tr>
<tr>
<td>Low vision</td>
<td>2.4 (2.0)</td>
<td>3.9</td>
</tr>
</tbody>
</table>

* Omits Mexican Americans.
† Includes Mexican Americans.

61.8 million, and the Asian population will increase to approximately 34.4 million. Members of other racial/ethnic groups including American Indians, Alaskan Natives, Native Hawaiians, and other Pacific Islanders as well as those who identify themselves as being of two or more races/ethnicities will also increase. The older population will still be primarily non-Hispanic white in 2060 but this will change in subsequent years as the increasing numbers of persons of other races/ethnicities age.

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There are other factors that predictions based solely on projected differences in population by demographic changes do not account for. There are temporal changes in the distribution of risk factors (e.g., changes in care of persons with diabetes, increasingly frequent cataract surgery, changes in socioeconomic status, access to care, and changes in environmental exposures, such as exposure to UV-B light). In addition, there appear to be temporal patterns in disease incidence, which are also likely to affect prevalence in
DISCUSSION

Current projections of eye disease prevalence have been based largely on data that were collected many years ago and are restricted to a few eye conditions that are considered to be responsible for either visual loss (visual acuity poorer than 20/40 in the better seeing eye) or legal blindness (visual acuity poorer than 20/200 in the better seeing eye). These projections have been made for at best a handful of eye conditions. There are no known population projections for prevalence of dry eye, retinal vein occlusions, or many corneal conditions, which seem to be as prevalent as those for which projections have...
been made. These conditions should be considered when projecting disability from and remediation of age-related eye conditions.

Accurate estimates of prevalence and projections for future health care needs depend upon inclusion of all subgroups in the population. This implies systematic inclusion of samples of all persons including those currently undercounted and underserved. Access to care is likely to be improved by the Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act. In addition, information about such improved access as well as education about the benefits of using such care needs to be implemented.

In summary, projections of prevalence are critical for planning for preventive and health care services with implications for function, quality of life, and costs; accurate projections are difficult to make and should be time-limited; every effort must be made to consider factors that the census does and any important known risk and preventive factors as well as temporal changes in them; frequent reassessment of outcomes and risk/protective factors is essential; and funding and encouragement for training of ocular epidemiologists is imperative to optimize planning for public health priorities to prevent or diminish the toll of age-related eye disease.

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References

Vision Problems Are a Leading Source of Modifiable Health Expenditures

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According to recent studies, visual problems represent one of the top contributors to economic health burden in the United States. This burden is divided nearly equally between direct expenditures for the care and treatment of visual problems, and the indirect costs of outcomes caused by low vision, including productivity losses, the cost of care, and incremental nursing home placements. A large amount of academic research is devoted to visual science, the biology of the visual system, and the medical treatment of visual disorders. Compared to the burden, a disproportionate share of this research is devoted to the study of retinal disorders and glaucoma. This is understandable, as research into the retina and optic nerve has the potential to unlock fundamental insights into the nature of sight and visual cognition. However, population visual health and the functionality that depends upon it also may benefit greatly from additional research into areas of prevention, rehabilitation, and adaptation. In addition, comparative research into the benefits of resource allocation across prevention, treatment, and rehabilitative resources could lead to improvements in population health.

Keywords: economics, review, value of information, cost-effectiveness, resource allocation

Visual disorders represent one of the most important sources of economic medical costs in the United States. A recent study released by Prevent Blindness America (PBA) estimated the burden of visual problems at $139 billion annually in 2013, with direct medical costs representing $65.1 billion of the total burden. According to this estimate, the direct medical costs of visual problems is one of the leading sources of medical expenditures in the United States, possibly exceeded only by heart conditions, trauma, cancer, and mental health disorders.1,2 Visual problems also are associated with substantial indirect costs, many of which may be preventable through earlier or better detection and treatment, or through efforts to provide rehabilitative and support services to those with visual impairment and blindness.

The new estimation of the size of the economic impact of visual problems provides the opportunity to evaluate options and methods to focus research, treatment, and rehabilitative efforts to ameliorate the impact of visual impairment in the US population. The fields of health economics, outcomes, and operations research can help with decision making and resource prioritization by relating choices and investments to the potential quality and quantity of vision they produce, the degree of independent functioning they enable, or the insights and scientific information they may generate.

To suggest possible directions for future economic work in the field of visual health, this article reviews new estimates of the burden of visual problems and the causes of this burden. It then relates this burden to research efforts in the field to compare how current research maps to burden. Next, the article discusses the different uses of economic studies at different phases of the policy process, and compares existing economic research in the visual health field to those categories. Finally, the article concludes with some possible suggestions for prioritizing future economic research.

NEW ESTIMATES OF THE BURDEN OF VISUAL DISORDERS

The most comprehensive estimate of the burden of visual disorders comes from a recently released Prevent Blindness America study that estimated the economic burden of visual problems in the United States. According to this study, the burden of visual disorders represents one of the largest health care expenditure categories in the country, costing the US economy approximately $139 billion annually.1 Of these costs, direct costs accounted for 48% of the economic burden of visual problems and indirect costs accounted for 52%. It is instructive to consider what conditions and services were responsible for the majority of this burden. The study was able to allocate only the $65.1 billion associated with direct medical costs (the majority of direct costs) to individual disorders. Of direct medical costs, the study found that refractive error produced the greatest aggregate direct medical burden (24.7%), followed by cataract (16.4%), diagnosed visual impairment and blindness (16.0%), physical disorders (13.7%), disorders of the retina (13.4%), glaucoma and disorders of the optic nerve (8.9%), and other visual problems (6.9%). The major drivers of indirect costs, which the study did not allocate to individual disorders, were incremental nursing home placements and productivity losses.

COMPARISONS OF VISUAL BURDEN TO VISUAL RESEARCH

Understanding how scientific research maps to the drivers of burden can help us understand how current research priorities roughly map to areas of economic consequence. To develop a measure of scientific volume, I compiled PubMed search results...
related to the visual sciences and used these results to estimate the number of articles in each general visual health condition area. I then compared research volume to drivers of direct medical costs as estimated in the PBA study.1,3

To do so, I first created a list of search terms associated with the topic areas of “Cataract,” “Glaucoma,” “Ocular Physical Disorders,” “Ocular Health Researchers,” “Refractive Error,” “Retinal Disorders,” and “Vision Problems and Blindness” (Supplementary Appendix A), and their associated Medical Subject Headings (MeSH), and created an inclusive search for articles referenced by PubMed using these terms over the last five years (July 5, 2008 to July 3, 2013). This search resulted in an aggregate total of 134,582 articles related to visual science over the last five years. A cursory quality check of these results indicated that, while a few references were tangential or unrelated, the majority of articles did include some reference to or research regarding a visual science topic. As a further limitation, this search likely also omitted some relevant articles that were not captured directly by one of the search terms. However, given the review and commentary nature of this article, this study accepted the list of 134,582 articles as an adequate, if rough, measure of visual science research priorities over the last five years.

To allocate these articles to individual conditions, I next searched within this restricted list to identify the number of articles that referenced each condition. Article identification was not mutually exclusive in that a single article could be counted in more than one topic area if it contained references to multiple condition categories. This generated a list of the aggregate number of articles that discussed each condition area over the last five years (Table 1). Following article identification, the number of articles in each topic area was divided by the total number of articles identified using all terms to identify the percentage of total articles in which the topic was mentioned.

Table 1 compares each visual condition’s percentage contribution to direct medical costs to its percentage contribution to scientific articles over the last five years. Table 1 also shows the ratio of the percentage of articles to the percentage of direct medical costs. When viewed in this manner, the areas of refractive error and cataract generated a lower proportion of scientific articles compared to what would be expected if articles were driven purely proportionally by direct medical costs. Likewise, the areas of retinal disorders and glaucoma generated a larger proportion of articles as did “Other vision problems,” which included all ocular research other than the visual disorders listed. Vision problems and ocular physical disorders generated articles in proportion to their burden.

This rough measure is descriptive in nature and is not meant to be taken as a prescriptive recommendation to study more or less in certain areas. Studies directed toward the retina, the causes of glaucoma, and the functioning and impairment of the optic nerve represent fundamental areas of remaining mystery in the visual sciences. Unlocking the secrets of these systems may result in paradigm shifting breakthroughs in our understanding of vision, aging, and cognition. At the same time, the results are suggestive that certain areas of visual dysfunction may warrant additional attention. Also clear is that the indirect consequences of visual disorders often are overlooked within these articles on visual health. For example, searching within the 134,582 articles for the term “Rehabilitation” resulted in 3191 articles, searching within these articles for “Productivity” resulted in 1935 articles, and searching within these results for “Long Term Care,” “Nursing Home,” or “Skilled Nursing Facility” resulted in only 670 articles.

### Economics in Visual Research by Policy Stage and Use

A number of types of health economic studies potentially could help rationalize and direct the flow of visual health resources towards the areas that are most likely to increase the quality of visual health, and to mitigate or reduce the burden of visual disease. Different types of economic studies are appropriate at different stages of the health care policy process (Table 2). In the formative stage of policy, economic burden studies can help describe the magnitude of a condition compared to other problems, health valuation studies can assign comparative utility values to morbidity from a condition, and value of information research can help identify where specific research investments potentially can yield the greatest benefits.

Several excellent examples of each type of work have been reported over the last five years. For example, Wittenborn and Rein estimated the burden of visual disorders among those in the United States who were younger than age 40.4 Wittenborn et al. also estimated the PBA study discussed above.1 In an extremely important study, Tahhan et al. established and quantified the utility impact of uncorrected refractive error, a finding that should elevate the importance of interventions for this condition.5 Although value of information research has been used rarely in the visual sciences, Karmon et al. demonstrated its potential in an analysis of how additional research on the utility impact of monocular visual impairment could alter...
decisions to disinvest in amblyopia screening programs in the United Kingdom.6

In the deliberative stage of policy analysis, cost–utility and cost–benefit studies are of use in determining the relative value of new interventions or health technologies to address visual problems; actuarial or insurance studies illustrate how changes in medical recommendations can impact payers, and how these costs can be managed over time; and resource allocation studies can be used to optimize desired outcomes (e.g., days of healthy vision) given several cost-effective, but also costly visual interventions. As with formative studies, excellent work has been conducted in these areas over the last five years, primarily in the area of cost–utility analysis. Crane et al. used an advanced simulation and primary data sources to provide objective evidence on the relative cost-effectiveness of different treatment decisions for patients with glaucoma in Australia.7 Gower et al. used cost–utility analysis to demonstrate that ranibizumab was a cost-effective alternative to either pegaptanib or photodynamic therapy in the treatment of AMD-related choroidal neovascularization.8 Rein et al. used an agent-based model of six different eye disorders to argue that universal dilated eye evaluations at Medicare entry was a cost-effective policy that should be pursued.9 Compared to cost–utility work, work on financing care for visual conditions or on allocating resources across visual interventions was sparse, although a few good examples were identified.10,11

In the action stage of policy, economic research can assist with the identification of best practices across divergent implementation methods, to identify the aggregate and marginal production costs of health services, and to determine the financial return on investments in new practices or technologies to different payers. Many strong examples of economic evaluations of implementation work have been published over the last five years. For example, Li et al. estimated the implementation cost of telemedicine monitoring for diabetic retinopathy in a federally qualified health center compared to the costs that would have been experienced if the same patients had received a retinal exam by an eye care professional.12 Beauchamp et al. used a return on investment approach to argue for the value and importance of investments to improve childhood amblyopia screening programs.13 Also in the field of amblyopia screening, Rein et al. estimated the implementation costs of three state screening programs,14 and Longmuir et al. used cost-assessment methods to measure the programmatic costs of photo screening methods.15 Vinekar et al. collected primary data on the implementation costs of retinopathy of prematurity screening in India to demonstrate best practices and the feasibility of expanded implementation of simple programs that can save vision in the developing world.16

**Current Needs and Future Directions for Economic Research in the Field of Visual Science**

Despite the outstanding economic work that has been published in the field of visual sciences, opportunities exist to expand the generalized uses of economic and financial concepts in the management of research and prevention dollars related to visual health. Primary areas of opportunity include using value of information (VOI) methods to prioritize research, taking a portfolio perspective to funding research, and finally developing resource allocation models around visual objective functions of interest in an effort to prioritize research, prevention, and treatment dollars. In addition, efforts to use systematic reviews to determine best practices and preferred practice patterns to standardize care around quality standards have the potential to improve the quality of care and lower costs.

**Value of Information**

VOI refers to a series of methods developed in the decision sciences and used to quantify the value of additional research to reduce uncertainty regarding specific decisions. In generalized terms, VOI methods account for the size or economic burden of a problem, the degree to which a problem could be mitigated through action, and the cost of that action, and the level of uncertainty regarding a decision to take action. Several factors contribute to a larger VOI for a specific problem, action, or decision. For example, problems with higher burden, problems that currently or potentially can be solved, problems with costlier solutions, and problems where the outcome of a treatment or intervention is uncertain all are more likely to result in a higher VOI gained from research conducted in the area.17

VOI calculations could be used to justify the need for research much in the same way power calculations are now used to justify that research has the ability to capture the relevant effect size. Research could be prioritized based on objective criteria regarding the nature of information sought, its uses to other scientists or policy makers, the level of uncertainty in specific parameters regarding the phenomena, and the burden of a phenomenon to be studied.

For example, in the visual sciences, in 2009 a Cochrane Review concluded that no systematic evidence existed to demonstrate the utility impact of amblyopic monocular blindness on patient utility, and without such evidence the cost-effectiveness of widely adopted amblyopia school screening programs could not be established.18 Cost-effectiveness analyses identified utility losses from monocular visual loss as the driving factor in determining the cost-effectiveness of amblyopia screening programs and recommended additional

| TABLE 2. Health Economic Studies by Policy Stage and Purpose |
|---|---|---|---|
| **Policy Stage** | **Purpose** | **Types of Knowledge Gaps** | **Types of Health Economic Studies** |
| Formative | Agenda and priority Setting | Size of problem | Burden of disease |
| | | Patient health impacts | Health utility assessment |
| | | Modifiable burden | Value of information |
| Deliberative | Decision making | Value of interventions | Cost–utility, cost-benefit |
| | | Financing implications | Actuarial |
| | | Trade-offs and optimization | Resource allocation |
| | | Financial benefit per payer | Return on investment |
| | | Resource requirements | Costs, costs per outcome |
| Action | Implementation | | |
research into this parameter.14,19 Concurrent VOI analyses estimated that research on utility losses from monocular vision loss were valued at as much as £45 million in England and Wales (equivalent 2012 value of $355 million in the United States after adjusting this figure for inflation, currency exchange rates, and larger population size in the United States) in terms of the information's ability to guide optimal policy decisions.19 Such concrete information on potential quantitative benefit of proposed research studies could be used to prioritize clinical trial development around policy needs and information gaps.

**RESEARCH PORTFOLIO MANAGEMENT**

Some bench scientists may recoil in horror at the idea that new scientific research must always be judged based solely on its monetized value in shaping today's policies or treatment protocols. Many scientific questions may not be connected easily to immediate shifts in policy. Science directed at today's most pressing problems or questions will always appear to be a high priority, but without investments in basic science we may never achieve the breakthroughs that drive the evolution of visual science.20

Funders of research can address the conflict between immediate medical and decision-making needs, and investments in the future by taking a portfolio approach to their research funding. In the same way that smart financial investors will diversify their investments among different vehicles, funders of research can diversify their investments into research. Such funders can allocate research resources explicitly among a few large scale, established research investments likely to yield important, but incremental knowledge tied directly to current known policy or scientific needs, and many smaller more speculative investments in less orthodox ideas. Examples of criteria that can be used to evaluate appeals for scientific support include the potential near term impact on the quality and quantity of vision experienced by the population, the impact of the condition on economic burden, the relative need for research in an area, the level of innovation or novelty of a research idea, and finally the transformational potential of the research. By spreading money across these priority areas while making sure to invest in each, the funding agency can assure annual incremental progress through sound and safe investments, while also allowing opportunity for the development of new transformational information.

**RESOURCE ALLOCATION MODELS**

Resource allocation models offer another area of possible opportunity for the field of health economics to contribute to vision research. In general terms, resource allocation models refer to any system (usually a set of linear equations) that attempts to distribute finite resources among alternative uses in a manner that maximizes a given output. Resource allocation models can help policy makers in visual health think about investments that maximize one of several outcomes of relevance. Such models could focus on maximizing the quantity and quality of visual perception experienced across a target population, minimizing the functional impacts of visual impairments, or some combination of both outcomes.

Currently, medical resources in visual health are allocated across multiple conditions based primarily on disease prevalence and the availability of medical treatment technologies. Whether treated or untreated, these conditions result in visual consequences such as annual productivity losses and incremental nursing home placements whose annual costs exceed those of medical treatment.1 Resource allocation models can help think through questions of new investments in resources and research in a way that minimizes the negative consequences of disease. Research allocation models have been developed in fields such as cancer, human immunodeficiency virus (HIV), and tuberculosis treatment and prevention, although their overall use in health care is rare.21-25 Such models are ideal for visual health because multiple conditions and circumstances affect a common functional system; human vision and the activities that depend on it.

**CONCLUSIONS**

Recent economic research suggests that the cumulative direct medical costs of vision problems rival the burden of other major medical conditions, such as cancer, heart disease, diabetes, and mental health.1,2 In addition to direct medical costs, visual problems also are responsible for an equal to slightly greater burden in the form of productivity losses, costs of informal care, and incremental nursing home placements. If the utility losses from visual losses could be monetized to reflect their personal toll on well-being and happiness, the costs of visual problems would be greater still.

Much of the burden of visual disorders potentially could be mediated through at least the three avenues: Prevention and diagnostic screening, medical treatment of diagnosed conditions, and rehabilitation and support services for those with visual impairment. Annually, tens of thousands of articles across these areas are published discussing medical, policy, and economic aspects of visual problems. Despite this excellent and growing body of work, insufficient research is directed toward comparative research across conditions and across domains of service. For example, research comparing the population benefits of investments in medical treatments for those with vision-threatening disease compared to rehabilitation and adaptive services for those who have previously-acquired impairment is virtually nonexistent. Research to determine comparatively which strategies and practices maximize the population’s quality and quantity of vision, and minimize the personal and familial impacts of visual impairment is needed to inform future allocations of resources in visual health. Additionally, work to communicate scientific achievements in the visual sciences in terms of gains in vision and decrements in disability, outcomes that the public understands, may help boost external support for visual health research that is commensurate with the economic burden of the field.

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Leading Source of Modifiable Health Expenditures


Numerous anatomic changes occur in the eye with age. These changes generally include loss and attenuation of cells, such as the corneal endothelium and RPE; degenerative processes, such as vitreous liquefaction; and accumulations of materials, such as drusen. There are research opportunities to image the effects of aging, thus, predicting diseases that are characterized by abnormal or premature aging as well as understanding the effects of aging on therapeutic drug delivery to arrest ocular disease.

CORNEA
As the eye ages, the cornea flattens. The thickness of Bowman’s layer, 8 to 10 μm, remains constant throughout life. There is a tendency for calcific deposition at the periphery of Bowman’s layer with aging. Arcus senilis, a deposition of lipid near the limbus, also may occur with aging. The stromal keratocyte density appears higher in children than adults. Arcus senilis, a deposition of lipid near the limbus, also may occur with aging. The stromal keratocyte density appears higher in children than adults.

Trabecular Meshwork
With age, the trabecular meshwork changes histologically from a long, wedge shape to a shorter, more rhomboidal form. The trabecular meshwork becomes progressively thickened and ultrastructural examination shows a change in the appearance of extracellular materials. The trabeculae become collagenized, there are choroidal vascular changes, and Bruch’s membrane thickens. Retinal vessels become hyalinized and there is a loss of rods before cones in the macula. RPE morphometric changes occur with aging. The vitreous becomes liquefied and there is a loss of vitreous compartmentalization. The sclera becomes rigid and may become calcified. The optic nerve exhibits structural changes with age.

Keywords: aging, anatomy, pathology
Aging and Eye Disease

**Ciliary Body**

With advancing age, the stroma of the ciliary processes becomes collagenized, the processes appear to become less vascularized, and they also appear shorter and more blunt. The cellularity of the ciliary body appears to diminish with age and the ciliary body smooth muscle bundles undergo age-related changes in morphology suggestive of an antero-inwards displacement of the muscle mass. Occasionally, age-related hyperplasia of the ciliary body nonpigmented epithelium occurs and forms a Fuchs adenoma. This is a benign lesion that may occur as an incidental finding in eye bank eyes, although occasionally it clinically mimics a malignant neoplasm.

**Lens**

The shape of the crystalline lens in histologic sections changes with age. In infants, the lens assumes a reniform configuration, whereas in adults, it is more oval. The lens increases in weight from approximately 90 mg at birth to 150 mg at age 20 years, 190 mg at age 40 years, and 240 mg at age 80 years. Cataracts are associated with aging and are manifest with color changes in the lens due to oxidation of lens proteins. The most common age-related histologic cataractous changes are equatorial and posterior cortical degeneration. These changes result in inward turning of equatorial cortical fibers, and in a difference in staining with hematoxylin and eosin between the lens nucleus and cortex. This may be accompanied by posterior migration of the lens epithelium. These cells may lie along the inner surface of the posterior capsule, and become balloon-like and swollen (Wedl cells). A proliferation of these cells along the posterior capsule results in posterior subcapsular cataract.

**Retina**

With aging, there is diffuse thickening of the internal limiting membrane of the retina and diminution of neural elements with gliosis in the peripheral retina. These changes lead to disorganization in the area of the ora serrata, and the RPE may migrate into the sensory retina in this area. There may be a reduction of nuclei in the outer nuclear layer of the retina with age. Corpora amylacea may be observed in the peripapillary retinal nerve fiber layer, optic nerve head, and optic nerve as an aging process. These bodies appear to be accumulations of intracellular organelles, including neurotubules, mitochondria, and dense bodies. Curcio et al. have demonstrated a progressive, age-related loss of rods before cones in the macula with an accompanying decline in scotopic sensitivity compared to photopic sensitivity. Typical peripheral cystoid degeneration, which is not seen in infant eyes, is present in virtually 100% of adults eyes. Retinal vessels exhibit changes associated with aging. These include widespread loss of cellularity in the peripheral capillaries of elderly persons with attachment of the inner limiting membrane to the peripheral vascular arcades. Additionally, there is a diminution in the number of capillaries around the fovea. Arteriosclerotic changes also can occur in retinal vessels with aging. These include thickening and hyalinization of the vessel wall. Other arteriosclerotic changes, including hyperplasia of the muscular layer and fibrinoid necrosis of the vessel wall, occur in the setting of hypertension. Peripheral retinal degenerations are associated with aging, including typical and reticular peripheral cystoid degeneration (TPCD), pitting stone (cobblestone) degeneration, and lattice degeneration. TPCD, which appears as microscopic cystoid spaces in the inner to outer plexiform layers, is observed in approximately 87% of autopsy eyes of all age groups, and nearly 100% of eyes of older adults. These cystoid spaces are bridged by Müller cells, and when these bridges collapse, age-related retinoschisis may ensue. Reticular peripheral cystoid degeneration is similar to TPCD with the exception that the cystoid spaces are in the nerve fiber layer. Peripheral chorioretinal atrophy (paving stone degeneration, cobblestone degeneration) is seen in up to 27% individuals over the age of 20 years. This degeneration is thought to be due to choroidal vascular insufficiency and results in ovoid areas of RPE atrophy, with overlying outer retinal atrophy surrounded by RPE hypertrophy and hyperplasia. Lattice degeneration of the retina is found in approximately 11% of autopsy eyes. It is age-related, occurs in the mid-periphery, is caused by vitreoretinal traction, and is characterized by inner retinal thinning, glial proliferation around the edges of the lesion, overlying liquid vitreous, hyalinized vessels, and underlying hypertrophy and hyperplasia of the RPE. Lattice degeneration results in areas of retinal structural weakening and retinal holes may appear in areas of this degeneration.

**Retinal Pigment Epithelium and Bruch’s Membrane**

The RPE increases in density from birth to two years of age, when the adult density is achieved. With aging, the RPE becomes more pleomorphic, with the macular RPE becoming narrower with an increased height, and opposite occurring in the periphery. Peripheral RPE cells become broader, lower, vacuolated, and pleomorphic with aging. Lipofuscin accumulates in the cytoplasm with aging and the lipofuscin-associated A2E-epoxides may be toxic to RPE. There is clinical interest in RPE lipofuscin-related fundus autofluorescence patterns with regard to aging and age-related macular degeneration, although the histologic correlations of these findings are unclear. Autofluorescence imaging of the RPE with the adaptive optics scanning laser ophthalmoscope (AOSLO) or a two-photon tunable dye laser may prove to be tools for further evaluation aging changes of the RPE mosaic. Sub-RPE nodular drusen accumulate with age. These drusen are excrescences formed on the inner aspect of Bruch’s membrane, and are composed of granular substance, lipid, protein, crystalline deposits of calcium, and residual bodies. There are several histopathologic types of drusen, including hard, soft, confluent, and large drusen. Hard drusen are nonspecific and age-related. Soft, confluent, and large drusen are associated with age-related macular degeneration. Eosinophilic, brush-like material that accumulates external to the basement membrane of the RPE with age is termed “basal laminar deposit.” This material contains granular material, noncoated and coated vessels, and widespread collagen. Although the presence of basal laminar deposit may be associated with aging, it becomes very thick in age-related macular degeneration. Basal linear deposit, which accumulates between the basement membrane and plasma membrane of the RPE, may be a specific ultrastructural...
marker for AMD. Bruch’s membrane itself becomes thickened and may become calcified with aging. The thickening includes focal and diffuse thickening of the inner aspect of Bruch’s membrane. Lipid, including cholesterol, accumulates in Bruch’s membrane with aging. Curcio et al. have noted that Bruch’s membrane ages like the arterial intima and other connective tissues for which lipoproteins are the source of extracellular cholesterol. Some of the lipid in Bruch’s membrane appears to arise from esterified cholesterol-rich apolipoprotein B-containing lipoprotein particles produced by the RPE.

CHOROID

There are clinical data using optical coherence tomography (OCT) indicating an inverse relationship between age and choroidal capillaris density. Histopathologic studies have shown a negative correlation between age and choriocapillaris density. Although there may be an early increase in choriocapillaris density in age-related macular degeneration, eventually there is a decrease that is more pronounced than in normal aging.

VITREOUS

With aging, vitreous attachments to the retina weaken, thus resulting in posterior vitreous detachment. The space between the detached vitreous and retina is filled with liquefied vitreous. In one study of 786 eyes examined postmortem, 16% of the eyes from patients aged 45 to 65 years and 41% of eyes from patients aged over 65 years had a posterior vitreous detachment. A subsequent study showed that posterior vitreous detachment was present in 63% of postmortem eyes from patients aged in their 70s. Posterior vitreous detachment may result in the formed vitreous contracting forward to the vitreous base, thus causing traction on the peripheral retina and occasionally a retinal tear. As the vitreous liquefies and the formed vitreous collapses with aging, vitreous channels and compartments collapse, thus potentially affecting intravitreal drug delivery to the posterior retina.

SCLERA

The sclera becomes more rigid as a person ages. There may be relative dehydration, especially anterior to the insertion of recti muscles, resulting in calcium salt deposition. The midportion of the involved sclera in this area contains a calcified plaque. A similar age-related process may occur posteriorly, thus resulting in posterior scleral calcification.

OPTIC NERVE

Connective tissue within the fibrovascular pial septae becomes more abundant with age. Such thickening may result in impairment of exchange of nutrients and other metabolites between the capillaries and nerve fibers. Cellular and extracellular material may accumulate in the meninges and optic nerve fiber bundles with age. These include arachnoid cell nests and corpora arenacea (psammoma bodies) in the meninges, and corpora amylacea, which were described previously in the retina section. Schnabel cavernous degeneration of the optic nerve has been determined to be an age-related phenomenon related to chronic vascular occlusive disease. Histopathologic findings include loss of nerve fiber bundles and proteoglycan accumulation within the optic nerve.

FUTURE DIRECTIONS FOR RESEARCH

The anatomic alterations in the eye associated with aging offer potential areas of research and therapeutic intervention. Studies may be directed toward decreasing corneal endothelial cell loss with age. Research regarding trabecular meshwork aging changes, including extracellular matrix modulation, may prevent the decrease in outflow facility that occurs with age. Ciliary body dynamics may be studied with regard to aging changes to lessen the severity of presbyopia. Pharmacologic intervention for the prevention of cataracts may be investigated. Aging changes occur in the retinal and choroidal vasculature. These changes are related to retinal vascular disease, such as branch retinal vein occlusion and hypertensive retinopathy, as well as outer retinal ischemia secondary to choroidal vascular insufficiency. Potential areas of research related to these findings include real-time retinal and choroidal blood flow studies, such as may be determined using laser Doppler, and therapeutic interventions that result in normalization of these blood flows. Neuroprotection may be investigated as a way to lessen age-related loss of photoreceptors and retinal ganglion cells. Another potential area of research based on anatomic considerations of aging is in vivo imaging aging changes in the retina and RPE over time for early prediction of disease and early therapeutic intervention. An example of this is AOSLO imaging of the RPE mosaic as a method to predict age-related macular degeneration before there are fundus and vision changes. The AOSLO has been developed and may image the RPE mosaic. There are early histologic signs of AMD involving the RPE/Bruch’s membrane complex that do not result in visible fundus changes. Imaging the RPE with predictive modeling may result in early detection of AMD and allow for early pharmacologic intervention. Analysis of RPE morphometry has been useful in identifying murine phenotype and age (Jiang Y, Chrenek MA, Gardner C, Boatright JH, Grossniklaus HE, Nickerson JM, unpublished observations, 2013). Comparison of in vivo fundus images of the RPE mosaic with ex vivo flat mounts including the underlying anatomic changes (Fig. 1) may be used to model and predict AMD progression. Investigations may be directed toward maintenance of Bruch’s membrane. Another area of research is drug delivery to the
There are areas of opportunity to study these 
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Genetic and Environmental Underpinnings to Age-Related Ocular Diseases

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Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the United States, and the prevalence of AMD is expected to increase by up to 97% by 2050.1–3 AMD adversely affects quality of life and activities of daily living, and leads to loss of independence in retirement years.4 This complex disease has both environmental and genetic contributing factors. Modifiable factors include smoking and overall abdominal obesity and dietary factors, including antioxidants and dietary fat intake.2–4 Several common genetic variants with small to moderate impact and recently discovered rare genetic variants with much stronger effect are known to lead to the development and progression of AMD.5–9 The knowledge of epidemiologic and genetic factors gained over the past 2 decades has formed the scientific basis for new ways to prevent and manage this prevalent disease.

Relative Contribution of Genetic and Environmental Factors

The large population-based twin study of more than 12,000 World War II veterans in the National Academy of Sciences-National Research Council Twin Registry, found that genetic factors explain 46% to 71% of the occurrence of the disease, with the highest heritability for the more advanced forms of AMD and environmental exposures accounting for approximately 19% to 37% of the variance (Ref. 10 and Seddon JM, et al. IJOVS 1997;38:ARVO Abstract S676). Similar results were seen in a survey of female twins.11

Environmental Factors

Smoking is an avoidable risk factor for AMD. In a prospective cohort study, smoking 25 or more cigarettes per day (approximately a pack) and past smoking increased risk of incident AMD more than 2-fold compared with never smokers.2–5 Nutritional factors are known to modulate the risk of AMD and its progression. The initial study to systematically evaluate the relationship between dietary intake and nutritional factors and AMD showed a protective effect of dietary lutein and zeaxanthin on risk of neovascular AMD.12 The highest quintile of intake was associated with a 43% reduction in risk, and frequent consumption of spinach and collard greens, high in these carotenoids, markedly reduced risk. Beta-carotene derived from food intake did not reduce risk of AMD. Some studies have confirmed these findings and showed similar effects. The Age-Related Eye Disease Study (AREDS)13 later found that antioxidant and mineral supplements reduced risk of progression from intermediate to advanced levels of AMD. AREDS2 compared a modified AREDS1 formula to the original or modified AREDS formula referred to as "placebo" in the primary analyses, which did not show added benefit.14 In subgroup analyses, there was a statistically significant reduced risk of progression to advanced AMD for lutein and zeaxanthin supplements among participants with low dietary lutein and zeaxanthin intake. The AREDS group recommends lutein plus zeaxanthin supplements rather than beta-carotene supplements for prevention of AMD. Higher total dietary fat intake increases risk of progression to advanced AMD almost 3-fold for the highest dietary fat intake compared with the lowest intake. In contrast, a diet rich in omega-3 fatty acids has been shown to be protective in several studies with a reduction in risk of 30% to 50%.2,5,15 The proposed mechanisms through which omega-3 fatty acids may exert a protective effect on macular degeneration include antioxidative, anti-inflammatory, and antiangiogenic effects.

AMD and cardiovascular disease (CVD) share common antecedent risk factors.16 In addition to smoking and diet, overall obesity and abdominal adiposity are also important modifiable factors. Higher BMI and waist circumference increase risk of progression, and vigorous physical activity...
reduces risk. There is some evidence linking cholesterol level to AMD, but the results have been inconsistent. Inflammation plays a central role in the pathogenesis of drusen and AMD. C-reactive protein (CRP) is a marker for systemic inflammation as well as cardiovascular disease, and homocysteine is an amino acid that adversely affects the vascular endothelium. CRP serum levels are significantly elevated in individuals with advanced AMD, adjusting for age, sex, body mass index (BMI), and smoking, and higher levels increase risk of progression. Higher homocysteine levels may also be associated with AMD. Serum CRP and homocysteine were associated with dietary and behavioral risk factors for AMD. Increased plasma levels of complement activation fragments Bb and C5a were also independently associated with advanced AMD and these complement markers are related to smoking and higher levels of BMI.

**GENETIC FACTORS**

AMD is a common, complex disease with numerous associated AMD genetic loci. These genetic factors have small to moderate effects on risk and increase susceptibility to the disease in addition to environmental factors, and the heritability is as high as 71% in advanced cases (Ref. 10 and Seddon JM, et al. *IOVS* 1997;38:ARVO Abstract S676). Genetic linkage studies found several peaks in many chromosomes, including 1 and 10 where the initial AMD genes were located. Candidate gene studies based on genes associated with macular and retinal Mendelian diseases were done; but did not yield strong or consistent results. Since 2005, at least 20 known genes have been confirmed for AMD. Many are in the complement pathway. Some genes play a role in pathways related to high-density lipoprotein cholesterol, collagen, and extracellular matrix and angiogenesis, and the pathway is not yet known for several genes. Rare, highly penetrant mutations also contribute to AMD risk, including *CFH* R1210C, which is one of the first instances in which a common complex disease variant led to the discovery of a rare penetrant mutation and the first one reported for AMD. Rare variants in complex disease variants led to the discovery of a rare penetrant R1210C, which is one of the first instances in which a common pathway is not yet known for several genes. Rare, highly penetrant mutations also contribute to AMD risk, including *CFH* R1210C, which is one of the first instances in which a common complex disease variant led to the discovery of a rare penetrant mutation and the first one reported for AMD. Rare variants in complex disease variants led to the discovery of a rare penetrant R1210C, which is one of the first instances in which a common pathway is not yet known for several genes.

**COMBINATION OF GENES AND ENVIRONMENT**

There is an interaction between docosahexaenoic acid intake and *ARMS2/HTRA1* on risk of developing geographic atrophy (GA). Smoking increases risk for all *CFH* and *ARMS2/HTRA1* genotypes. In monozygotic twins discordant for signs of AMD, smoking was heavier for the twin with the more advanced stage of AMD and dietary intakes of betaine and methionine were higher for twins with less advanced AMD. These effects of smoking and diet suggest that epigenetic changes can modify gene expression and lead to different phenotypes in genetically identical individuals. Methylation changes were also evaluated in a small study of AMD-discordant twin pairs. Predictive models have been developed using an algorithm to create a risk score combining the effects of demographic, behavioral, macular, and genetic factors on risk of progression to advanced AMD from no maculopathy or early and intermediate disease. For example, an individual with large drusen in both eyes with a high-risk profile has a 60% chance of progressing over 10 years to advanced AMD based on the predictive algorithm, whereas a person with the same fundus findings and a low-risk profile has a 20% chance of progression. Validation of the predictive model indicates the model is useful for clinical studies.

There has been marked progress over the past few decades regarding the environmental and genetic underpinnings of AMD, which has formed the scientific basis for the preventive management of AMD. Genetic factors lead to various levels of susceptibility and the environment modifies the effects of this predisposition to varying degrees depending on the level of genetic risk. Genotyping may become a useful tool for identifying individuals who are at high risk for disease and who may therefore benefit from increased surveillance and personalized treatment strategies. The discovery of genetic and environmental mechanisms provides targets for new therapies. Risk prediction models will facilitate clinical trials of these potential treatments with reduced sample size and lower costs.

**DIABETIC RETINOPATHY**

Diabetic retinopathy is another common cause of visual impairment that is increasing in developing countries. Environmental factors play a large role in the development of type 2 diabetes, most notably diet and obesity. Heritability has been estimated as high as 52% for the advanced form of proliferative retinopathy with retinal neovascularization. However, genetic studies have not yet identified large or consistent genetic susceptibility loci for this disease.

**GLAUCOMA AND CATARACT**

Glaucoma and cataract are common diseases of aging, which are reviewed in other sections of this supplement. Smoking is a known risk factor for cataract. Environmental risk factors for glaucoma are less conclusive. Genetic studies have suggested some susceptibility loci with small effects. Larger studies with well-defined phenotypes may lead to more insight into the genetics of these diseases.

**UNMET NEEDS AND OPPORTUNITIES**

All of these diseases provide an opportunity for improved preventive management and better therapies. Great strides have been made for AMD in terms of prevention, slowing progression, and treatment of the neovascular form of the disease. However, treatments can be improved for the neovascular forms of AMD and need to be developed for the dry stages. Diabetic retinopathy can be reduced with cultural and lifestyle changes and behavioral modification, as well as improved therapeutic targets. Glaucoma requires elucidation of more definitive environmental and genetic factors to enable earlier diagnosis, prevention, and intervention. Cataract has a successful surgical intervention, but preventive measures and other types of therapies could provide enormous economic benefit.

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Common Cell Biologic and Biochemical Changes in Aging and Age-Related Diseases of the Eye: Toward New Therapeutic Approaches to Age-Related Ocular Diseases

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Reviews of information about AMD, cataract, and glaucoma make it apparent that while each eye tissue has its own characteristic metabolism, structure, and function, there are common perturbations to homeostasis that are associated with age-related dysfunction. The commonalities appeared to be biochemical stresses and their sequelae. Recognition of shared etiologic factors for age-related debilitating allows rationalization of comparable risk factor-disease incidence relationships—such as nutritional risk factors for AMD and cataract (as well as cardiovascular disease and diabetes)—and informs about potential new therapeutic avenues, such as stress reducers (i.e., antioxidants) and/or proteolysis enhancers. It also maximizes the return on the investment in research effort and costs. For example, drugs or nutrients that protect against AMD may also prove effective against cataract, glaucoma, or/and other age-related neurodegenerative deilities.

This article summarizes cell biologic and biochemical changes in aging and age-related diseases of the eye. Clearly, this is a larger challenge with a richer literature than can be properly treated in a short review such as this. In this short review, we focus on age-related stresses and current and anticipated means to diminish the stress. Recognizing that almost all age-related diseases such as Alzheimer and Parkinson diseases, cataract, AMD, glaucoma, diabetes, and the premature aging diseases such as progeria, have in common the accumulation of damaged proteins, we select three aspects of age-related biochemical changes that are common to most eye tissues: oxidative stresses; problems associated with and/or due to damaged proteins that accumulate in the retina, lens, and cornea; and intracellular degradative capacities that usually keep levels of damaged proteins in check in early life or when tissues are not stressed, but that may fail upon stress or aging (Figs. 1, 2). We offer apologies to investigators whose work we do not cite or can acknowledge only via reviews.

The most rapidly growing segment of many societies is the elderly. The prevalence of cataract, AMD, and glaucoma accelerates with age. Among those who are aged 75 years or older, prevalence rates of cataract, AMD, and glaucoma are approximately 60%, 15%, and 20% of the population, respectively. These estimates almost double for people aged just 10 years older. Like most tissues in general, most eye tissues suffer from the accumulation of damaged proteins. Such accumulation appears to involve post-synthetic modifications to proteins and limits on the proteolytic capacities that are normally available to degrade and remove the altered or obsolete proteins before they transform into cytotoxic aggregates. Collectively, we call the sum of synthesis, post-synthetic modification, editing and removal of proteins “proteopoise.” Compromises to proteopoise are also thought to be etiologic for many age-related neuropathies and premature aging syndromes.1–7 Herein, we work our way from the anterior of the eye, or cornea, through to the lens and on to the posterior segment or retina, recalling common themes of age-related changes and protein quality control.

AGE-RELATED CHANGES IN THE CORNEA, LENS, AND RETINA

The cornea is a multilayered tissue containing three distinct cellular layers, epithelium, stroma, and endothelium, and two membrane structures: Bowman’s layer, separating the epithelium and stroma; and Descemet’s membrane, separating the stroma from the endothelium. The major functions of the cornea are to protect the rest of the eye from environmental insults and to refract light.

Structural and biochemical changes have been noted in all layers of the cornea upon aging. The corneal epithelium becomes more permeable with age,8 possibly due to alterations in the distribution of 26 and β4 integrins, transmembrane receptors that mediate the attachment between a cell and its surroundings.9 Age-related alterations in the human (diurnal) cornea appear to involve cumulative, prolonged ultraviolet radiation exposure as well as stresses that are associated with aging per se. This leads to the generation of reactive oxygen species that, in turn, cause oxidative stress. Accordingly, it is not surprising that protein oxidation is a frequent insult to the cornea.10 This involves advanced glycation-end products...
(AGEs) that form due to a nonenzymatic reaction between proteins and aldehydes and ketones, most of which are derived from sugars. Levels of AGEs increase upon aging in corneal collagen, lens, and probably all eye tissues and may be further increased by diabetes or due to consuming high-glycemic index diets. AGE-modified collagen may contribute to the increase in collagen fibrils and decreased corneal flexibility observed upon aging. Age-related thickening of Bowman’s layer and Descemet’s membrane also involves post-synthetic modification.

Additional evidence of age-related oxidative damage derives from analyses of genetic material. GenOMIC and mitochondrial DNA are damaged with age and corneas from older donors show increased 8-OHdG, a marker of DNA oxidation, a consequence—at least in part—of the age-related compromise in DNA damage repair capacity. Ascorbate and glutathione are important nonenzymatic antioxidants in the cornea. Ascorbate levels are significantly higher in the cornea than in the serum or aqueous humor. Surprisingly, there is a trend toward increased ascorbate, glutathione peroxidase, and the antioxidant cytoglobin in aged human corneas. However, there was a decrease in both mRNA and protein expression of superoxide dismutase-1 and γ-glutamyl–transpeptidase activity. Similarly, in aged rabbit corneas, the levels of glutathione peroxidase, superoxide dismutase, and catalase were significantly decreased. Because these antioxidant enzymes provide critical protection against oxidative stress, age-related losses in their activity would confer enhanced susceptibility to stress.

With mounting stress, it is not surprising that damaged proteins and other potentially harmful moieties also accumulate. Mutations also cause accumulation of abnormal proteins, many of which have been etiologically associated with disease. An example is optineurin. Although incompletely characterized at present, optineurin appears to have roles in apoptosis, inflammation, vasoconstriction, morphogenesis, membrane, and vesicle trafficking, as well as in transcription activation. Mutations in optineurin have been related to risk for glaucoma, and are also found in inclusions in patients with amyotrophic...
lateral sclerosis (ALS). Such accumulation of altered proteins are thought to be exacerbated by insufficient proteolytic or other degradative capacity and etiologically related to many premature age-related diseases including Parkinson, Alzheimer, and ALS.2,4,5,26,27 Corneal endothelial cells show increased expression of p21$^{19}$ and p16$^{INK4A}$31,32 and senescence-associated beta galactosidase33 during aging, consistent with diminished proliferative capacity and cell density with age.34 Since p21$^{19}$ is a substrate of the ubiquitin proteasome proteolytic pathway, it is possible that intracellular proteolytic capacities are compromised upon aging (see Age-Related Changes In Proteolytic Capacities During Aging In Cornea, Lens And Retina section).

Light coming from the cornea must pass through the fiber cells of the lens nucleus en route to the retina. Of all the tissues in the eye, it is probably easiest to recognize deficits in proteopoiése in the lens. Fiber cells are functionally analogous to a fiber optic. When young, they are filled with a clear solution of native proteins. The lens is also equipped with very high levels of glutathione, ascorbate, and antioxidant enzymes.3 However, upon aging and stress, these levels decline and the antioxidant enzymes are rendered less active. Consequently, proteins are gradually modified, often by oxidation, deamidations, racemizations, and they lyse or aggregate and precipitate.1-3,6,7,24-26 In recent years, there has been increased interest in the damage that is caused by elevated levels of dietary sugars, or AGEs because elevations in intake of carbohydrates has recently been related to enhanced risk for cataract, AMD, cardiovascular disease, and diabetes.12,35 The rates of accumulation of many of these post-synthetic alterations appear to accelerate upon aging (Figs. 1, 2).

The retina is composed of a myriad of cell types. They can be very roughly divided into neural retina, RPE, and the choroidal vessels that feed the rear of the retina. The choroidal vessels at the rear of the eye supply nutrients and oxygen to the outer layer of the retina, and actively transport waste away from the retina. Clearly, they are essential for maintaining retinal health, but upon aging, they are partially lost in humans.56-57 In contrast with thinning in humans, in mice there is evidence of increased choroidal thickness upon aging.38 Retinal pigmented epithelial cells and photoreceptors are also lost, particularly in AMD.

Multiple studies have identified oxidative stress as an etiologic factor in AMD.5-9,11 The retina a fertile environment for oxidative stress. This is due to the presence of two blood supplies, the highly oxygenated environment, along with the presence of high levels of photosensitizers and readily oxidizable lipid, protein and carbohydrate substrates. This is exacerbated by a huge proteolytic burden, particularly in the RPE, due to the requirement to degrade the tips of photoreceptor outer segments that are shed nightly. Oxidative stress is indicated by the contents of basal laminar deposits and drusen that herald the onset of AMD and by the marked increase in risk for AMD in smokers. Additionally, Handa and colleagues found evidence of AGE modification of choroidal proteins in an aged donor, who exhibited no age related eye disease,42,43 and this was expanded by observations of elevated levels of AGEs and harbinger of AMD in older animals that consumed higher glycemic index diets.44 Importantly, we find a systemic burden indicated by the higher levels of AGEs throughout the eye and many bodily tissues of mice that consumed higher GI diets.45 Emphasizing that this is a diet GI-AMD risk relationship, there is increased risk for each category of AMD in people who consume the highest GI diets.45 Since people who consume higher GI diets are at increased risk of AMD, as well as cardiovascular disease and diabetes, it is likely that the accumulation of AGEs and disease are mechanistically linked and that treatments for one malady may bear benefits for other etiologically linked debilities.46 Importantly, findings from the Age-Related Eye Diseases Study 2 indicate that intake of elevated levels of vitamins C and E as well as zinc and lutein confer some protection against progress of intermediate to advanced AMD.47 Clearly, it would be of greatest interest to find the means to avoid onset of AMD.

Genetic variations in complement factor H confer major risk for AMD, but the mechanism is unknown. The hypothesis that oxidative stress or its sequelae are involved in risk for AMD was corroborated by Weisemann’s recent observation that mutant complement factor H cannot detoxify lipid oxidation products as effectively as the normal protein.48 This is the first mechanistic link between robust epidemiologic associations regarding risk for AMD and the multiple studies that have associated genetic mutations, particularly genes that regulate immune and inflammatory responses, with risk for AMD.49,50 The relationship between inflammation and risk for AMD is also supported by observations of increased numbers of macrophages in the choroid of aged mice,38 as well as increased levels of prostaglandin, PGE2, and its receptor PGE2-E2P in the choroid of aged rats.51 The age-altered cytokine profiles and macrophage responses to retinal laser insult52 inform about new targets for therapy.

**AGE-RELATED CHANGES IN PROTEOLYTIC CAPACITIES DURING AGING IN THE CORNEA, LENS, AND RETINA**

In addition to post-synthetic modifications, damaged or obsolete proteins may accumulate because they are not recognized as obsolete, or because of insufficient proteolytic capacity.5-8,12-20 Such proteins may aggregate, as is observed in cataract, or be otherwise cytotoxic. Recognition of damaged proteins in the cytoplasm is usually accomplished by ubiquitination. In the ubiquitin pathway, ubiquitin is attached to substrates by the sequential activities of E1 (ubiquitin-activating enzymes); E2s (ubiquitin-conjugating enzymes); and E3s (ubiquitin ligases). The exquisite selectivity of ubiquitin conjugation is achieved by the combinatorial activities of dozens of E2s together with hundreds of E3s.53 Ubiquitinated proteins are delivered to the proteasome where the ubiquitin is removed and recycled and the substrate is degraded to peptides that are eventually reduced to amino acids by aminopeptidases.54 Selectivity is also achieved by the many deubiquitinating enzymes that, by regulating the extent of ubiquitination, control access of the ubiquitinated substrate to the proteasome. An important observation regarding links between proteolytic capacities and oxidative status derives from observation that all the conjugating enzymes of the UPS are sulfhydryl enzymes and the GSH/GSSG ratio controls their activities.55

A parallel—if less selective—pathway involves autophagy. In this pathway, parts of the cytoplasm are engulfed by a membrane and delivered to the lysosome for degradation. Multiple recent papers document that the UPS and autophagic pathways work in concert.12,56 Calpains also complement the UPS and autophagosomal pathways and recent discoveries indicate that these pathways may be linked (Liu and Taylor, unpublished observations, 2013).

What are the proteolytic capacities in cornea, lens, and retina and what is their fate and functional status during aging and upon stress? In the cornea, the larger literature to date deals with extracellular proteases and collagenolysis.57 Evidence regarding additional proteolytic capacities is being developed, in part, via high-throughput analytical methods.58 Since protein aggregation and precipitation is clearly related to cataract, much effort has been devoted to documenting
proteolytic capacities in the lens and their fate upon oxidative stress and aging. While lenses contain all of the ubiquitin, lysosomal, and calpain machineries in the young nucleated cells, by virtue of the lens fibers degrading their organelles, any opportunity for renewal and much of the autophagic lysosomal proteolytic capacity is lost during differentiation and aging. There are also some species differences, such as in the complement of calpains in lenses from different species. Ubiquitin-conjugating activity decreases in old rat lenses as compared with younger rat lenses. The conjugating activity is also decreased from the outer cortex (newer fiber cells) to the lens nucleus (oldest fiber cells). In the human lens, the three peptidase activities of the proteasome did not change with aging, but they are found at decreased levels in cataractous lenses, consistent with a requirement for these activities to rid lens cells of damaged proteins. As noted above, even when the cells have the full complement of ubiquitination enzymes, increased oxidative stress can diminish their efficacy (Fig. 1). Similarly, oxidative modifications to substrates may alter access to these systems. Thus, it has been demonstrated that while mild oxidative stress or deamidation makes some substrates better proteasomal substrates, glycation has the reverse effect. Aminopeptidase activities also decline with age and certainly in older developmental zones of the same lens.

It is probable that the lens neutral protease first described by Van Heyningen and later studied by Wagner, and which was found at reduced activity in the older, central regions of the lens, is the proteasome. An age-related decline in functional proteasome was also reported in brains, mainly due to associated decreased assembly of 26S proteasome. Interestingly, overexpression of the proteasome subunit Rpn11 can prevent the decline of proteasome activity and prevent accumulation of neurodegeneration-related polyQ. Rpn6 also appears to play roles in 20S and 26S proteasome assembly and ectopic expression of Rpn6 is sufficient to increase proteasomal assembly and activity. Thus, modulation of proteasome subunits may be a viable approach to enhancing proteasomal activity lost during aging.

In the neural retina, the chymotrypsin-like activity of the proteasome decreases with aging, but this decrease was not proteasomal activity lost during aging.

UNMET NEEDS AND OPPORTUNITIES

Taken together, it is clear that a vast array of antioxidant and proteolytic capacities maintain homeostasis, when they are functional and unimpaired. However, upon aging or stress, these capacities are inactivated and become insufficient. Thus, there ensues a vicious cycle of stress, accumulation of damaged proteins, and diminished proteolytic capacity that leads to accelerated accumulation of cytotoxic materials, and disease. We know that adequate nutrition is crucial for maintenance of eye function. Accordingly, massive educational campaigns should be instituted that relate risk for blindness to nutrition, smoking, obesity and exercise. These are bound to bear positive results. We could eliminate much age-related disease if salutary behavior changes or treatment could be implemented earlier. To encourage this, we need to determine biomarkers that will allow us to anticipate incipient disease. Current technologies make this an achievable objective. Education about healthy lifestyles and eating habits is probably the least costly and most effective investment with regard to achieving prolonged eye function. It has recently been demonstrated that electron recycling agents can delay mitochondrial disease. Since the age-related debilities noted here all have origins in oxidative stress, it is likely that such agents can also delay formation of the offending moieties and/or preserve function of the degradative machines (UPS, autophagic/lysosomal) that remove oxidized products. Recent findings that degradation of neurodegeneration-related proteins can be enhanced should be translated to therapy for other age-related protein precipitation diseases including cataract, AMD, and possibly glaucoma. New and more potent antioxidants can be discovered or constructed for delivery to eyes to enhance protection against oxidative stress. Elucidating components of age-related vision loss that are not due to retina or lens damage will provide needed understanding and open up new alternatives for vision restoration for people with neurologic damage.

Given the promise for success and the low cost of this research relative to the gains in sight maintenance from its successful completion, it is clear that additional funding would be a wise investment.

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Age-Related Changes in the Visual Pathways: Blame It on the Axon

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AGING AND VISION

Age-related loss of sensory activity represents a costly and socially debilitating aspect of general senescence of the central nervous system (CNS). For human beings, this loss is felt most strongly through decline of the visual system, upon which we depend more than other sensory modalities. Accordingly, the visual areas represent the lion’s share of cortical representation of sensory function. As we age, peripheral tissues of the eye (cornea, lens, vitreous humor, and so forth) undergo myriad structural changes that influence the efficiency of optical transmission.1 Certainly, age-related degradation in the optics of the eye contributes to some aspects of declining visual function.2-5 Decline in other key functions, such as spatial contrast sensitivity and motion sensitivity, must have a neural basis, since optic changes cannot account for the loss.5 Still, other functions remain remarkably intact, and this persistence may inform how well particular visual neural pathways age.6,7

The aging visual system is marked by a decline in some, but not all, key functions. Some of this decline is attributed to changes in the optics of the eye, but other aspects must have a neural basis. Across mammals, with aging there is remarkable persistence of central structures to which retinal ganglion cell (RGC) axons project with little or no loss of neurons. Similarly, RGC bodies in the retina are subject to variable age-related loss, with most mammals showing none over time. In contrast, the RGC axon itself is highly vulnerable. Across species, the rate of axon loss in the optic nerve is related inversely to the total number of axons at maturity and lifespan. The result of this scaling is approximately a 40% total decline in axon number. Evidence suggests that the consistent vulnerability of RGC axons to aging arises from their high metabolic demand combined with diminishing resources. Thus, therapeutic interventions that conserve bioenergetics may have potential to abate age-related decline in visual function.

Keywords: aging, retinal ganglion cell, optic nerve, lateral geniculate nucleus, superior colliculus, neurodegeneration, axonopathy

SURVIVAL OF CENTRAL STRUCTURES

Structural studies indicate little or no age-related change in neuronal density or morphology in the primary visual cortex.3,10 This is not to say that the aging cortex is invulnerable to the ravages of time. Myriad transformations that affect physiological function occur at the cellular and subcellular levels.11 However, if age-related decline in visual function, even if only for a subset of perceptual modalities, reflects loss of tissue, more likely targets are structures that form the projection to the cortex.

The mammalian brain is characterized by a highly conserved projection of the retina into multiple central structures.12 At the optic chiasm, retinal ganglion cell (RGC) axons from the two eyes cross in forming the ipsilateral and contralateral optic tracts to the brain. In rodents, the contralateral projection dominates, while in other mammals RGC axons are parsed more evenly. In the human and nonhuman primate brains, the lateral geniculate nucleus (LGN) of the thalamus receives the primary RGC relay to the primary visual cortex, while in rodents this function is served by the more distal superior colliculus (SC) of the midbrain with a smaller LGN projection to the cortex. In late stages of glaucoma, relay neurons in the LGN of nonhuman primates diminish in number, as do those in postmortem tissue from human patients.13-15 This loss lags substantially behind degeneration of RGC axons in the optic nerve.14 Similarly, in the DBA2J mouse model of glaucoma, we found that SC volume begins to diminish in the oldest animals, but again well after RGC axonopathy in the optic nerve and tract has progressed significantly.16

The story is much different in normal aging. Magnetic resonance imaging of the human LGN shows approximately a 15% reduction in structural volume between 20 and 70 years of age.17 Histologic analysis of postmortem tissue indicates a more dramatic decline (30%).18 Interestingly, in nonhuman primates and rats, LGN volume increases slightly with age, which can lead to an apparent decline in neuronal density.19,20 Despite these changes in tissue volume, the number of neurons in the LGN—regardless of species—does not change.16-20 Similarly,
there is remarkable constancy in the physiological response properties of individual LGN neurons in monkeys.5

Though the number and response qualities of RGC relay neurons do not appear to change with age, other aspects of the RGC projection do. The size and complexity of RGC axonal arbors in the mouse SC diminish with age.31 In the aging rabbit, the rate of slow axonal transport along RGC axons to central targets decreases.32 Similarly age-related shrinkage of the DBA2J SC follows deficits in RGC axonal transport after a period of persistence.16 Taken as whole, these observations suggest that even as aging has little influence on the structure of cortical projections from RGC central targets, the RGC axon itself may be more vulnerable.

AGE-RELATED DECLINE IN RGC AXONS

The RGC axon is distinguished from the axons of other glutamatergic neurons in the retina by several important characteristics. Unlike photoreceptor and bipolar cell axons, which by necessity are completely unmyelinated, only the shortest segment of the RGC axon is unmyelinated. This corresponds to the length of axon that courses through the nerve fiber layer, through which light must pass to reach the photoreceptors. As the axon penetrates the laminar region of the optic nerve head it becomes myelinated, remaining so throughout the nerve proper and into the optic tract. The number of RGC axons in the optic nerve differs greatly between species, by a factor of 30 between mouse and human, as does the total length of the nerve.23 Even so, across mammals most RGC axons are very thin (0.2–0.7 \textmu m in diameter), approximately half as thick the cone photoreceptor axon despite being 50-fold longer.24 While optimized for minimal firing rate and energy use,25,26 the small size of RGC axons has implications for susceptibility over time to light-induced damage, metabolic stress, disruption of Ca2+ homeostasis, and cytoskeletal degradation.12,27 This susceptibility may explain why axonal transport from the retina to the brain is affected early in glaucoma, and why decline in function is detected first at the distalmost projection sites.12,28 A small axon, especially one with a bioenergetically inefficient unmyelinated segment, also is at a disadvantage should available ATP diminish.29,30 Aging of the CNS includes as one

PERSISTENCE OF RGC CELL BODIES WITH AGING

Certain neurons are highly susceptible to age-related loss. For example, the population of rod photoreceptors in the central human retina declines by 30% over a lifetime; the number of cones remains remarkably stable.46 One might assume prominent loss of RGC axons in the optic nerve as described across mammalian species must translate ipso facto to a corresponding decline in RGC bodies in the retina. This is not so. Whether RGC bodies in the retina also are susceptible to age-related loss is a far more equivocal question—at least when it comes to comparing human retina to that of other mammals.

In the rhesus monkey retina, over a near 30-year lifespan the number of RGC bodies does not change regardless of eccentricity from the fovea or retinal quadrant.47 The same is true of the marsupial wallaby retina, where RGC body number remains constant (approximately 200,000) even for those animals living the longest in captivity, up to 15 years.48 In C57BL/6 mouse retina, over a two-year lifespan the number of RGCs does not change.21 However, the dendritic arbors of at least some types of mouse RGC shrink by approximately 20% with a concomitant decrease in the density of inner plexiform layer synapses.21 Other reports that show age-related RGC body loss in C57 retina again used measurements based on retrograde axonal transport of Fluoro-Gold (Santa Cruz Biotechnology, Inc.) from the superior colliculus.49 It is not surprising the noted decrease was similar to axon loss, approximately 40%.30 Finally, the number of RGC bodies in the rat retina does not change with age (up to 30 months), though the retina itself enlarges.50 This enlargement can explain why cell density (cells per unit area), rather than total number, diminishes significantly.51 Thus, across several mammalian species RGC bodies persist over a lifetime.

Accurate cell counts in the human retina are difficult to obtain, due to varying health (and treatments) between subjects and differences in postmortem treatment of tissue. Immune-labeling of RGCs is difficult for a variety of technical reasons, so counts of ganglion cell layer neurons generally include RGC bodies and displaced amacrine cells. This practice is mitigated somewhat by focusing on changes in the central retina, where the fraction of displaced amacrine neurons is below 5%.52 Finally, variability even within tissues of the same age and health is quite high. Whether
the RGC population is assessed by axon number in the optic nerve or cell body count in the retina, the possible range can differ 2-fold between normal donors. The human retina, like that of rodents, expands over a lifetime, increasing in area by approximately 15%. An early study found that RGC density in the human central retina, where displaced amacrine cells are fewest, decreases by a similar amount. If so, the result could be explained without actual RGC dropout. However, subsequent studies found a greater decline in central retina density ranging from 25% to 43%. This decrease cannot be attributable entirely to expansion of retinal area, as total neuron number in the ganglion cell layer also declines by 30% to 45%. This decline is faster outside of the central retina, but a far greater fraction of displaced amacrine cells there makes estimating actual RGC loss more difficult. It is important to note that many postmortem samples from even the oldest donors demonstrate cell counts in the range for the youngest donors—and vice versa. Even so, it seems likely that the human retina, unlike that of nonhuman primates and other mammals, does in fact demonstrate some RGC body loss over a lifetime. This is a bit enigmatic, since the rate of RGC axon loss in other animals is far faster.

**THE AGING VISUAL PATHWAYS: KEY NEEDS AND OPPORTUNITIES**

Could loss of visual function in normal aging bear mechanistic similarities to the most common age-related optic neuropathy, glaucoma? It seems likely. The critical question then is whether by abating age-related decline therapeutically we also can reduce susceptibility to age-related diseases, such as glaucoma. In glaucoma, progression is marked by early RGC axonal dysfunction followed by outright degeneration. Central targets in the brain and RGC bodies in the retina persist for a period following axonopathy that represents a window of therapeutic opportunity. Similarly, the broad survey presented here indicates a special vulnerability of the RGC axon to age-related decline, with a consistent loss of approximately 40% of the axons in the optic projection over a lifetime regardless of species. This decline occurs even as downstream neurons in central projection sites and in the primary visual cortex persist. Axon degeneration with
aging is approximately proportional to the extent of expended lifespan. Thus, just as rate of progression in glaucoma depends on the degree of IOP-related stress,12 perhaps progression in normal aging depends on the actual extent of the lifetime. This could explain why only the human retina appears to progress to actual RGC body loss with age.

Most mechanistic models of aging invoke a substrate as a drive for decline and changes in metabolic resources due to diminished mitochondrial efficiency.11 A correlative result is reduced mitochondrial capacity to maintain homoeostatic balance of intracellular Ca2+, decreased Na+/K+-ATPase activity, and increased oxidative injury.58 These changes in turn increase CNS vulnerability to stress or injury.11 Older mice with optic nerve crush demonstrate an accelerated loss of RGC bodies.26 Axons are particularly vulnerable to the effects of reduced metabolic capacity, since the generation of action potentials is a severe strain on available ATP—more so than even synaptic transmission.89

It seems likely that the visual pathways, like the rest of the brain, are susceptible to diminished metabolic resources with aging. Thus, potential interventions to ameliorate age-related decline should include strategies either to boost bioenergetics or counter oxidative injury resulting from mitochondrial stress. Systemic administration of α-lipoic acid, a natural antioxidant, increased Na+/K+-ATPase activity and reduced neuronal lipofuscin in cortical and subcortical brain regions in aging rats.89 We found that dietary administration of α-lipoic acid reduced lipid peroxidation, protein nitrosylation, and DNA oxidation in retina of the aged DBA/2J mouse, while improving overall axon function and survival in the optic nerve.61 Along these lines, systemic delivery of histone deacetylase (HDAC) inhibitor can reduce the transcriptional down-regulation that precedes outright RGC degeneration in the DBA/2J.62 HDAC inhibitors also rescue axonal mitochondria, increase ATP levels and reduce excitotoxic levels of glutamate in metabolically challenged optic nerve.63 Thus, targeting oxidative and metabolic stress may be promising avenues for ameliorating the effects of aging on the visual pathways.

The mechanisms through which RGCs age intrinsically, individually and as a network, must inform the development of new neuro-enhancing therapies. Like glaucoma, which, after all, is age-related, normal aging involves a specific challenge to RGC axons in the optic projection. Part of this challenge doubtlessly is associated with axonal milieu in the optic nerve head and associated structures. However, the unmyleinated segment of the RGC axon, in the retina and optic nerve head, also forms close contacts with the processes of astrocyte glia. Since astrocytes are important mediators of neuronal health, any strategy to combat age-related decline must include a more systematic understanding of their contribution.

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Nutrition Effects on Ocular Diseases in the Aging Eye

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Purpose. We reviewed the data from the clinical trials of nutritional supplements for the treatment of age-related cataract and age-related macular degeneration (AMD) to determine future directions of research and treatment.

Methods. Data from the controlled clinical trials are presented and reviewed for potential opportunities for further research into the treatment of cataracts and AMD.

Results. Two trials using daily multivitamins/minerals demonstrated a reduction in the progression of nuclear cataract, but increased the risk of posterior subcapsular cataract. For AMD, the Age-Related Eye Disease Study (AREDS) formulation (vitamins C, E, beta-carotene, zinc, and copper) reduced the risk of progression to advanced AMD by 25% at 5 years. Because beta-carotene is associated with increased lung cancer in former smokers, lutein/zeaxanthin could replace beta-carotene and provide an incremental increase in the beneficial effects beyond the effects of the AREDS formulation. In addition, a randomized clinical trial of B vitamins demonstrated a beneficial effect for AMD with the vitamin B complex.

Conclusions. Future evaluation may include additional assessments of nutrients for the progression of cataract and AMD. A modest reduction would have significant impact as the numbers of persons affected with these two leading causes of blindness are projected to double in the next decade. An important step would be to develop surrogate outcomes to increase efficiency in clinical trials. More detailed phenotyping, especially of AMD, is required as it appears to be not one disease, but a group of diseases. Genotype-phenotype analyses may help to target pathways that are important in AMD.

Keywords: age-related macular degeneration, cataract type, antioxidants

Age-related cataract and macular degeneration (AMD), two leading causes of blindness in the United States, are age-related ocular conditions in which nutritional risk factors have been evaluated extensively with observational and interventional studies. The results of a number of observational studies have provided the hypotheses and rationale for the interventional studies. The results of these interventional trials will be presented to identify potential opportunities for further research in these ocular conditions of significant public health importance. The Table gives a compilation of randomized controlled clinical trials for age-related cataract and AMD, including the nutrients evaluated and the study results.

Age-Related Cataracts

Age-related cataract is the leading cause of vision loss in the United States and its prevalence is rising; an estimated 30.1 million Americans will be affected by 2020.1 Treatments that can delay the progression of lens opacities likely would reduce the burden of disease markedly. Numerous observational epidemiologic studies have demonstrated inverse relationships between dietary micronutrients and the development of age-related cataract or cataract surgery.2–7 These studies have generated interest in micronutrients with antioxidant capabilities because of the potential importance of oxidative damage in cataract formation. Several controlled clinical trials have tested whether selected micronutrients with antioxidant characteristics or multivitamins affect cataract development.8–14 The results of some of these studies will be discussed below and areas of future research will be considered.

Controlled Clinical Trials of Nutritional Supplements for Age-Related Cataract

The Linxian Cataract Trials

These trials were ancillary studies in a nutritionally deprived population at high risk of developing esophageal/gastric cancer living in Linxian, China.10 Separate clinical trials tested multivitamins/minerals (n = 2141), and a mixture (n = 3249) containing retinol and zinc, riboflavin and niacin, vitamin C and molybdenum, selenium, vitamin E, and beta-carotene, using a factorial design with these four different vitamin/mineral combinations. In the studies, the risk of nuclear cataract progression was decreased by at least 36% and 44%, for multivitamins and mixture, respectively, in 5 to 6 years. However, there appeared to be an increased risk of posterior subcapsular cataract with the use of riboflavin/niacin. In this population, the results of the two trials suggest that vitamin/mineral supplements may be beneficial for slowing the progression of lens opacities. Further research is suggested in a less nutritionally deprived population before such results can be translated into general recommendations.
### Table. Randomized Controlled Clinical Trials for Age-Related Cataract and AMD

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<td>Linxian Cataract Trial&lt;sup&gt;10&lt;/sup&gt; (China)</td>
<td>Study I: ( n = 2,141 ) (ages 45–75)</td>
<td>I: Multivitamin/mineral</td>
<td>I: decrease by 36% in 65–74 y for nuclear cataract progression</td>
</tr>
<tr>
<td>Follow-up: 5–6 y</td>
<td>Study II: ( n = 3,249 )</td>
<td>II: Retinal/zinc, riboflavin/niacin, vitamin C/molybdenum, vitamin E/beta-carotene</td>
<td>II: decrease by 44% in 65–74 y nuclear cataract for riboflavin/niacin</td>
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<td>Increased risk of posterior subcapsular cataract</td>
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<td></td>
<td>11,545 male physicians, ≥50 y</td>
<td>Vitamin E (440 IU every other day)/vitamin C (500 mg daily)</td>
<td>Vitamin E: HR 0.99 95% CI, 0.88–1.11</td>
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<td></td>
<td>Follow-up: 8 y</td>
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<td>Vitamin C: HR 1.02 95% CI, 0.91–1.14 for incident cataract</td>
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<tr>
<td><strong>Physicians’ Health Study&lt;sup&gt;15&lt;/sup&gt;‡</strong></td>
<td>22,071 male physicians, ≥50 y</td>
<td>Betacarotene (50 mg every other day)</td>
<td>RR 1.00, 95% CI, 0.91–1.09 for incident cataract</td>
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<tr>
<td>Follow-up: 8 y</td>
<td></td>
<td></td>
<td>RR 1.00, 95% CI, 0.89–1.12 for cataract surgery</td>
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<tr>
<td>Women’s Health Study&lt;sup&gt;12&lt;/sup&gt;‡</td>
<td>39,876 female health professionals ≥45 y</td>
<td>Vitamin E (600 IU every other day)</td>
<td>RR 0.96, 95% CI, 0.88–1.04 for incident cataract</td>
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<td>Follow-up: 9.7 y</td>
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<tr>
<td>Age-Related Eye Disease Study (AREDS)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>4,629 men and women 55–80 y</td>
<td>Daily vitamins C (500 mg), E (400 IU), beta-carotene (15 mg), zinc (80 mg), copper (2 mg, AREDS formulation)</td>
<td>OR 0.97, 95% CI, 0.84–1.11 ((P = 0.55)) for any incident cataract event</td>
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<tr>
<td>Follow-up: 6.3 y</td>
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<tr>
<td>Age-Related Eye Disease Study 2 (AREDS2)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>3,159 men and women 50–80 y</td>
<td>Lutein 10 mg and zeaxanthin 2 mg with the AREDS formulation</td>
<td>HR 0.95 95% CI, 0.83–1.09</td>
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<td>Follow-up: 4.7 y</td>
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<tr>
<td><strong>Italian-American Clinical Trial of Nutritional Supplements</strong></td>
<td>1,020 men and women 55–75 y</td>
<td>Multivitamin/mineral formulation: (Centrum; Lederle Laboratory, Inc., Pearl River, NY)</td>
<td>HR 0.82 95% CI, 0.68–0.98 ((P = 0.03)) for incident cataract</td>
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<tr>
<td>(CNTS)&lt;sup&gt;14&lt;/sup&gt; (Italy)</td>
<td>Follow-up: 9 y</td>
<td></td>
<td>HR 0.66 95% CI, 0.50–0.88 ((P = 0.004)) for incident nuclear cataract</td>
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<td>HR 2.00 95% CI, 1.35–2.98 ((P = 0.001)) for incident posterior subcapsular cataract</td>
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<tr>
<td><strong>Randomized, double-masked, placebo-controlled age-related macular degeneration trials</strong></td>
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<tr>
<td>Randomized trial of Zinc&lt;sup&gt;11&lt;/sup&gt;</td>
<td>151 with early AMD, 42–89 y</td>
<td>Zinc sulfate (100 mg); equivalent to 80 mg of elemental zinc</td>
<td>Visual acuity change (final compared to baseline vision) was significantly less likely to deteriorate in the zinc treated group ((P &lt; 0.05))</td>
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<tr>
<td>Follow-up: 12–24 m</td>
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<td>OR 0.72, 95% CI, 0.52–0.98 ((P = 0.002)) for progression to advanced AMD</td>
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<tr>
<td>Age-Related Eye Disease Study (AREDS)&lt;sup&gt;17&lt;/sup&gt;</td>
<td>3,640 men and women 55–80 y</td>
<td>Daily vitamins C (500 mg), E (400 IU), beta-carotene (15 mg), zinc (80 mg), copper (2 mg, AREDS formulation)</td>
<td>Primary analyses using the entire study population did result in statistically significant differences</td>
</tr>
<tr>
<td>Follow-up: 6.3 y</td>
<td></td>
<td></td>
<td>Main effects analyses of lutein/zeaxanthin vs. NO lutein/zeaxanthin: HR 0.90, 95% CI, 0.82–0.99, ((P = 0.04))</td>
</tr>
<tr>
<td>Age-Related Eye Disease Study 2 (AREDS2)&lt;sup&gt;18&lt;/sup&gt;</td>
<td>4,205 men and women 50–85 y</td>
<td>Lutein 10 mg and zeaxanthin 2 mg and omega-3 fatty acids (DHA and EPA 1 g) along with the AREDS formulation</td>
<td>RR 0.66, 95% CI, 0.47–0.93 ((P = 0.02)) for development of advanced AMD</td>
</tr>
<tr>
<td>Follow-up: 5.0 y</td>
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<tr>
<td>Women’s Antioxidant and Folic Acid Cardiovascular Study</td>
<td>5,205 female health care professionals at risk or with preexisting cardiovascular disease ≥ 40 y</td>
<td>Folic acid 2.5 mg, pyridoxine hydrochloride or B&lt;sub&gt;6&lt;/sub&gt; 50 mg, cyanocobalamin or B&lt;sub&gt;12&lt;/sub&gt; 1 mg</td>
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Physicians’ Health Study

The Physicians’ Health Study evaluated aspirin and a number of nutrients, including vitamins E, C, and beta-carotene, in a randomized, double-masked, placebo-controlled trial for cardiovascular disease and cancer. Secondary analyses included the ocular end-points of age-related cataracts and AMD in male physicians 50 years or older. These outcomes were obtained with self-reports and confirmed by medical records.

Vitamins E and C. In a randomized, double-masked, placebo-controlled trial of vitamin E (400 IU) every other day and vitamin C (500 mg) daily in 11,545 male physicians, the rates of incident cataract were investigated.15 After 8 years of treatment and follow-up, there were no beneficial or harmful effects of this treatment regimen of vitamins E and C on the development of incident cataract in comparison of those treated versus the placebo group. The hazard ratios (HRs; 95% confidence intervals [CI]) were 0.99 (95% CI, 0.88–1.11) for vitamin E versus placebo and 1.02 (95% CI, 0.91–1.14) for vitamin C versus placebo.

Beta-Carotene. In a secondary study of a randomized controlled clinical trial of beta-carotene (50 mg on alternate days) versus placebo for cataract in 22,071 male physicians followed for a mean of 12 years, incident cataract and cataract surgery were the main outcomes.9 There was no statistically significant difference between beta-carotene versus placebo on the incidence of cataract (relative risk [RR] of 1.00; 95% CI, 0.91–1.09) or cataract surgery (RR of 1.00; 95% CI, 0.89–1.12).

Women’s Health Study

The Women’s Health Study was a randomized, double-masked, placebo-controlled trial to investigate the effects of beta-carotene (50 mg every other day), and daily vitamin E and aspirin in the primary prevention of cancer and cardiovascular disease.12 The study participants were 39,876 female health professionals aged at least 45 years. The main ocular outcome measures were visually-significant cataract and cataract extraction, based on self-reports with confirmation with medical records.

After a median follow-up of 2.1 years with beta-carotene, the randomization was stopped. There were neither statistically significant beneficial nor harmful effects of beta-carotene on the development of cataract. For the development of incident cataract, the RR was 0.95 (95% CI, 0.75–1.21) and for cataract extraction, the RR was 1.04 (95% CI, 0.78–1.39). This study also evaluated vitamin E (600 IU on alternate days) versus placebo for a mean follow-up of 9.7 years for incident cataract.16 Again, there was no significant difference between vitamin E and placebo for the development of cataract (RR of 0.96; 95% CI, 0.88–1.04). No differences also were noted for the subtypes of cataract or cataract surgery.

Age-Related Eye Disease Study (AREDS)

This was a randomized controlled clinical trial that evaluated antioxidant vitamins (500 mg C, 400 IU of E) and beta-carotene (15 mg) daily for the treatment of cataract in persons with varying degree of AMD.17 The mean follow-up was 6.3 years in 4629 AREDS participants, both men and women aged 55 to 80 years. There was no effect on progression of the three types of cataract or the incidence of cataract surgery (odds ratio [OR], 0.97; 99% CI, 0.84–1.11; P = 0.55 for progression to any cataract event.

Age-Related Eye Disease Study 2 (AREDS2)

The AREDS2 is a randomized controlled clinical trial of lutein/zeaxanthin for the treatment of age-related cataract.18 The 3159 AREDS2 participants, aged 50 to 80, were followed for a median of 4.7 years. The HR for progression to cataract surgery, the main outcome measure, was 0.95 (95% CI, 0.83–1.09; P = 0.49), comparing lutein/zeaxanthin versus no lutein/zeaxanthin. Lutein/zeaxanthin was not recommended for treatment of cataract, although those participants whose dietary intake of lutein/zeaxanthin was in the lowest quintile experienced a beneficial effect of the supplement. These data will need to be investigated further in similar studies of lutein/zeaxanthin for cataract progression.

The Italian-American Clinical Trial of Nutritional Supplements and Age-Related Cataract (CTNS)

This 13-year single-center clinical trial was designed to evaluate the role of multivitamin/mineral supplement (Centrum; Lederle Laboratory, Inc., Pearl River, NY) for the treatment of age-related cataracts. A total of 1020 participants was enrolled at the University of Parma, Parma, Italy, and followed for a mean of 9 years.14 In general, there was a decrease in the total number of subjects with lens progression in those participants assigned to Centrum compared to those assigned to placebo (HR, 0.82; 95% CI, 0.68–0.98; P = 0.03). Progression to nuclear cataract was particularly decreased (HR, 0.66; 95% CI, 0.50–0.88; P = 0.004). Posterior subcapsular cataract (PSC) events, however, were increased with the use of Centrum compared to placebo (HR, 2.00; 95% CI, 1.35–2.98; P = 0.001). Because of these mixed results, that is, opposite effects on nuclear and PSC, no recommendations had been made by the investigators for the treatment of cataract.

Age-Related Macular Degeneration (AMD)

Age-related macular degeneration is the leading cause of blindness, accounting for more than 50% of blindness in the United States.19 Therefore, this is an ocular disease of major public health importance. It is predicted that by 2020, there may be nearly 3 million individuals in the United States with advanced AMD.20 Although anti-VEGF agents have reduced the risk of vision loss from neovascular AMD, to our knowledge there are no proven treatments for the atrophic (dry) form of AMD. The role of nutritional supplements has been raised by a number of observational and randomized clinical trials.

Controlled Clinical Trials of Nutritional Supplements for Treatment of AMD

The pathogenesis of AMD is unknown, although oxidative stress is considered to have a role. Since 1988, evaluation of the National Health and Nutrition Examination survey suggested that persons eating a diet with increased sources of vitamins A and C had an inverse association with AMD. Other observational studies also have implicated inverse dietary associations with AMD.21–26 Observational data from AREDS and epidemiologic studies provide a rationale for examining the potential impact of other nutrients on the development of AMD, specifically higher dietary intake of lutein/zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids (LCPUFAs; docosahexanoic acid [DHA]/eicosapentanoic acid [EPA]) are associated with a decreased risk of developing advanced AMD.27–40 These studies have provided data to support hypotheses that were tested in the controlled clinical trials of nutrients for the treatment of AMD presented below.
Randomized Trial of Zinc Supplements

This was a single center study of a randomized controlled clinical trial of zinc versus placebo in 151 individuals with early AMD. A daily dose of zinc sulfate (100 mg) versus placebo was tested with 1:1 randomization. The outcome measurement was visual acuity change compared to baseline. There was a significantly positive treatment effect with zinc \( (P < 0.05) \). Importantly, the final visual acuity was significantly less likely to deteriorate in the zinc-treated group.

The AREDS

The AREDS was a randomized, double-masked, placebo-controlled clinical trial designed to evaluate vitamins C (500 mg), E (400 IU), and beta-carotene (15 mg), with or without zinc (zinc oxide 80 mg), with copper (2 mg cupric oxide), in a factorial design for the treatment of AMD. The 3640 AREDS participants, aged 55 to 80 years, had varying severity of AMD and were followed for a mean of 6.3 years. The combination of the antioxidant vitamins with the minerals demonstrated a statistically significant odds reduction for the progression to advanced AMD \( \text{OR, 0.72; 99\% CI, 0.52–0.98; } P \text{ statistically significant} \). This treatment effect appeared to persist following 5 additional years of follow-up after the clinical trial was stopped. The AREDS formulation became the standard of care for persons who are at high risk for AMD, either intermediate AMD or large drusen in both eyes, or advanced disease in one eye with large drusen in the fellow eye.

The AREDS2

The AREDS2, a multicenter, randomized, double-masked, placebo-controlled clinical, was conducted in 4203 participants, aged 50 to 85 years, who had intermediate AMD (bilaterally large drusen) or large drusen in 1 eye and advanced AMD in the fellow eye. They were assigned randomly to placebo, lutein (10 mg)/zeaxanthin (2 mg), omega 3 fatty acids (DHA 350 mg and EPA 650 mg), or the combination of lutein/zeaxanthin and omega-3 fatty acids. In addition, all the participants were administered either the original AREDS formulation (vitamins C, E, and beta-carotene, and zinc with copper) or some modification of the AREDS formulation (either elimination of beta-carotene, lowering of the zinc, or the combination of the two). The participants were followed for a median of approximately 5 years. Approximately 50% of the participants were former smokers and 7% were current smokers.

The primary analyses consisted of comparing each treatment group with the placebo group, using only half of the study population (~2000) for each of these analyses. These three treatment groups did not demonstrate additional beneficial effects beyond the effects of the AREDS formulation. However, in the analyses which used the entire population (4000+) to conduct the analysis of the main effects, that is, evaluating all those assigned to lutein/zeaxanthin \( (n = 2123) \) versus those not assigned lutein/zeaxanthin \( (n = 2080) \), there was an added 10% reduction in the risk of progression to advanced AMD \( (HR, 0.90; 95\% CI, 0.82–0.99; P = 0.04) \). When analyses were restricted to those with lowest dietary intake of lutein/zeaxanthin, there was a further reduction in the risk of advanced AMD \( (HR, 0.75; 95\% CI, 0.59–0.94; P = 0.01) \). When lutein/zeaxanthin with AREDS formulation minus the beta-carotene treatment group was compared to the AREDS (with beta-carotene and no lutein/zeaxanthin) treatment group, the HR was 0.82 \( (95\% CI, 0.69–0.96; P = 0.02) \). The adverse effect associated with beta-carotene was the increased risk of lung cancer in former smokers. A number of other secondary analyses, some prespecified and others were post hoc, as well as the emergence of this important adverse effect contributes to the totality of the evidence that suggest adding lutein/zeaxanthin and eliminating beta-carotene from the AREDS formulation may result in an incremental increase beyond the beneficial effects of the AREDS formulation for reduction in the risk of developing advanced AMD.

Vitamin B Complex, the Women’s Antioxidant, and Folic Acid Cardiovascular Study

The Women’s Antioxidant and Folic Acid Cardiovascular Study was a randomized controlled clinical trial of female health care professionals \( (n = 5442) \) who were 40 years or older with preexisting cardiovascular disease, or who have three or more cardiovascular disease risk factors. They were randomized to a combination of B vitamins (folic acid 2.5 mg, pyridoxine hydrochloride or B6 at 50 mg, cyanocobalamin or B 12 at 1 mg) or placebo daily. A total of 5205 women, who were not diagnosed with AMD at baseline, was followed for a period of 7.3 years. The outcome was incident AMD that was self-reported and confirmed by medical records. The results demonstrated that daily supplementation of the B vitamins, folic acid, pyridoxine, and cyanocobalamin may reduce the risk of AMD \( (RR, 0.66; 95\% CI, 0.47–0.93; P = 0.02) \). Since these were secondary analyses, further studies are warranted before making clinical recommendations for use of B vitamins in the treatment of AMD.

DISCUSSION: UNMET NEEDS AND OPPORTUNITIES FOR FUTURE RESEARCH

Cataract

The data from randomized controlled clinical trials mostly have failed to demonstrate beneficial effects of nutritional supplements for the treatment of cataract. However, two randomized controlled clinical trials of multivitamins/minerals have suggested a beneficial role for the treatment of age-related cataracts, one in a nutritional deprived population in Linxian, China, and another in a well-nourished population in Parma, Italy. The beneficial effect for nuclear cataract was countered by the harmful effect of developing PSC cataract. One study suggested that riboflavin/niacin may be contributing to this deleterious effect. None of these studies has evaluated the individual nutrient that may be important in the multivitamin/mineral combination. Future studies may have the opportunity to provide clarification. However, such a trial may be extremely costly, requiring tremendous numbers of subjects and lengthy follow-up. Thus, an important area of future research is to find clinically meaningful surrogate outcomes that would allow clinical research to be conducted in a shorter interval of time with smaller number of participants. An example of this would be the potential use of the technology designed to detect precataractous lens protein changes clinically using dynamic light scattering. The dynamic light-scattering device has been used to evaluate \( \alpha \)-crystallin, a molecular chaperone protein that has been demonstrated to bind to damaged lens proteins, which prevent their aggregation. This measure of an \( \alpha \)-crystallin index decrease was associated with increasing nuclear lens opacities \( (P < 0.002) \). Even in clinically clear lens, significant decreases in \( \alpha \)-crystallin can be detected.

A small reduction in the progression of age-related cataract would have a profound effect on the costs of American health, as this condition currently is a significant public health issue.
problem, with large numbers of people affected with the disease projected to increase markedly with increasing longevity. Currently, one of the most commonly performed procedures in the United States is cataract surgery. A successful preventive measure would reduce the cost of this condition to society, and to the individuals and their families.

Although the pathogenesis is not well understood, antioxidant properties of nutrient-based therapies are attractive for these chronic conditions. The therapeutic effects seen in those with the lowest dietary intake of lutein/zeaxanthin, for example, suggest that nutrient therapy may have a role in preventing cataract. The public health message of “You are what you eat” is important. Eating well, and having a diet replete with fish and many colored vegetables, especially the green leafy ones, are public health messages that might be particularly important to communicate to the entire population. This has implications for general well-being as well as potential reduction of ocular diseases.

Age-Related Macular Degeneration

The nutritional supplement, known as the AREDS formulation, has been demonstrated to reduce the progression to advanced AMD by 25% in 5 years in persons with intermediate AMD (bilateral large drusen) or having large drusen in one eye and advanced AMD in the fellow eye. There is an incremental increase in the efficacy of the AREDS formulation when beta-carotene is replaced by the addition of lutein/zeaxanthin to this formulation. Again, those in the lowest dietary intake group of lutein/zeaxanthin appear to have the greatest benefit. Thus, the public health message of proper diet is essential for prevention of chronic disease, such as AMD and other systemic conditions.

Aside from the beneficial effects of folic acid during pregnancy for the prevention of spina bifida and calcium for prevention of osteoporosis, the AREDS formulation is the only other nutritional supplement known to have beneficial effects on any disease. All the previous studies of nutritional supplements for cardiovascular disease and cancer have been proven to be negative. For example, nutritional studies of the B vitamins for cardiovascular disease were negative, while the ancillary studies in ocular disease demonstrated a beneficial effect for AMD. Ideally, it would be prudent to have a duplicate randomized, double-masked, controlled clinical trial to support the AREDS formulation and its effects on the retina. With limited resources, the feasibility of replicating the AREDS is unlikely as the AREDS formulation has become the standard of care for many of the individuals at risk for developing advanced AMD. One is reassured by the beneficial effects that persisted in the observational study that followed the clinical trial. At 10 years, there was still a 27% reduction in the risk of developing advanced AMD. In addition to the nutrients evaluated in AREDS2, should other vitamins be studied? Do we need further analyses with observational studies of nutritional intake? The Women’s Antioxidant and Folic Acid Cardiovascular Study of B complex of vitamins suggested a beneficial effect for AMD. Would further randomized trial be feasible and be warranted, given the preliminary findings of a protective effect of the B vitamins for AMD? These are questions that yet must be answered.

An explosion of genetic information is occurring in the field of AMD. Additional pathways have been emerging as potential disease mechanisms from studies of genetic associations. These include pathways that involve inflammatory, complement, and high-density lipoprotein (HDL) cholesterol pathways that potentially are part of AMD pathogenesis. The further analyses of these genetic associations with the dietary intake and the randomized trials of nutrient supplement should give us clues as to the potential for personalized medicine and potential targets for future treatment.

An important step in the research for AMD includes the need for better phenotyping, as AMD is likely to include a number of conditions that may be separated genetically. We also need a better understanding of the functional and structural correlations of the disease process. The technologies for imaging have developed rapidly, and may provide better tools for developing and improving our outcome measures for cataract and AMD outcomes for clinical trials.

Finally, it is important to understand that a modest protective effect on the progression of AMD (and cataract) still would have a significant impact on patient welfare and on cost control given the large and increasing numbers of patients affected. Areas of unmet medical need include finding effective therapy for geographic atrophy and for primary prevention of AMD. Prevention certainly would be favored over intravitreal injections, even though they may be successful in reducing the risk of vision loss. We believe the next decade will witness some major changes in the way we will treat AMD.

Acknowledgments

Disclosure: E.Y. Chew, None

References


Aging of the ocular surface and corneal tissues, major components of the visual system, causes major eye disease and results in substantial cost in medical and social terms. These diseases include the highly prevalent dry eye disease that affects the ocular surface and its glands, leading to tear film alterations, discomfort, and decreased vision. Studies show that 14.4% of the population in the United States older than 50 years have dry eye disease and demonstrate that it is particularly prevalent among women. Annual medical costs per patient with dry eye in the United States are estimated at $783 per year, with an overall medical cost adjusted to prevalence of $3.84 billion per year. Because there are few effective treatments for the disease, more research on its etiology and mechanisms is warranted and needed. Increased public education about risk factors for the disease is also required.

Another major age-related eye disease of the cornea that leads to vision impairment and potentially blindness if left untreated is Fuchs' endothelial corneal dystrophy. This disease leads to loss of the endothelial cells on the internal side of the cornea that are responsible for keeping the cornea in the proper hydration state to ensure its transparency to light. The mechanism of cell loss is unknown, and the only treatment available to date is surgical transplantation of the cornea or inner part of the cornea. These medically costly procedures require donor corneas, eye banking, and medical follow-up, with accrued costs. Fuchs' endothelial corneal dystrophy is a major cause of corneal transplantation in the United States; therefore, research support is needed to determine the mechanism of this age-related disease, to develop medical, nonsurgical methods for treatment.

Keywords: age-related diseases of cornea, dry eye, Fuchs' endothelial corneal dystrophy, cornea, ocular surface
gland produces and secretes water and a myriad of other protective proteins, and the conjunctival goblet cells and the corneal epithelium secrete mucins and release membrane mucins into the tear fluid, respectively. The age-related changes that have been documented occur in most components of the ocular surface system. Examples of these changes within the meibomian gland include keratinization of the gland ducts, gland dropout, and alteration in lipids of meibum. For an excellent review of meibomian gland development, anatomy, physiology, and changes in age and disease, see the 2011 article by Knop et al.3 The lacrimal gland shows diminished levels and composition of secretion with age, and gland inflammation and ductal fibrosis (especially in women) have been reported.4 As a result of glandular changes with age, the tear film composition changes; for a review, see the 2007 article by the Research Subcommittee of the International Dry Eye WorkShop.1 Findings by McGill et al.5 indicate that the levels of lactoferrin and lysozyme decrease with age. However, it is unknown to date whether age affects the myriad of other important tear proteins or whether tear osmolarity, an increase of which occurs in dry eye, changes with age.

Age-related alterations also occur in the integrating components of the ocular surface system. First, there is a well-known diminution of sex hormones that occurs with age in both sexes that affects glandular functions of the ocular surface system.3 Second, the number of nerves in the corneal epithelial subbasal plexus decreases with age,6 leading perhaps to the loss of sensitivity observed with age.7 Third, although not specifically demonstrated in the eye, there is a systemic loss of immune

FigURE 1. Major age-related changes in the ocular surface system components (A) and in the components that integrate the functions of the ocular surface system (B).
function with age. Major age-related changes in the ocular surface system are summarized in Figures 1A and 1B.

**Dry Eye Disease, the Major Age-Related Disease of the Ocular Surface**

Because various functions of the ocular surface system are integrated and because epithelial specializations provide different products for the tear film, it is not surprising that alterations in any one or more functions of the ocular surface system components with age will cause a disruption of the tear film. This will lead to drying of the ocular surface, which in turn leads to a decrease in visual acuity and subjacent epithelial injury with ensuing inflammation. Therefore, dry eye is a multifactorial disease of the ocular surface that results in symptoms of discomfort, visual disturbance, tear alterations, and tear film instability with damage to the ocular surface. It is accompanied by increased osmolarity of the tears and inflammation of the ocular surface. Mild to severe forms of the disease are noted.

Dry eye disease has multiple etiologies, all of which may be derived from alterations in one or more components of the ocular surface system. The majority of patients with dry eye have meibomian gland disease (MGD); for a review, see the article by Knop et al. Dry eye can be secondary to Sjögren’s syndrome, rosacea, or systemic or topical medication use, to name a few. In fact, patients show a wide variety of presentations and symptoms, and the lack of definitive diagnosis and etiology frustrates ophthalmologists and patients. Thus, because of the multifactorial and elusive etiology of dry eye, effective treatments are often unavailable.

Risk factors for dry eye disease have been summarized. Those that have been most consistently described include older age, female sex, postmenopausal estrogen therapy, imbalanced ratios of omega-3 to omega-6 fatty acids, antihistamine use, other medication use, connective tissue disease, LASIK and refractive laser surgical procedures, radiation therapy, hematopoietic stem cell transplantation, vitamin A deficiency, hepatitis C infection, and androgen deficiency.

While major progress has been made recently in developing hypotheses for the mechanism of dry eye disease, proof of the mechanism remains elusive because of its multifactorial nature. Several hypotheses have been advanced. One hypothesis, based on extensive studies in mice, is that defects in tear amounts or composition lead to epithelial surface injury and stress, which in turn lead to an immune-mediated inflammatory response. Having autoimmune characteristics, the inflammatory response becomes chronic. This hypothesis relates to the common postinjury pathway of the disease but does not identify the source of the injury, which is or can be multifactorial. Although the autoimmune designation has been proven for mice, data from human studies are at best suggestive. Another hypothesis, one particularly relative to the prevalence of dry eye in women, is that hormonal changes with age drive alterations in ocular surface epithelial functions, which in turn promote epithelial injury and dry eye; these data are supported by the appearance of dry eye in patients with androgen deficiency (for a review, see the 2004 article by Sullivan).

**Prevalence of Dry Eye Disease.** Estimates of the prevalence of dry eye in the worldwide population older than 50 years range from 5% to 30% depending on the study (the range is accounted for by variable definitions of dry eye disease). In the United States, studies indicate that at least 14% of the population older than 50 years have dry eye, indicating that it is one of the major eye diseases in the country. Moreover, the disease in the United States is prevalent among women. While 3.23 million women are reported to have moderate to severe dry eye, only 1.68 million men are estimated to do so.

**Economic Burden of Dry Eye in the United States.** A recent, first estimate of the economic burden of dry eye in the United States indicates that the average annual cost of managing dry eye is $783 per patient, with an overall cost adjusted to prevalence of $3.84 billion. From a societal perspective, the cost of lost productivity is estimated to be $11,302 per patient per year, with overall costs adjusted to prevalence of $55.4 billion per year. These data indicate that dry eye disease is an enormous economic burden to individuals and society.

**Age-Related Infections of the Ocular Surface**

Infections of the ocular surface can cause corneal blindness and until recently were second only to cataract as the major cause of blindness worldwide. With improved hygiene and economic status in developing countries, there has been great progress in reducing the burden of blindness from these diseases, particularly from trachoma. Moreover, these diseases occur mostly in younger people and are therefore not considered age related. However, one infection that often occurs at the ocular surface and cornea is age related is herpes zoster ophthalmicus (HZO). This disease, also known as shingles, is a painful rash that occurs mostly in tissues innervated by the trigeminal nerves shared by the skin around the eye, as well as the ocular surface and its adnexa. Caused by reactivation of the varicella-zoster virus that lies dormant in nerve ganglia, HZO occurs typically in older adults. Progress in treating the disease has been made with the development of antiviral medications and a vaccine against the virus. While the vaccine has helped prevent the disease, it is not a cure; recurrences occur following vaccination, albeit with decreased severity. Thus, work to improve the efficacy of the vaccine is needed to eradicate this painful debilitating disease. Estimates of the prevalence of HZO indicate that 20% of the US population have had herpes zoster and that 10% to 20% of those affected have ocular zoster.

**AGE-RELATED CHANGES AND DISEASES OF THE CORNEA**

**Age-Related Changes in the Cornea**

Major changes in the cornea with age include thickening of both the epithelial and endothelial basement membranes, the latter known as Descemet’s membrane. As stated above, nerve density in the subbasal plexus, below the epithelium, decreases. Moreover, a decrease in the number of conjunctival keratocytes has been reported.

However, the most important and clinically relevant change in the cornea with age is the well-documented loss of corneal endothelial cells. Continual loss of these nonmitotic cells can lead to disease, as described below. Figure 2 shows the major age-related changes in the cornea.

**Age-Related Diseases of the Cornea**

Corneal endothelial cells are vital for maintaining corneal transparency to light because they provide a barrier function and pump water, which can accumulate in the corneal stoma from the anterior chamber. People are born with a fixed number of corneal endothelial cells, and that number gradually declines with age. Because the endothelial cells do not divide, cell loss induced by age or disease cannot be reversed, and the relative state of cornea dehydration cannot be maintained. As a
result, fluid accumulation leads to corneal edema and loss of corneal transparency. This condition, termed bullous keratopathy, is characterized not only by opaque corneas but also by separation of the corneal epithelium from its underlying matrix in small blister-like elevations known as bullae. The following two major causes of bullous keratopathy are both age related: (1) Fuchs’ endothelial corneal dystrophy (FECD) and (2) iatrogenic endothelial damage due to cataract or other surgery. Left untreated, bullous keratopathy represents a serious sight-threatening corneal disease, the only current treatment for which is corneal transplantation or endothelial keratoplasty such as Descemet’s stripping endothelial keratoplasty or Descemet’s membrane endothelial keratoplasty, in which only the posterior portion of the cornea is replaced. These two diseases are the major causes of corneal transplantation, approximately 40,000 of which occur annually in the United States. The incidence of iatrogenically induced bullous keratopathy is decreasing with the improvement in cataract and other corneal surgical methodologies and will not be discussed herein.

**Fuchs’ Endothelial Cell Dystrophy.** Fuchs’ endothelial corneal dystrophy is characterized not only by loss of endothelial cells but also by the development of mounds of extracellular material on Descemet’s membrane, under discrete regions of endothelium, termed guttae. Cells on these mounds, or guttae, are attenuated and have an aberrant structure. Fuchs’ endothelial corneal dystrophy is primarily a late-onset genetic disorder. The genetic basis of FECD is complex and heterogeneous, demonstrating variable expressivity and incomplete penetrance. To date, several causal genes (ZEB1, SLC4A11, TCF4, and LOXHD1) have been identified, representing a small proportion of the total genetic load of FECD. Another gene, col8A2, has been identified in early-onset FECD (1% of the population with FECD).

Risk factors for FECD include family history, female sex, and age. It is unknown whether environmental or lifestyle factors influence progression of the disease.

Because the genetic basis of FECD is complex, the search for a common pathophysiologic mechanism of the disease has led to the hypotheses that endothelial cells of patients with FECD have an alteration in their antioxidant system that results in diminished capacity to prevent cell damage due to oxidative stress, which can lead to apoptosis and endothelial cell loss.

The hypothesis (Fig. 3) is based on the demonstration of decreased antioxidant gene expression and increased oxidative DNA damage in endothelium of corneas from patients with FECD compared with that of age-matched control subjects.

**Prevalence of FECD.** A recent study of 8 million enrollees in a national managed care network throughout the United States estimated the overall prevalence of corneal dystrophies to be 0.13% of the population, with the specific prevalence of FECD at 0.078%. Based on a population of 310 million, it is estimated that approximately 166,800 people in the United States carry the disease. Older studies have found
higher prevalences of FECD. In 1980, Rosemblum et al. reported a prevalence of 4%, and Waring et al. in 1978 reported that guttae occur in 5% to 70% of patients and that their numbers increase with age. Variations in the results of these studies are because of differences in study methods.

The economic burden, both medical and social, from this age-related corneal dystrophy has not been assessed to date. However, along with iatrogenic bullous keratopathy, FECD represents the leading cause of corneal transplantation and Descemet’s stripping endothelial keratoplasty. Considering that the medical costs per patient per transplantation may approach $5500 (provided in the public domain at http://www.healthcarebluebook.com/page_results.aspx?id=280&dataset=MD), the annual costs per 20,000 corneal transplantations would approach $110 million.

WHAT CAN BE DONE TO SLOW OR PREVENT CORNEAL AND OCULAR SURFACE AGING AND DISEASE?

The enormous and growing effects of age-related diseases of the ocular surface and cornea are recognized as both social and medical burdens. The following recommendations are made to governmental agencies that control federal support for research and public education, as well as to professionals treating patients and to academicians doing research.

Aging

- Improve normative age-related data on changes in the ocular surface, cornea, and tears in humans with no apparent clinical disease;
- Enhance data on the effects of environmental stress, the microbiome, and lifestyle on the ocular surface, cornea, and tears in humans; and
- Educate the public on prevention, emphasizing risk factors that predispose to ocular surface or corneal stress.

Corneal and Ocular Surface Disease

Dry eye. Because it is highly prevalent and costly to treat, increase funding for research on dry eye, specifically the following:

- Identify biomarkers that distinguish the etiology of this multifactorial disease (e.g., MGD and lacrimal gland insufficiency);
- Verify the autoimmune hypothesis of the mechanism of this chronic disease in humans and thereby identify possible targets for immunobased therapy;
- Determine the basis of sex differences in dry eye disease, and
- Develop treatments specific to the various etiologies of dry eye disease.

Fuchs’ endothelial corneal dystrophy.

- Fund research to determine the mechanism of FECD, to develop early, nonsurgical therapies; and
- Determine if lifestyle or environmental factors influence disease progression in FECD.

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References

Aging and Age-Related Diseases of the Ocular Lens and Vitreous Body

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Reduced quality of life and financial burden due to visual impairment and blindness begin to increase dramatically when individuals reach the age of 40. The major causes of age-related vision loss can be traced to changes in the structure and function of the lens, one of the tissues responsible for focusing light on the retina. Age-related nuclear cataracts, which are caused by aggregation and condensation of proteins, diminish vision because they impede the transmission and focusing of light on the retina. In addition to the slow-developing age-related form, cataracts often develop rapidly as a complication of ocular surgery, such as following vitrectomy or as a consequence of vitreous gel degeneration. Posterior capsular opacification, which can develop following cataract removal, is caused by proliferation and inappropriate accumulation of lens epithelial cells on the surfaces of intraocular lenses and the posterior lens capsule. Presbyopia is a loss of accommodative amplitude and reduced ability to shift focus from far to near objects. Onset of presbyopia is associated with an increase in lens hardness and reduced ability of the lens to change shape in response to ciliary muscle contraction. Avenues of promising research that seek to delay or prevent these causes of low vision are discussed in light of our current understanding of disease pathogenesis and some challenges that must be met to achieve success.

Keywords: cataract, PCO, presbyopia, vitreous humor

The lens is a remarkable tissue that is responsible for diffracting light so that it focuses precisely on the retina. Proper functioning of the lens requires it to be optically transparent, allowing light to travel unimpeded through the ocular media to reach its target. To meet the demands of near and far vision, the lens also must be pliable so that the surface curvature can change when needed to adjust the focal distance. These simple requirements are fulfilled for most people during their first 3 decades of life. But at later ages, clear vision begins to deteriorate. Corrective measures are then required to restore visual acuity to the level needed to live, work, and play effectively. Vision problems arise when the lens loses its transparency (cataract) or diminishes in its ability to change shape (presbyopia). Living with presbyopia requires a lifestyle many would prefer to avoid. Corrective lenses (reading glasses, contact lenses) are nonsurgical answers to presbyopia, but they can be unacceptable in some occupational settings. We also pay a high price to restore vision degraded by cataracts. Although cataract surgery is safe and effective, it is not without complications. As a consequence of the sheer number of surgical procedures performed annually in the United States in recent years, cataracts were the most expensive eye disease, costing the Medicare budget more than any eye or vision condition with a medical diagnosis.

The goal of the following pages is to briefly review what we know about mechanisms leading to the most common forms of cataract and lens defects, and to identify promising areas of research that could lead to more effective treatments than the ones currently available.

Cataract as a Global Burden

According to a 2012 World Health Organization report, it is estimated that 39 million people are blind worldwide. Cataract is responsible for the largest cause of blindness, affecting almost 18 million people. When one examines the global distribution of blindness due to cataracts, it is obvious that the burden disproportionately affects low- and middle-income countries. The incidence of cataract is known to increase with age, and no region of the world is immune to the age-related onset and development of vision-threatening cataract. However, the medical infrastructure and financial resources necessary to treat millions of cataracts each year is simply not available in many underdeveloped countries of the world. The scientific community is faced with a major challenge that must be met to effectively deal with the most common cause of blindness in the world. To do so, we must know more about the pathogenesis of cataracts. And we must determine key steps in cataract pathogenesis that can be targeted by new therapeutic strategies to delay or substantially prevent cataract blindness.

Cataract Mechanisms

Cataract is essentially an aggregation disease involving the crystallin proteins that accumulate to exceedingly high concentrations in fiber cells of the lens. The genes encoding α, β, and γ-crystallins are dramatically upregulated as lens cells differentiate from epithelium into elongated fiber cells. Due to...
the combined upregulation of gene transcription, robust levels of protein biosynthesis, and low levels of endogenous endoproteases, the protein content of human lens fiber cells rises to approximately 350 mg/mL. The high protein concentration is thought to subserve the refractive properties of the lens and is likely responsible for the refractive gradient necessary for proper optical performance of the lens. Lens fiber cells lose most of their intracellular organelles during the differentiation process. Nuclei, mitochondria, and the protein biosynthetic capacity are lost in a process of organelle breakdown. Therefore, lens cells have an extremely limited capacity to restore crystallins that may become functionally damaged during the aging process. Similarly, breakdown of mitochondria limits capacity to generate ATP.

Cataract can be considered a “perfect storm” if one considers the biological context of the lens and the human eye. The fiber cells, which are the major cell type that constitutes the lens, are endowed with extremely high concentrations of proteins that are not replenished and that remain in situ for the lifetime of the tissue itself. Under normal conditions, lens cells will experience decades of exposure to stresses that are well known to destabilize proteins: ultraviolet light and chemical insult. Worse yet, abnormal conditions can place lens proteins at higher risk for destabilization. Chronic hyperglycemia induces posttranslational modifications of lens crystallins, such as formation of advanced glycation end products. Furthermore, the supply of enzymes that usually “search and destroy” damaged proteins is also limited, thus completing the “perfect storm.”

Extensive research has been carried out to better understand biochemical changes to lens crystallins that accumulate with aging and that may play a role in cataract formation. Posttranslational changes, including truncated forms of α- and β-crystallins, are commonly found at early ages in the noncataractous lens, but the abundance of these altered forms appears to be relatively small in comparison with the much larger pool of corresponding full-length proteins at early ages. Other structural changes seem to be associated with older lenses and cataract onset. For example, homo- and hetero-oligomeric protein complexes cross-linked through disulfide bridges accumulate to higher levels in cataracts. Formation of such abnormally cross-linked protein species are most likely a result of oxidative stress and loss of redox balance of glutathione, the major antioxidant in lens cells. The end result of these posttranslational changes is to reduce the stability of crystallin proteins and make it more likely that they will become structurally denatured and condense into aggregates containing other similarly destabilized proteins. Lens cytoplasm containing aggregates of proteins gives rise to refractive discontinuities because light must travel through protein-rich and protein-poor pockets as it traverses the lens. Such refractive discontinuities result in diffraction and back scatter of incident light rather than transmission along the optical axis to the neural retina. Light scattering induced by protein aggregates is responsible for the poor visual acuity, overall loss of light sensitivity, and white appearance of the lens in patients with cataract.

The major classes of crystallins expressed in the mammalian lens can be allocated on the basis of structural and functional properties into one of three groups, designated α-, β-, and γ-crystallins. The human α-crystallins are expressed from two related genes, αA- and αB-crystallin, which produce approximately 20-kDa protein subunits. αA and αB subunits associate in roughly a 3:1 ratio to form α-crystallin hetero-oligomeric complexes containing approximately 40 subunits in total. As the α-crystallins are evolutionarily related to the family of small heat shock proteins, they appear to be ideally suited as chaperone-like molecules capable of suppressing the aggregation of other proteins in the immediate cellular environment. Extensive studies have demonstrated the ability of both αA- and αB-crystallins to prevent the aggregation of client proteins that have been destabilized by a variety of insults. Structure-function studies point to a critical role for a highly conserved “α-crystallin domain” that is present among small heat shock proteins that express the chaperone-like ability to suppress protein aggregation. Indeed, synthetic peptide fragments containing amino acid sequences derived from the α-crystallin domain demonstrate chaperone-like activity when tested under a variety of conditions.

Although α-crystallin in cytoplasm forms dynamic oligomeric complexes of approximately 100 nm in size, much larger complexes are formed after interaction with client proteins. Using dynamic light scattering to detect and size-estimate light-scattering elements, Datiles and coworkers reported an age-related loss of the smaller α-crystallin complexes in a human lens after development of a nuclear cataract. Perhaps this reflects a loss of chaperone-like capacity required to avoid aggregation of other lens proteins as they undergo transient unfolding induced by environmental and metabolic stresses over time. Because of the biosynthetic limits of lens cells to replenish native-size α-crystallin, it is possible that loss of native-sized α-crystallins therefore represents a risk factor but not necessarily a de facto cause of cataract development.

What are the strategies that can be envisioned to offset the loss of native α-crystallin complexes and restore enough chaperone-like activity to prevent or substantially delay cataract formation?

Recent research has focused on introducing intact α-crystallin protein subunits or peptides containing the α-crystallin domain as a means to restore the protective effects in target cells. Peptides containing the α-crystallin domain (mini-chaperones), as well as full-length αB-crystallin have been shown to protect human fetal retinal pigment epithelial cells from the cell death and caspase activation induced by oxidative stress. Efficacy against the cataractogenic effects of oxidative and chemical stress has also been demonstrated with the use of α-crystallin-derived mini-chaperone peptides. As a replacement strategy against human cataract will likely require efficient delivery of therapeutic effectors to the lens cell cytoplasm, considerable effort is now being focused on strategies to enhance the penetration of therapeutic crystallins and associated peptides into target cells. Fusion of crystallin polypeptides to cell penetration peptide domains, as well as encapsulation of crystallins into biodegradable nano- and micro-particles, is being explored.

In a modern cataract procedure, the surgeon removes the cataractous lens by phacoemulsification. In this procedure, the hard lens nucleus is fragmented into small pieces using a narrow probe with a tip that vibrates at ultrasonic frequency. After aspiration of the resulting fragments of lens nucleus, as well as tissue from the outer cortex, an artificial IOL is placed into the “empty” capsular bag and the patient’s vision restored after a recovery period of a few hours. Although cataract surgery is considered a safe and effective surgical procedure, it can be conservatively estimated that up to 20% of cataract cases develop posterior capsular opacification (PCO), which results in a loss of clear vision following a period of weeks to months after surgery.

After the phacoemulsification procedure, a thin layer of lens epithelial cells (LECs) usually remain adherent to the inside of the capsular bag (Fig. 1). A portion of these residual LECs become stimulated to proliferate and migrate along the inner lining of the capsular bag until they reach the posterior aspect

**Posterior Capsular Opacification**
spikes in IOP. Therefore, YAG capsulotomy may not be suitable for patients who have a history of retinal disease or glaucoma.

Given the possible sight-threatening complications and costs associated with treating PCO, there is a critical need to understand the cellular mechanism that leads to PCO and possible ways to target this complication with either pharmaceutical strategies or by the development of new technologies in IOL materials and design.

Surgical trauma to the eye, as in cataract extraction, induces the production of cytokines and growth factors as part of the wound response. In the context of PCO, TGFβ is one of the major growth factors involved in the response to cataract extraction.16 The TGFβ convey its information by engaging cell surface receptor complexes, which then transmit their signal through the cell membrane to activate signaling pathways in the cytoplasm and nucleus. In LECs, TGFβ receptor binding causes activation of Smad proteins, which act by increasing the transcription of a battery of genes involved in cell proliferation.17 Thus, TGFβ leads to a shift in the behavior of LECs, transforming them from stationary, rarely dividing cells into cells that proliferate, adopt a fibroblast-like morphology, and express new protein markers, such as alpha smooth muscle actin (αSMA). This transformation from epithelial to a mesenchymal phenotype is known as EMT. By measuring cell proliferation and EMT markers in both human and nonhuman capsular bag models, a large number of laboratories have confirmed a central role for TGFβ.18 However, other factors are likely involved to some extent, as experimental models of PCO can be influenced by blockade of many other growth factors (epidermal growth factor, hepatocyte growth factor, FGF) or factors involved in the inflammatory response (IL-1, IL-6, aldo-keto reductases).18,19 Clearly, much work remains to be accomplished to work out a better understanding of the postsurgical response leading to PCO.

Use of optimized materials and design considerations in the manufacture and placement of IOLs may also diminish the risk of PCO development. It is now well recognized that IOLs made from hydrophobic materials are less favorable substrates for LEC adherence and migration. Manufacturers have adapted by innovating new materials and IOL surface coatings to optimize optical performance while minimizing the risk for PCO.

Mechanical factors relating to the placement of the IOL in the capsular bag also influence the risk of developing PCO. IOLs that have sharp edges are associated with significantly lower risk for PCO, presumably because this design facilitates formation of an efficient barrier to cell migration between the IOL and the inner surface of the lens capsule. IOL design enhancements are constantly being refined, with the next major goal being the production of an IOL that prevents PCO, functions as an accommodating lens, and performs without distacting visual defects such as halos and glare.

**Presbyopia**

Presbyopia is the condition whereby the ability to focus on near objects becomes diminished. The impact of presbyopia is nearly universal among people as they enter their middle-age years. Although near vision can be regained simply by the use of reading spectacles, for practical and professional reasons there is great demand for a solution that does not require corrective lenses.

The biological basis for presbyopia has received intense study over the years. To adjust for near vision, it is necessary for the lens to “round up” from its unaccommodated shape. This shape change is made possible when the ciliary muscles contract, drawing together the tissues that surround the lens in a sphincter-like motion (Fig. 2). In response, the body of the...
lens assumes a more rounded shape, altering the radius of curvature mainly at the anterior surfaces. The accommodation response reduces the focal length of the lens to allow clear focusing of near objects on the retina. Thus, the process of accommodation for near vision relies on a change in lens shape in response to contraction of the ciliary muscles.

Pliability is a critical factor that underlies the ability of the lens to change shape. Many investigators have shown that the human lens hardens over time, leading to the hypothesis that presbyopia occurs when the lens becomes too hard to change shape in response to ciliary muscle contraction. Studies by a variety of methods have demonstrated a marked increase in lens stiffness beginning in the third to fifth decade of life, which is roughly the age when loss of accommodation becomes noticeable in the early stages of presbyopia.20

The molecular basis for increased lens stiffness is not well understood. Fiber cells in the lens nucleus are held together by an array of intercellular adhesion molecules, gap junction complexes, and ball-and-socket–like interdigitations along their extensive lateral membranes. As the lens ages and more of the lens mass becomes internalized into the nuclear region, it is likely that cells are riveted together with these intercellular junctions, perhaps contributing to the diminished deformability of the tissue.

Metabolic changes in the aging lens could also contribute to a change in its mechanical properties. Recent evidence suggests that the nucleus becomes less accessible to glutathione as a result of the formation of a diffusion barrier in older lenses.21 Lack of sufficient levels of glutathione would result in a redox environment that would facilitate the disulfide-mediated crosslinking of proteins and structural elements in lens cells, which could lead to reduced diffusion of cytoplasmic protein complexes and associated loss of cellular pliability.

Other functional elements of the accommodation process also have been examined as factors in the pathogenesis of presbyopia. Given the key role of ciliary muscle contraction in lens accommodation, many have hypothesized that loss of muscle contractility could contribute to the disease mechanism. However, careful study of ciliary muscle function in the context of age-related effects has demonstrated that muscles retain a sufficient degree of contractility to support the accommodation process. Therefore, it is generally accepted that diminished ciliary muscle contractility is not a likely cause of presbyopia. Similarly, increased stiffness of the capsule could explain a resistance to lens shape changes, but the available data do not support this as a likely explanation.

Given the decades of experience with cataract surgery, one reasonable approach to the treatment of presbyopia would be to replace the aged lens with one that has accommodation properties. However, despite innovations in the design and fabrication of IOLs, a simple accommodative device that is free from surgical defects has yet to be developed. Many of the new accommodative IOL designs rely on the adjustable positioning of multiple optics or changes to flexible surface membranes to achieve the appropriate correction in focal length. Time will tell whether some of these designs will pass the challenges of long-term durability and optical performance in patients. In contrast to the IOL approach, some investigators are developing injectable materials that can be introduced as a liquid into the capsular bag following removal of the natural lens. A chemical or light-activated curing process is then used to induce transition of the material to a gel-like consistency.22 Although the resulting artificial lens is able to undergo shape changes in response to ciliary fiber contraction, further work is needed to create the refractive gradient index that will be required to achieve optical performance coming close to the natural lens.

Vitreous Degeneration

The vitreous body is a clear, gel-like substance that fills the cavity of the eye behind the lens and helps to stabilize various retinal layers and retinal vasculature. The gel-like characteristics of the vitreous body result from a network of collagen fibrils that extend throughout the gel. Because the vitreous gel has no circulatory flow and does not mix, it effectively impedes the distribution of signaling molecules or nutrients that may be released from surrounding tissues.

Although the vitreous gel is remarkably stable, over time there is a gradual tendency for the gel to collapse, likely a result of degradation or alteration of the collagen fiber network. Patients with degenerate vitreous bodies are at increased risk for tractional forces to develop on the underlying retina, which predisposes them to retinal detachment and disruption of the delicate laminations that characterize the healthy retina. Apart from age-related vitreous liquefaction, other conditions can require removal of the vitreous gel, such as uncontrolled hemorrhaging from unstable retinal blood vessels, typical of
patients with diabetic retinopathy. In such conditions, a vitrectomy procedure is used to remove the natural gel along with entrapped blood components followed by replacement with a balanced salt solution.

Although vitrectomy is a major therapeutic advance in the treatment of retinal disease, it carries with it a high risk for nuclear cataract development. Recent studies point to oxygen as a cataract-inducing by-product of the vitrectomy procedure. Most oxygen in the vitreous gel is thought to originate from the retinal vasculature. Because of its diffusion-limiting physical properties, an oxygen gradient exists in the native eye, with highest levels nearest the retina and comparatively lower levels farthest away near the posterior surface of the lens (Fig. 3). When the contents of the vitreous humor are removed by vitrectomy and replaced with a saline solution, the physical barrier to oxygen diffusion is destroyed. Because components in the vitreous replacement solution mix freely, small molecules released from retinal vessels are distributed throughout the vitreous cavity, thus exposing the posterior lens to abnormally high levels of oxygen. Compelling evidence implicating oxygen as a primary cause of nuclear cataracts after vitrectomy comes from the study of diabetic patients who have lower oxygen in their vitreous due to retinal ischemia. Such patients had less progression of nuclear opacification and nuclear cataracts in the year after vitrectomy. In contrast, more than half of nondiabetics and diabetics with no ischemic retinopathy required surgery for nuclear cataracts within 12 months after vitrectomy.

Mechanistic studies point to a diminished ability to fight off oxidative stress as an important factor in nuclear cataract formation. Even though the vitreous gel probably protects the aging lens from exposure to oxygen, the inexorable accumulation of oxidatively damaged proteins and lipids likely predisposes the lens to cataract development. Current evidence suggests that vitrectomy results in higher oxygen levels in the vitreous cavity, which would cause accelerated oxidative changes to proteins and lipids in the lens nucleus. Further study will be required to test the hypothesis linking increased nuclear sclerotic cataract to increased protein oxidation resulting from exposure to elevated oxygen levels in vitreous substitute solutions.

NEEDS AND OPPORTUNITIES IN LENS RESEARCH

Advances in basic research suggest new strategies to delay or prevent vision loss due to age-related changes to the lens. Following is a list of unmet needs and challenges that must be met to achieve the goal of preventing age-related vision loss due to lens defects.

Research Needs and Opportunities in Age-Related Cataract

- Confirm and extend the observation that nuclear cataract formation correlates with loss of native-size \( \alpha \)-crystallin complexes in the living human lens. At present, we have no validated biomarkers in the precataractous lens that can be monitored noninvasively to monitor disease onset and progression. Recent measurements of \( \alpha \)-crystallin changes by dynamic light scattering open the door to this possibility. Additional clinical studies need to be carried out to validate this observation and extend the approach to other patients at high risk for cataract formation, such as in diabetic patients or in patients after vitrectomy.
- Loss of native \( \alpha \)-crystallin complexes in the aging eye has been correlated with increased risk for nuclear cataract formation. This finding opens the possibility that restoration of \( \alpha \)-crystallin, or functional equivalents in the form of small peptides, may delay the onset of cataract formation. Research needs to be conducted to develop effective inhibitors of protein aggregation and to identify the means of introducing these to the lens. Drug-delivery challenges must be overcome to ensure that inhibitors can reach the inner portions of the lens. More research is needed to better understand the structure and distribution of pores that connect lens fiber cells and that could facilitate the transit of therapeutic crystallins or aggregation inhibitors to the lens nucleus.
- Drug targets need to be identified to block the development of PCO. The cataract surgery itself seems...
to provide a good opportunity for drug delivery, given that the site of disease pathogenesis is readily accessible at the time of surgery and the target cells of therapy are compartmentalized in the lens capsule.

- Strategies need to be developed to delay protein oxidation and to eliminate damaged proteins as they accumulate in the aging lens.

**Research Needs and Opportunities in Presbyopia**

- More research is needed to identify factors that contribute to the onset and development of presbyopia. Can they be modified?
- Research is needed on the composition and delivery of materials that can be introduced to replace the natural lens after cataract surgery. Challenges must be met to have the replacement material restore accommodation and prevent PCO in the recovery period. In parallel, research is needed on the design and production of new IOLs that are free of visual defects (glare, halos) and that have design elements known to inhibit PCO.

**Research Needs and Opportunities in Vitreous Degeneration and Substitution**

- More research is needed to better understand why vitrectomy is associated with significantly elevated risk for cataract. Current evidence suggests that oxygen in vitreous substitutes could contribute. Can this be validated? Are other factors involved?
- Research is needed to develop and test the efficacy of vitreous substitutes with gel-like behavior. Do such materials protect the lens from oxygen released from the retinal vasculature and result in reduced risk for postvitrectomy cataract?

Almost 3 decades ago, in its national plan, the National Eye Institute reported that the need for surgery to correct cataract blindness would be reduced by 45% if a therapeutic strategy could be developed to delay the onset and progression of lens opacities by 10 years. Even though we have not yet achieved this ambitious goal, the problem has become only larger and more of a burden to the global health care enterprise. The 10-year goal remains a target worthy of the efforts of academic research and industry and deserves a renewed commitment.

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**References**

Glaucoma: A Disease of Early Cellular Senescence

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This review examines glaucoma as a disease of early cellular senescence. There is ample evidence for this position, for both the anterior and the posterior ocular segments. The existing evidence to support this view of glaucoma and avenues to treatment, both existing and new, will be examined in the light of glaucoma pathophysiology as a premature aging process.

Age is a Strong Risk Factor for Glaucoma

Of all the risk factors that have been reported for glaucoma, age is among the most consistent and strong. All epidemiological studies have concluded that age is an important risk factor for glaucoma. These include the Baltimore Eye Survey,1 the Beaver Dam Eye Study,2 the Blue Mountains Eye Study,3 the Melbourne Visual Impairment Project,4 the Rotterdam Study,5 the Barbados Eye Study,6 Proyecto VER,7 and the Los Angeles Latino Eye Study.8 In Caucasian patients, the prevalence begins to increase sharply after the age of 60, while in African American and Hispanic subjects, the prevalence begins to increase at an earlier age, starting around 40. Other risk factors, including intraocular pressure (IOP), family history, high myopia, low blood pressure, and others, are more variable and less consistent than age. While the relative risk of glaucoma increases with increasing IOP, patients with glaucoma can suffer visual loss associated with either high or low pressures, yet the majority of patients with high IOP never develop glaucoma. In some populations, most markedly Asian, glaucoma seems to progress at relatively low IOPs.9,10

Coexistent with the age-related increase in the prevalence of glaucoma is the age-related decrease in anterior segment outflow facility. That is, the resistance to fluid flow across the trabecular meshwork (TM) increases with age in a linear fashion, and begins at a fairly young age.11 This decreased outflow facility is largely responsible for the elevated IOP that is encountered in Western populations with increasing age. Markers of cellular senescence are found in the TM of patients with primary open-angle glaucoma (POAG) to a much greater degree than in age-matched controls. It is thought that aging of these cells leads to their decreased function and therefore a consequent decreased outflow facility.12 It is hypothesized that aging failure of the normal, regulatory proteolytic systems in the TM may be responsible for the observed pathophysiological alterations of the outflow pathway that may contribute to glaucoma.13

Along with the decreased function of the outflow apparatus with age is a decreased population of retinal ganglion cells (RGCs) in the retina. The RGC is the pivotal cell in the retina that electrically couples the retina with the brain; it is the cell that is primarily damaged by glaucoma. Pathological studies have shown a steady attrition of RGCs with normal aging, starting at a young age, in the amount of approximately 5000 cells per year.14 Given that the average RGC population is approximately 1 million in the human eye, and that an individual can lose approximately half of that population before significant visual dysfunction occurs, every person would normally develop glaucoma by the age of 100! Glaucomatous loss of RGCs can be viewed as a premature aging effect, causing the typical and unique optic neuropathy that clinicians diagnose as glaucoma, and the consequent characteristic patterns of visual field loss. Clinical studies have also shown a decrease with age in the thickness of the nerve fiber layer in normal individuals.15 The nerve fiber layer carries the axons of the RGCs to the optic nerve, where they exit the laminar cribrosa and connect to their targets in the central nervous system.

Biomechanical factors within the optic nerve head have been hypothesized to play a central role in RGC physiology, and contribute to the optic neuropathy of aging and glaucoma.16 The posterior sclera of old monkeys is significantly stiffer than that of younger individuals and leads to lower strains associated with elevated levels of IOP. This age-related stiffening of the sclera significantly influences the biomechanical properties of the optic nerve head and may contribute to age-related susceptibility to glaucomatous optic nerve damage.17 Similar changes occur in humans, which may be an important underpinning of the age relationship with glaucoma.18

Research on the association between glaucoma and cerebrospinal fluid (CSF) pressure has recently been reported.19 One hypothesis posits that the translaminar gradient of pressure is more important than the level of IOP. The IOP would represent the pressure anterior to the lamina, while CSF pressure is that which is posterior to the lamina. This hypothesis suggests that the magnitude of CSF pressure is just as important as IOP as a risk factor for glaucoma. The lower the CSF pressure, the greater the translaminar gradient at any given
IOP and the greater the risk of glaucomatous damage. It has been shown that CSF pressure decreases with age. 20 Thus, changes in CSF circulatory physiology in the aging individual may be important in the pathogenesis of some forms of POAG, particularly that type sometimes referred to as “normal tension glaucoma.” 21 Comparisons have been made between glaucoma and other age-related neurodegenerations, most notably Alzheimer’s disease (AD). Comparisons between these two diseases regarding their pathogenesis and course could provide insight with respect to causative mechanisms. 22 A loss of ganglion cell axons from the optic nerve in AD, similar to that seen in glaucoma, has been reported. 23 An increased prevalence of glaucoma occurs in AD patients: 26%, compared to 5% in an age-matched non-AD control group. 24 Substantial similarities between rodent models of AD and glaucoma with respect to retinal damage have been reported. 25 An approved treatment of AD with a glutamate receptor blocker, memantine, was the subject of a recent clinical trial of neuroprotective treatment for glaucoma. Although the results of the trial were not encouraging (Memantine Study, Allergan, Inc., unpublished data, 2008), it is still unclear whether or not this drug, or drugs like this, would benefit a subset of patients with progressive POAG.

Although much of this review is focused on POAG, the most common form of glaucoma in Western countries, it is important not to exclude the substantial societal load posed by the existence of angle closure glaucoma. This is clearly an age-related disease, and tends to affect Asian populations to a greater extent than Western populations. The most important cause for primary angle closure glaucoma is related to anterior chamber narrowing and closure of the anterior chamber angle and to the aging increase in size of the crystalline lens. 26

**Rate of Disease Versus Longevity**

Figure 1 represents a conceptual schematic of the relationship between visual function and longevity in various scenarios of chronic glaucoma. It is apparent that a faster rate of disease will cross a threshold to a level of visual disability earlier in one’s lifetime. A corollary of this would be that if the rate of disease is slow, some patients may do quite well without treatment, and will live their entire lives free from visual disability. There is a large body of clinical trial data demonstrating that early intervention is more effective at slowing the rate of progression than late intervention. 27, 28 When this is applied to the schematic with respect to “fast progressors,” one can see that early intervention has a chance of keeping patients with a fast-paced disease from becoming visually disabled, even with long longevity. This becomes an important concept given the aging population and the imminent explosion of the proportion of older individuals in our population. 29

Estimates of the rate at which individuals deteriorate help direct treatment to the right patients at the right time. This also allows us to avoid the artificial dichotomy of glaucoma patients being either “stable” or “worse”; in reality, all patients are getting worse, but at different rates. We should also accept that the functional and structural scales with which rates are measured are not synchronous, nor are they linear. A considerable body of clinical research has been devoted to the most appropriate way to measure the rates of visual field loss in glaucoma. These approaches are largely confounded by (1) the high level of intertest variability inherent in psychophysical measurements; (2) the limitations of the sensitivity and specificity of the technique; (3) a low signal-to-noise ratio; (4) the requirement to perform multiple tests to reduce the noise and make the signal detectable; (5) the requirement for confirmatory tests; (6) the lack of a “gold standard”; and (7) the slow course of the disease, which may progress over years or decades. 30

Regressions of visual field thresholds over time, in either a pointwise, cluster, or global fashion, have been used. The most frequently applied thus far, and the simplest, is a linear model. Evidence suggests, however, that a linear model may not be the best for all patients. 31 A recent approach uses a pointwise exponential regression and isolates fast and slow components of visual field decay in glaucoma. 32 Such an approach can be used to identify patients who are progressing very quickly, and can be used to predict patterns of future visual field loss within appropriate confidence intervals. This approach has been shown to be effective across a wide range of disease severity.
and can identify “rapid progressors” for appropriately aggressive treatment. Figure 2 shows an example of this approach applied to a patient having many visual fields over a period of nine years. While the superior paracentral area of the visual field is getting worse very quickly (at the rate of approximately 30% per year), the remainder of the field is quite stable and shows essentially no damage. This is a patient who should be classified as a fast progressor, given the dramatic loss in near-central vision with great impact on quality of life. Such focal but important worsening of visual function can be missed by inspection of global indices such as MD or VFI alone because of their inherent lack of sensitivity to localized defects. A search for baseline prognostic factors that can predict which patients are at highest risk for rapid visual deterioration is in progress. Preliminary results suggest that age, and measures of underlying damage such as the severity of visual field loss and the vertical cup-to-disc ratio, are significant and important prognostic factors (Lee J, Caprioli J, Coleman A, et al., unpublished data, 2008).

CELLULAR SENESCENCE CONTRIBUTES TO RETINAL GANGLION CELL DEATH

Figure 3 summarizes many of the genetic defects heretofore reported to be important in the pathogenesis of glaucoma. Most of these genetic defects are encountered in the congenital and developmental forms of glaucoma that are relatively rare. So far, no single gene or group of genes can be held responsible for a significant proportion of patients with the adult form of POAG. It is this author’s opinion that a host of genetic variants are involved in the pathogenesis of glaucoma, not to mention posttranscriptional alterations and environmental interactions. Glaucoma most likely represents a group of diseases with diverse molecular mechanisms of pathogenesis, which have in common a final common pathway of the typical optic nerve damage and consequent characteristic patterns of visual field loss that we call glaucoma, and which may progress to blindness in the most severe cases. Because of the diverse nature of the causes of glaucoma and the heterogeneity of the disease, it appears that both IOP-dependent and IOP-independent processes are at work. Different patients may have varying contributions from these two broad categories of insults, on a spectrum that may vary from completely IOP-dependent to completely IOP-independent disease.

Figure 4 is the conceptual organization of some of the leading theories of the pathogenesis of RGC damage in glaucoma. While a comprehensive review of these pathogenic theories is not possible within the scope of this review, I would like to focus on the ubiquitin-proteasome system (UPS) and chaperone system (CS) in aging. The UPS is the main intracellular pathway that regulates protein turnover and is...
essential for cellular homeostasis. This system allows the cell to regulate its protein expression and respond to changing physiologic conditions caused by disease. The major theory regarding the causes of cellular aging invokes the concept that the UPS becomes slowly and progressively dysfunctional with age. Cellular protein “junk” thereby accumulates in the cell, causing a protein constipation that can no longer be processed by the aging UPS, and ultimately leads to cellular dysfunction and death.34,35 Stress proteins, also known as protein chaperones or heat shock proteins, play a similar role in helping proteins fold into their appropriate, functional conformations, thereby also preventing the accumulation of dysfunctional proteins within the cell. Heat shock factors are known to stimulate the expression of these stress proteins in RGCs.36 Figure 5 shows an overexpression of heat shock factor 2 in aging rats compared to younger rats, likely a consequence of a decreased constitutive expression of heat shock proteins. Anti-heat shock protein antibodies have been described in the
sera of patients with POAG compared to controls. A dysfunctional CS associated with aging can lead to increased vulnerability of RGCs to a variety of insults, including those that lead to glaucoma.

The only known maneuver that extends life in animal models of longevity is calorie deprivation. This is a case in which a little starvation improves health and longevity. It has been shown in a rat model that calorie restriction, as mimicked by the administration of 2-deoxy-D glucose, protects RGCs against ischemia and excitotoxicity, two possible mechanisms for RGC death from glaucoma.

STEM CELLS PRESENT OPPORTUNITIES AND CHALLENGES TO PREVENT AND REPAIR OPTIC NERVE DAMAGE

Stem cells offer the advantages of having unlimited self-renewal and of being pluripotent; that is, they can form cells and tissues from any of the three embryonic germ cell layers. There are three types of stem cells: embryonic, induced pluripotent, and somatic (adult). Advances in stem cell technology have provided us with the means and opportunity to replace damaged or diseased cells with normal functioning cells. This approach could be used to replace abnormal, diseased, or missing cells in either the anterior or posterior segment of the eye. Aging changes in the TM lead to progressive dysfunction with age. Normal TM cells secrete matrix metalloproteinases, phagocytose debris, and provide fluid transport into Schlemm’s canal. Decreased TM cellularity is associated with decreased outflow facility and increased IOP. It has been observed that laser trabeculoplasty increases TM cell division, and that most cell division occurs in the anterior TM at the insertion zone near Schwalbe’s line. It has been suggested that this insertion zone may contain somatic stem cells. TM contains a cell population that exhibits markers of pluripotent stem cells. It has been shown that TGF-β2 induces premature senescence-associated TM changes and activates a senescence-related signal transduction pathway. Blocking or reducing TGF-β2 levels in TM could help prevent the aging process in the meshwork, and thereby aid in the treatment of open-angle glaucoma.

Another avenue for stem cell–related treatment of glaucoma is the delivery of neurotrophic factors to RGCs at risk. For instance, brain-derived neurotrophic factor (BDNF) is a 14-kDa protein that is essential for RGC development and survival. Retrograde transport of BDNF from the thalamus to RGCs is interrupted in animal models of increased IOP. Delivery of BDNF can prevent ganglion cell death under these circumstances. Stem cells injected into the vitreous and manipulated to secrete BDNF or other survival factors may be used to deliver these factors to the specific target tissue in therapeutic concentrations.

The final frontier of stem cell therapy resides in the theoretical ability for RGCs that are dysfunctional or lost to be replaced by new ones. Such an approach lags considerably behind similar approaches to replace photoreceptors by injecting stem cells under the retina. The challenges to stem cell RGC replacement include (1) cell integration into the ganglion cell layer; (2) the successful formation of local synapses within the retina; (3) the extension of axons through the lamina cribrosa to targets in the brain; and (4) the formation of correct, topographically oriented connections to the central nervous system (in humans, mostly in the lateral geniculate nucleus). Preliminary work has shown that human Müller cells can differentiate into RGCs with appropriate molecular manipulations, including notch inhibition and fibroblast growth factor supplementation. However, such
cells have thus far not been shown to make functional connections to their central targets.

The associated risks of stem cell therapy should be noted. These include teratoma formation, immune rejection, viral integration into the human genome, and ethical concerns.

**HOW TO SLOW OR REVERSE AGE-RELATED DAMAGE: APPROACHES TO SAVING SIGHT IN GLAUCOMA**

Treatments in three general arenas can be described as effective treatments for glaucoma: neuroprotection, neurorescue, and neuroregeneration. Neuroprotection, through IOP reduction or other treatments, is directed to prevent damage to RGCs. Neurorescue provides treatment to improve the function of dysfunctional RGCs, that is, those that are damaged but are still present and are recoverable. Neuroregeneration refers to the replacement of RGCs with functional neurons that make appropriate synapses to their correct central nervous system targets and can restore visual function to those who have already lost vision from glaucoma.

Animal models have been used to demonstrate a relationship between IOP and glaucomatous damage to RGCs. After several weeks of moderately elevated IOP in the rat, significant loss of RGCs can be demonstrated in a dose-dependent fashion (a product of time and IOP level). While the revelation of exact molecular mechanisms of damage remains elusive, presumably due to the complexity of the underlying cellular pathophysiology, models like this have been used to demonstrate new approaches to neuroprotection and neurorescue, and have begun to elucidate the complex challenges presented by neuroregeneration. Since information about exact molecular mechanisms of damage is lacking, and since glaucoma may represent a diverse group of diseases with different molecular mechanisms, one realistic approach would be to treat the disease on a regulatory (mechanism-nonspecific) basis. I have discussed the central role of the ubiquitin–proteasome and chaperone systems in aging. One appealing approach may be to improve the function of the increasingly dysfunctional protein regulatory systems (UPS and CS) in the aging organism. Heat shock protein induction with heat, zinc, and certain drugs is an effective approach toward reducing the vulnerability of RGCs to IOP-induced damage in the rat model. Drugs currently approved for other indications and nutraceuticals should be considered as possible effective means of treatment through endogenous neuroprotective regulatory pathways.

Our goals in the treatment of glaucoma are to slow, stop, or repair damage to the RGCs caused by the disease. Heretofore, it was a general clinical dictum that visual loss from glaucoma cannot be reversed. Recent work from the laboratory and the clinic suggests that this may not be so. The IOP and age dependence of RGC dysfunction has been studied in the DBA/2J mouse model of glaucoma. RGC susceptibility to IOP elevation increases with age, and RGC dysfunction in older mice can be improved with IOP reduction. Recent clinical evidence suggests that robust IOP reduction in humans with glaucoma can improve visual sensitivities in the portion of the visual field most affected by glaucoma. Figure 6 shows a summary of the behavior of the fast and slow components of visual field decay after glaucoma surgery and robust IOP reduction. While there is significant slowing of the fast component of VF decay after surgery, it is also apparent that there is a significant improvement of visual sensitivities at these locations after surgery. This improvement is typical, is not uncommon, and is significant in amplitude and appears to be sustained. Such observations from the laboratory and the clinic are consistent with the concept that a population of RGCs that has become dysfunctional from glaucoma, but is not yet dead, may respond to treatment and that its function can be restored. That is, there is a group of ganglion cells that may be sick but not dead, and can be revived. This repair may be considered neurorescue and may already be available in the form of treatment by robust IOP reduction.

The concept of neurorescue is relatively new as it pertains to glaucoma treatment. There are hints that robust IOP reduction through surgery, or perhaps through new drug delivery systems, may offer promise to rescue RGCs that may
be sick but not yet dead from glaucoma. The delivery of growth factors or survival factors, either through the injection of stem cells tuned to deliver these factors or through novel, long-term drug delivery systems, also offers hope for new effective treatments.

The reduction of IOP is the only proven treatment that provides neuroprotection against glaucoma. The evidence for this comes from numerous high-quality clinical trials and a large body of clinical evidence; it is strong and irrefutable. Recent evidence, both basic and clinical, suggests that alpha agonism may provide neuroprotection beyond that which can be attributed to its IOP-lowering properties.18,49 Confirmatory studies, however, are lacking, and alternative hypotheses can also explain the results.50 Future approaches would depend in part upon our ability to identify specific molecular mechanisms as triggers for RGC death. In the meantime, mechanism-nonspecific approaches through the manipulation of regulatory pathways offer promise. Examples may include the regulation of the UPS and CS related to their important roles in the age-related dysfunction of cells.

Neuroregeneration, the final potential treatment realm for glaucoma, has been an elusive goal. There is evidence that retinal ganglion cell bodies exist in the retina long after their axons, and therefore their function, have vanished from the optic nerve.51 Appropriate triggers for these cells to regrow their axons along existing tracts and make appropriate synaptic connections to their central nervous system targets should be identified. Pluripotent stem cells have the ability to replace RGCs in the retina. Preliminary work with Müller cell differentiation holds promise. Formidable challenges exist; these include cellular integration, formation of synapses in the retina, extension of axons through the lamina to the correct targets in the brain, and the formation of topographically oriented connections. An additional hurdle may also exist: Target cells may actually disappear in the brain after the cessation of signaling from peripheral neurons.52

SUMMARY OF KEY NEEDS AND OPPORTUNITIES

- Methods to safely provide robust decreases of IOP require further development. Such approaches may be achieved through new forms of surgery or through drug delivery by novel intraocular sustained-release devices.
- Delivery of growth factors through new drug delivery platforms or by injection of stem cells into the vitreous may provide neurorescue of RGCs. Development of the basic techniques followed by clinical trials is required to establish the efficacy of the approach.
- The search for neuroprotective drugs should continue. Until the exact mechanisms of molecular damage are known, the pursuit of mechanism-nonspecific pathways, through the manipulation of regulatory pathways, may be productive. The manipulation of the aging UPS and CP, which result in protein dysfunction, is a particularly attractive area of research. Drugs that are already available, approved for other indications, and nutraceuticals should be considered as immediate and readily available targets for drug development.
- The challenges of neuroregeneration seem formidable. Early work has shown that Müller cells can differentiate into functioning RGCs. Work should begin on finding solutions to the considerable problems related to recreating central neuronal connections. The impact of even limited success in this area would be great, and could be readily extended to other neurodegenerative diseases.
Glaucoma as Early Senescence


Dry Age-Related Macular Degeneration: Mechanisms, Therapeutic Targets, and Imaging

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Age-related macular degeneration is the leading cause of irreversible visual dysfunction in individuals over 65 in Western Society. Patients with AMD are classified as having early stage disease (early AMD), in which visual function is affected, or late AMD (generally characterized as either “wet” neovascular AMD, “dry” atrophic AMD or both), in which central vision is severely compromised or lost. Until recently, there have been no therapies available to treat the disorder(s). Now, the most common wet form of late-stage AMD, choroidal neovascularization, generally responds to treatment with anti–vascular endothelial growth factor therapies. Nevertheless, there are no current therapies to restore lost vision in eyes with advanced atrophic AMD. Oral supplementation with the Age-Related Eye Disease Study (AREDS) or AREDS2 formulation (antioxidant vitamins C and E, lutein, zeaxanthin, and zinc) has been shown to reduce the risk of progression to advanced AMD, although the impact was in neovascular rather than atrophic AMD. Recent findings, however, have demonstrated several features of early AMD that are likely to be druggable targets for treatment. Studies have established that much of the genetic risk for AMD is associated with complement genes. Consequently, several complement-based therapeutic treatment approaches are being pursued. Potential treatment strategies against AMD deposit formation and protein and/or lipid deposition will be discussed, including anti-amyloid therapies. In addition, the role of autophagy in AMD and prevention of oxidative stress through modulation of the antioxidant system will be explored. Finally, the success of these new therapies in clinical trials and beyond relies on early detection, disease typing, and predicting disease progression, areas that are currently being rapidly transformed by improving imaging modalities and functional assays.

Keywords: drusen, complement, autophagy, functional imaging, therapeutic targets

Dry AMD Deposits

The pathogenesis of early AMD is characterized by thickening of Bruch membrane (BrM) due to lipid and protein accumulation that lead to formation of sub-RPE deposits that occur as discrete accumulations, called drusen, which can be hard or soft, or as continuous accumulations. The lipid build up is thought to primarily interfere with the fluid efflux from the RPE across BrM, thereby inflicting stress on the RPE.11 These and other stressors (e.g., oxidative stress from smoking and aging)
result in an increased accumulation of lipofuscin in RPE cells, which in turn affect lysosome function and cholesterol metabolism.\textsuperscript{12} Cells under stress are known to increase the release of membranous vesicles such as exosomes and it is possible that this process is in part responsible for the deposits in the sub-RPE region.\textsuperscript{13–16} In addition, a number of proteins found in drusen are serum proteins, suggesting that impairments in fluid transport across BrM also might play a more direct role in drusen formation and deposition.\textsuperscript{17,18}

Sub-retinal pigment epithelial deposits are classified as basal laminar deposits (BlamD) or basal linear deposits (BlinD). Basal laminar deposits consist of membranous material and wide- or long-spaced collagen between the plasma membrane and basal lamina of the RPE.\textsuperscript{11} Basal linear deposits consist of vesicular material located in the inner collagenous layer of BrM. Basal linear deposits (0.4–2 μm) and soft drusen (30–300 μm) are considered differently sized assemblies (layer and protrusion) of the same aggregate.\textsuperscript{11} Hard drusen (<63 μm) have higher apolipoprotein content than soft drusen and are much less fragile upon dissection.\textsuperscript{11,19–21}

The composition of drusen has been investigated and described by a number of investigators,\textsuperscript{18,22–26} and are discussed in more detail below for their potential as targets for AMD therapies. The role of drusen in the pathogenesis of AMD has not been clarified, although it has long been known that they constitute hallmark lesions of AMD. Studies focused on delineating their components and origin have provided insights into pathways associated with early AMD,\textsuperscript{23} including the complement pathway and amyloid deposition discussed later.

As a result of the decreased flow of nutrients across BrM and the physical displacement caused by drusen, areas of hypopigmentation of the RPE monolayer on histologic tissue sections can be observed in the macula. Hyperpigmented areas are often located adjacent to hypopigmented regions, and have been proposed to be due to RPE cell proliferation as a response to RPE cell loss.\textsuperscript{27} On RPE flat mounts of AMD eyes the macular region contain many large and multinucleate cells (≥2 nuclei) as opposed to a healthy cell monolayer composed of mostly equally-sized mononucleate and a small proportion binucleate (∼3%) RPE cells.\textsuperscript{28–31} These areas of RPE cell heterogeneity may be due to RPE cell death and dropout. Ultimately, areas of confluent RPE cell loss can occur, which can be visualized by fundus autofluorescence (FAF) and SD-OCT, and are classified as GA (Fig. 2D, 2F).

Current Treatment Option

Age-Related Eye Disease Study Formulation

A number of studies in the 1980s and 1990s identified a link between antioxidant status, zinc levels, and risk of AMD.\textsuperscript{32–36} To further investigate these associations, the Age-Related Eye Disease Study (AREDS) was implemented. Results reported from the first AREDS (AREDS1) documented slowed progression to the late wet form of AMD when taking a formulation of beta-carotene, vitamin C, vitamin E, and zinc.\textsuperscript{37} However, the benefit of zinc in this formulation has been debated.\textsuperscript{38–41} A recent meta-analysis on the effect of zinc supplementation in prevention of AMD also concluded that available data are inconclusive.\textsuperscript{42} Recently, it has been shown that daily zinc supplements for 3 months in AMD patients lowered complement activation as measured by C3d/C3 ratio in serum, but this effect was only statistically significant in patients that already had high complement activation at the start of treatment.\textsuperscript{43} While intriguing, it is unknown whether this systemic zinc-mediated effect on complement activation also occurs in the eye and if so, how AMD progression is altered.

\textbf{FIGURE 1.} Ocular anatomy of a healthy eye relevant to AMD. (A) Cross-section schematic of a human eye showing major structures. (B) Color fundus photograph from an elderly patient covering the area indicated in (A) showing a healthy macula (dashed line, ø = ~6 mm), healthy fovea (solid line, ø = ~1.5–2 mm), and healthy optic nerve head (ø = ~1.5–2 mm), respectively (photograph courtesy of Eleonora Lad). (C) Immunohistochemical cross-section of the foveal region indicated in (B), foveola (ø = 0.2–0.3 mm, indicated by *), which contains only cone photoreceptors and no rods, is located at the center of the foveal pit. Photoreceptor layer (PR), RPE, BrM, and choroid, are indicated (fovea image courtesy of Christine Curcio).
Based on data from earlier studies suggesting protective effects of lutein plus zeaxanthin and omega-3 fatty acids in AMD, these ingredients were added to the AREDS formulation in AREDS2 and the results of AREDS2 supplementation are discussed in a companion chapter in this supplement by Emily Chew. To date, the only treatment for dry AMD consists of daily intake of an AREDS formulation.

Drusen-Associated Proteins

As discussed above, drusen, BlamD, and BlinD constitute some of the clinical hallmarks of AMD. These deposits consist of proteins and lipids that are also found in plaques and deposits in other age-related degenerative disorders such as atherosclerosis, Alzheimer’s disease, and a subset of Prion diseases among others. The deposited proteins include vitronectin, clusterin (ApoJ), apolipoprotein E (ApoE), (serum) amyloid P (SAP), complement components, and amyloid-β (Aβ). The appearance of a small number of hard drusen (< 63-μm diameter) is a normal age-related change in the eye. However, soft “diffuse” drusen correlate with progression of AMD. It is not known if drusen are the primary cause for the degeneration of RPE in AMD, but they do ultimately affect RPE health due to impaired transport across BrM. Thus, elimination of these soft drusen present as an obvious therapeutic target to slow or inhibit AMD progression. The direct approach to target individual components of drusen has demonstrated some promise. Recently, we demonstrated that systemic treatment with an antibody against Aβ protects against RPE damage and vision loss in an AMD mouse model. Clearance of Aβ from sub-RPE deposits coincided with protection of visual function and structural preservation of the RPE, identifying Aβ as a druggable target. Another approach to remove Aβ from these deposits could be to induce higher expression of ApoE. Apolipoprotein E promotes proteolytic degradation of Aβ, and this effect is thought to be the mechanism for the enhanced Aβ clearance in the brain of some models of Aβ deposition, although this study is being revisited due to recently published conflicting data.

Other constituents of drusen being targeted in preclinical and clinical trials include components of the complement system (e.g., C3 and C5). In addition, there are a number of drusen components that are potential drug targets that have not yet been pursued in treatment of AMD. Some obvious targets include vitronectin and clusterin, molecules involved in the acute-phase response to inflammation such as amyloid P component, and elements of lipid metabolism in addition to ApoE such as Apolipoprotein B, and peroxidized lipids.
Complement Pathway in AMD

The identification of polymorphisms in genes coding for complement factor H (CFH), factor B, and C3, which confer greater “risk” for developing AMD, supported earlier pathobiologic investigations that led to the identification of numerous complement proteins in drusen. These studies implicated the complement system as an important biological pathway in development of AMD. The complement system is a component of our antigen-nonspecific defense mechanism or innate immunity and it consists of three pathways, classical, lectin, and alternative that all converge on C3.77

It is now apparent that dysregulation of the complement cascade, and of the alternative pathway in particular, is a critical predisposing step in AMD development. Although the precise triggering event(s) that provokes RPE-choroidal pathology are unknown, it is clear that a major consequence is the deposition and sequestration of cellular and acellular debris in the sub-RPE space that leads to drusen formation. Complement activation products, produced as part of the inflammatory response, can have beneficial effects by facilitating phagocytosis and removal of cellular debris, or they can be detrimental by causing bystander damage to surrounding tissues. Currently, the bystander damage through complement dysregulation is suspected in AMD, where patients lacking sufficient alternative pathway-modulating activity have subsequently sustained complement attack, bystander injury to neighboring cells, continued formation of drusen and other sub-RPE deposits, and eventually vision loss.78-79 This is supported by the ocular phenotype in CFH knock-out mice, generated to model factor H deficiency in humans, which revealed that old CFH knock-out animals exhibit an age-related decrease in visual acuity (VA) with evidence of C3 deposition.

CFH, which is implicated as the strongest genetic risk factor for AMD, is an inhibitor of the alternative pathway of complement. Despite knowing for many years that CFH variants confer AMD risk, the underlying molecular mechanisms attributing to the risk factor activity of CFH remains unclear. CFH circulates at high concentrations in plasma but is also synthesized in the eye by the RPE, and the relative contribution of these sources of CFH to local complement regulation within sub-RPE deposits is not known. Recently, a study has shown that CFH may neutralize the pro-inflammatory effects of malondialdehyde (MDA)-induced inflammation in an AMD-risk associated manner. This study suggests that CFH also functions to attenuate oxidative stress insults leading to AMD, which may explain why clinical trials using complement inhibition-based treatment of AMD (targeting C3 or C5, e.g.) have produced disappointing outcome data that show minimal improvement in VA or reduction in disease progression.

Oxidative Stress

The retina is particularly susceptible to oxidative stress because of its high consumption of oxygen, large amounts of polyunsaturated fatty acids concentrated in the photoreceptors, and continual exposure to visible light. Oxidative stress has long been hypothesized to play a substantive role in the development of AMD due to the high oxidative stress environment of the fundus. Oxidative stress in the retina is aggravated by lipofuscin, which accumulates in the RPE with age, especially in AMD eyes. Cigarette smoking, considered a strong oxidative stressor, remains the most consistent preventable risk factor for AMD across all studies; considering these stressors, it is remarkable that most individuals maintain homeostasis throughout life. This is likely due to the presence of a range of efficient antioxidants and repair systems. For example, the macular pigment, formed by lutein and zeaxanthin, is a natural barrier protecting the central retina against oxidative damage believed to limit retinal oxidative damage by absorbing incoming blue light and/or quenching reactive oxygen species.

Antioxidants beyond vitamins and minerals (i.e., AREDS supplements, which have only been shown to be efficacious in the eye) are also being investigated as AMD therapies and may be effective by acting as neuroprotective agents, preventing toxicity in the retina as well as interfering with cell death pathways. Agents that augment the intrinsic antioxidant functions of the retina are promising candidates for the prevention and treatment of early AMD. These compounds exert their protective effects by modulating nuclear factor erythroid 2-related factor 2 (Nrf2), commonly involved in regulating the expression of genes encoding various antioxidants and antistress proteins.

Autophagy

Autophagy is an essential lysosomal pathway that degrades cytoplasmic proteins and damaged organelles. This is especially important in highly metabolically active and highly phagocytic nond不分iding cells such as the RPE, which phagocyte photoreceptor outer-segment discs daily. As discussed above, RPE cells run a high risk of oxidative damage due to their exposure to high levels of lipid peroxidation products from photoreceptors, constant exposure to light stimuli, and their high oxygen utilization. There are three autophagic pathways (chaperone-mediated, micro-, and macroautophagy), of which macroautophagy is the primary route for transport of organelles and protein aggregates to the lysosome. The focus, for this review, will be on the macroautophagy pathway, which will be referred to as autophagy. Autophagy is initiated by the formation of the autophagosome, a double-membrane vesicle containing lipids, damaged organelles and/or cytoplasmic proteins. After their formation, autophagosomes undergo a strictly controlled fusion process with lysosomes where their contents are degraded by lysosomal enzymes.

Autophagy pathways also have intracellular quality control functions, especially in the turnover of proteins that are prone to aggregation. It has been suggested that aggregate formation is prevented by autophagic degradation into oligomers and monomers. Thus, disturbances in autophagy in RPE cells may be a contributing factor in generation of protein aggregates seen in sub-RPE deposits and drusen in AMD. During RPE cell aging, autophagic, and lysosomal degradation pathways lead to the accumulation of lysosomal lipofuscin, which is considered to contribute toward the pathogenesis of AMD. There is considerable evidence that lipofuscin and one of its major fluorophores, A2E, can increase lysosomal pH and reduce lysosomal degradation which, in turn, further reduce the functional capacity of the RPE and increase cellular stress; thus, lipofuscin accumulation is a hallmark of RPE cell aging, which adversely affects the lysosomes’ capacity to degrade proteins. Numerous studies have shown a strong association between lipofuscin accumulation and retinal degenerations such as AMD. Furthermore, as a form of protein quality control, protein aggregates are delivered to the lysosome by autophagy pathways. This might be one of the few ways to remove large, preformed aggregates from the cell. Thus, disturbances in lysosomal function by accumulated lipofuscin may increase the misfolding of intracellular proteins by reducing the efficiency of this clearance mechanism. Though the precise mechanisms by which the RPE becomes compromised by aging and in AMD has not been
elucidated, a decrease in the removal and replacement of aggregated proteins and damaged intracellular organelles is likely to play a significant role.

It has recently been demonstrated that lysosomal activity decreases, and markers of autophagy accumulate in human AMD donor samples. In addition, as discussed in an earlier section, it is known that stressed RPE releases exosomes that are coated with complement and can bind CFH, suggesting that this may be a mechanism for sub-RPE deposit formation. Preservation of autophagic activity might be associated with a decrease of intracellular accumulation of damaged proteins, which may delay the RPE aging process. Conversely, autophagy may trigger cell death by excessive self-digestion. Thus, dysregulation of autophagy can result in cellular dysfunction. AMD has degenerative characteristics including protein deposits, and in certain cases, proliferative characteristics as occurs in wet AMD; thus, there is no consensus as to whether autophagy inhibitors or activators would be beneficial in AMD therapy, and how they should be used for different phenotypes of AMD.

A recently identified target for modulation of autophagy in RPE cells is the serine/threonine kinase mammalian target of rapamycin (mTOR) that regulates the damaging hypertrophy and dedifferentiation of RPE cells exposed to oxidative stress. Rapamycin-induced inhibition of mTOR can prevent these effects and preserve photoreceptor functions. However, rapamycin has a number of off-target effects, which have limited its practicality in age-related neurological disorders. Intraocular delivery of drugs could potentially circumvent a number of systemic side effects that would otherwise be an issue with many autophagy-modulating therapies. Gene therapy for treatment of AMD targeting autophagic pathways is also an interesting future option.

Several environmental and genetic risk factors for AMD progression may be associated with lysosomal dysfunction, including buildup of sub-RPE deposits, drusen, lipofuscin, and chronic inflammation and likely lead to decreased autophagy flux in RPE cells. Thus, autophagy may represent an important therapeutic target in AMD.

**Immune Cells in AMD Microglia**

Microglia are resident immune cells in the central nervous system (CNS) and retina and constitute the main immune defense in CNS. They enter the retina during development and are activated by retinal injury and degeneration, transforming from quiescent stellate-shaped cells into large amoeboid-shaped cells. Activated microglia proliferate, migrate to areas of damage, degrade and clear debris, and secrete pro-inflammatory cytokines and chemokines. Long-term activation of microglia results in chronic neuroinflammation. Studies of AMD retinas suggest that widespread activation and migration of microglia does not occur during early stages of AMD. However, at intermediate to late stage dry AMD and GA, RPE and photoreceptor damage leads to accumulation of activated microglia at the site of macular injury suggesting that these may be relevant targets in late disease.

**Macrophages**

Though AMD is not a classical inflammatory disease, increased numbers of macrophages have been detected in areas of BrM damage and RPE atrophy. Importantly, macrophages are also found in the choroid of healthy human eyes, but do not express the activation marker inducible nitric oxide synthase (iNOS). However, choroidal macrophages (as well as endothelial cells and pericytes) do express iNOS when they have been recruited to BrM in early AMD eyes with soft drusen or thick continuous BlAmD. Macrophages recruited to active disciform scars also express iNOS.

There are two subtypes of macrophages: the pro-inflammatory M1 macrophages, and the mostly anti-inflammatory M2 macrophages, whose main function is scavenging and tissue remodeling. M2 macrophages are thought to perform the beneficial, long-term housekeeping role of scavenging deposits such as degrading and removing drusen in early stages of the disease. M1 macrophages on the other hand, might incite and exacerbate the inflammatory responses to retinal injury. Interestingly, a recent study by Sene et al. found that altered cholesterol homeostasis due to decreased ABCA1 expression in aging macrophages promoted a switch from the M1 to the M2 phenotype. In the paradigm of CNV, the pro-angiogenic properties of M2 macrophages have been shown to promote progression of wet AMD. However, in the case of dry AMD, it is entirely unknown which of the two macrophage subtypes would be the most beneficial for degradation of drusen and prevention of RPE cell loss. Thus, the mechanisms of polarization of macrophages into M1 or M2 subtypes represent an interesting target for cellular intervention in different stages (early versus late) of dry AMD pathogenesis and warrants further investigation.

Modulation of the recruitment of microglia and macrophages to the site of injury is also a potential target for AMD treatment. Polymorphisms in the CX3CR1 chemokine receptor found on microglia and macrophages have been associated with increased risk of AMD. The CX3CR1 polymorphisms result in decreased affinity for its ligand (CX3CL1), which in turn negatively affects microglial and macrophage migration. In vitro studies suggest that accumulation of microglia due to impaired migration may cause direct damage to the photoreceptors. In the case of macrophages, impairments in migration may interfere with recruitment from the circulation into the choroid and BrM in order to clear deposits at the site of injury. Previous reports on mice lacking expression of both the chemokine, CCL2, and the receptor, CX3CR1, described a phenotype similar to that seen in human AMD. However, the intraretinal rather than subretinal lesions seen in this mouse model suggest that the phenotype is due to the rd8 mutation, which is now known to be present in the background mouse strain used in these studies. The rd8 mutation is a single nucleotide deletion in the Crb1 gene that can cause a distinct clinical ocular phenotype due to formation of retinal folds, pseudorosettes, as well as focal retinal dysplasia and degeneration.

There are still many details about the roles of microglia and macrophages in the pathophysiology of dry AMD that are unknown. Consequently, further studies will be needed to clarify whether microglia and macrophages do indeed represent feasible druggable targets in AMD. Mast cells have also emerged as immune cells of the choroid that may play a role in AMD. Lutty and colleagues recently described an accumulation of degranulated mast cells around GA lesions in the choroid of human donor eyes, suggesting that mast cell degranulation may contribute to the damage of this tissue in GA (Lutty GA, et al. IOVS 2013;54:ARVO E-Abstract 3051). This is particularly intriguing since activated complement stimulates degranulation of mast cells. Other immune cells and targets, including the inflamasome, will not be discussed in this review as they were addressed at length in a recent review by Ambati et al.

**Cell-Based Therapies**

A large body of evidence supports the concept that RPE cell loss precedes photoreceptor loss in AMD. Thus, it follows that if the RPE loss can be mitigated, visual function can most likely be maintained. A number of fetal and stem cell-based...
approaches to replenish the RPE in vivo have been attempted in the last 20 years, resulting in varying levels of reconstitution and/or visual function rescue in animal models. RPE cells are a highly polarized cell type and some studies suggest that for transplanted RPE cells to survive, they need to be polarized prior to transplantation. Therefore, subretinal implantation of polarized RPE cells on biocompatible supports was pursued, with some success. However, the major drawbacks using this approach are the traumatic implantation procedures and the possibility of rejection of the support/scaffold if it is not sufficiently immunologically inert.

Recently, studies using an approach based on adult hematopoietic stem cells (HSC) showed promising results in restoring damaged RPE layers in vivo. The authors reprogrammed adult HSCs by lentiviral expression of RPE65, which drove these cells to develop into RPE-like cells. Furthermore, systemic delivery via intravenous injection resulted in homing of these cells to the subretinal space in a mouse model of sodium iodate-induced RPE damage. This is significant since, in a human clinical setting, intravenous injection provides higher safety and ease of use than subretinal delivery. In addition, the prospect that the patient’s own HSCs could be used is particularly appealing as it avoids any issues related to transplant rejection. A logical next step will be to determine whether use of systemically delivered RPE-like cells will also home to the retina in a mouse model of early AMD in which there is more subtle RPE damage, and, hence, are likely to release less chemokines. Such a mouse model mimics the human disease more closely and a successful outcome may be a more relevant proof of concept for human trials in AMD. Unfortunately, there are no good animal models of GA but the current advances in RPE cell-based therapies suggest these cells could be ideal for saving, and potentially restoring vision in patients with GA.

The challenge of replacing lost photoreceptors is more daunting than replacing RPE as the transplanted cells not only have to develop normally, but they must also integrate into the damaged retina and, potentially most difficult, establish the nerve connections required to transmit the visual information to the brain. Recently, successful photoreceptor transplantation has been achieved in mice by harvesting rod precursor cells from healthy mouse retina to restore functional vision in a mouse model of stationary night blindness (alpha-transducin knock-out, Gnat1/−/−). The authors showed, for the first time, that the transplanted rods acquired the proper morphology including a classical triad synapse, had properly integrated into retinal circuits, and that signals from these cells were transmitted to the visual cortex. In order for photoreceptor cell transplantation to be a viable therapy in humans, a source of cells other than photoreceptor precursors will be required. Progress to this end was made by a team led by Robin Ali that established that embryonic stem cells can provide a source of photoreceptors for retinal cell transplantation. Although the percentage of integrated rod photoreceptors was low this is an important milestone toward developing cell therapy for regenerating lost photoreceptors.

Techniques for Diagnosis and Prediction of Dry AMD Progression

Currently, clinicians monitor morphological changes in the retina/RPE/choroid by fundus exam, color fundus photography, FAF, OCT, and infrared (IR) reflectance. In the past two decades, OCT imaging technologies have had a profound impact on early detection, monitoring of progression, and treatment-efficacy evaluation of dry AMD. The current generation of commercialized OCT systems, SD-OCT, provides volumetric and cross-sectional views of the retina facilitating the visualization, measurement, monitoring, and phenotyping of the retinal layers and RPE, hyperreflective foci, GA, and drusen in eyes with dry AMD (Figs. 2E, 2F). While SD-OCT imaging is currently widely used in clinics as the standard of care for dry AMD diagnosis and prognosis, some ophthalmologists and OCT technology vendors to paradigm shifts in the way that dry AMD imaging is performed for research and clinical applications. One such technology is the polarization-sensitive OCT (PS-OCT) with tissue-selective imaging capabilities. In PS-OCT imaging, the RPE layer appears distinct from other tissue layers and thus PS-OCT may provide complimentary information about RPE health, drusen subtyping, and GA progression. In the next decade, advances in OCT technology are expected to continue to impact our understanding of dry AMD pathologies. Development of swept-source OCT (SS-OCT) systems with speeds exceeding 1,000,000 A-scans/s (as compared with the current generation of ~30,000 A-scans/s commercial SD-OCT systems) will facilitate imaging and image analysis by reducing image acquisition time, noise, and motion artifacts. Moreover, SS-OCT systems are well suited to operate at approximately 1060 nm wavelength, which allows for enhanced visualization and monitoring of the choroidal structure, thickness, and vasculature pattern, as well as the inner retina’s distinct retinal capillary beds.

Indeed, other modern and classic, noninvasive, imaging systems such as en face fundus photography and FAF, which may predict the rate of GA progression, provide important and complementary information to OCT about dry AMD. It has been proposed that the in vivo hyperfluorescence detected by FAF around GA lesions (Fig. 2D), represents dying RPE cells full of lipofuscin, which is the main source of FAF in these cells. Recently, however, Rudolf et al. published evidence against this hypothesis by measuring the histologic autofluorescence in human donor eyes with GA as a means to establish the cellular basis of the hyperfluorescence in these GA border zones. They found that the areas with highest histologic autofluorescence at GA borders were often associated with vertically superimposed RPE cells and, therefore, that the increased FAF was not necessarily a harbinger of cell death. Their data also suggests that lipofuscin itself may not be a relevant target for AMD treatment.

Integration of adaptive optics (AO) into modern scanning laser ophthalmoscope (SLO) systems has made the in vivo visualization of individual photoreceptors (initially cones and very recently rods) and RPE cells in dry AMD eyes possible (Fig. 3). On another front, while SS- and SD-OCT create images based mainly on the scattering properties of the tissue, a novel three dimensional (3-D) imaging technology called photoacoustic ophthalmoscopy (PAOM) provides complementary information by creating images based on the absorption properties of the tissue. Photoacoustic ophthalmoscopy, which may operate in multiple wavelengths (e.g., 532 nm and 1064 nm), is especially suitable for melanin-related imaging (e.g., RPE), choroid capillary network imaging, and for measuring oxygen saturation in retinal microvasculature.

The large quantity of data created by these novel imaging technologies are often too large to be fully analyzed and interpreted manually. Thus, considerable work has been done in recent years to automate the segmentation of the imaging biomarkers of dry AMD. Due to the wide clinical applications of SD-OCT, most recent efforts have been focused on development of automatic segmentation algorithms to quantify individual retinal layer thicknesses, drusen, and GA in presence of dry AMD pathology (Fig. 4A). We have identified efficient quantitative imaging biomarkers to automatically...
Despite recent advances in automated segmentation of RPE cells in confocal microscopy images of flat-mounted AMD mouse models yielding cell count and mean cell area measurements has drastically sped up the experiment and analysis time (Fig. 4D).172 Despite recent advances in automated segmentation of cones173–176 and rods173 in healthy eyes (Fig. 4E), lack of automated software is still one of the main obstacles in large-scale clinical utilization of adaptive optics scanning ophthalmoscope (AO-SLO) systems for diagnosis and prognosis of dry AMD. Moreover, regardless of the imaging modality or segmentation algorithm used, for many dry AMD patients with severe pathology (e.g., patients with cataracts which reduces the quality of captured images), automated image analysis methods fail to provide reliable measurements. Novel image enhancement methods have been demonstrated to significantly improve the quality of SD-OCT images of dry AMD patients.177,178 and may improve the performance of automated segmentation methods.

**Functional Assessments of Vision in AMD**

Functional changes in vision of AMD patients reflect early dysfunction of the neurosensory retina and the supporting RPE. These changes are assessed by a variety of methods including measuring VA at normal and low luminance and/or reading speed, and by using microperimetry, assaying dark adaptation and contrast sensitivity. As with fundus imaging, these tests of retinal function may also be confounded by media opacity such as progressive cataract.

One of the earliest complaints of patients with AMD is difficulty with vision under dark-adapted conditions and is in most cases due to a decrease of rod photoreceptor function.179,180 Thus, methods that could precisely distinguish the early changes in function are an obvious outcome measure for testing the efficacy of therapies targeting early AMD. To date, widespread use of a single method for functional testing has been hampered by the time to test a patient, the reproducibility of the test between instruments, testing methods, and patient visits. Measurements of dark adaptometry are underway in a longitudinal clinical trial of early and intermediate AMD (National Eye Institute, NCT013552975).181–184 Low luminance VA deficit, poorer foveal dark-adapted sensitivity, and reduced reading rate have all been shown to predict subsequent VA loss in eyes with atrophic AMD that started with good acuity.185 Contrast sensitivity changes in standard photopic lighting have been used for many years in assessment of AMD progression, especially to neovascularization; more recently mesopic testing has been explored.180 Recently, advances in microperimetry suggest greater utility in early AMD when nonphotopic testing is performed. Several methods to obtain non-photopic microperimetry have been proposed and larger scale studies are needed to evaluate these methods. To support future therapeutic studies, simplified tests that are reproducible and can be commonly used across centers for functional assessment will be important. Equally important will be assessing the relationship of these tests to the other systemic and ocular measures of disease.

**Conclusions**

In general terms, therapeutic approaches to GA should be aimed at (1) reducing or stopping the stimuli of continuing damage, which depends on continued progress in identifying and characterizing relevant targets; (2) protecting remaining cells from further damage; and (3) repairing, replacing, or regenerating damaged cells. Currently, the third approach is gaining traction with the advances in RPE and photoreceptor cell-based therapies described earlier. That being said, the first two areas are experiencing steady progress. Together, the current and continued advances in understanding the molecular pathogenesis of early AMD and GA, which are identifying relevant therapeutic targets, coupled with the advances in detecting and measuring disease progression, should expedite breakthroughs in developing therapies that block and/or
Dry AMD Mechanisms, Targets, and Imaging

Figure 4. Application of novel automated segmentation algorithms for analysis of the anatomical and pathologic biomarkers of dry AMD. (A) Automated segmentation of the eight retinal boundaries on an SD-OCT image of a dry AMD patient with drusen using DOCTRAP software delineating the vitreous (at the top of the image) from the nerve fiber layer (NFL, blue line), NFL from ganglion cell layer and inner plexiform layer (GCL-IPL, pink line), GCL-IPL from inner nuclear layer (INL, aqua line), INL from outer plexiform layer (OPL, yellow line), OPL from outer nuclear layer and inner segment (ONL+IS) of the photoreceptor layer (green line), ONL+IS from outer segments (OS) of the photoreceptor layer (blue line), OS from the RPE and drusen complex (RPE DC, pink line), and the RPE DC from the choroid (aquag line). The top and bottom boundaries correspond to the inner limiting membrane (ILM) and the Bruch membrane, respectively. (B) Example of a 5 mm in diameter RPE DC thickness map centered at the fovea from a dry AMD patient. Thickening around the fovea (red and yellow regions) is indicative of drusen, while thinning (blue regions) is representative of GA. (C) DOCTRAP software automatically extracts areas of abnormally thin (cyan region) and thick (red region) RPE DC from the thickness map in (B), which we use to automatically distinguish AMD from healthy eyes. (D) Automatically segmented confocal fluorescence image of the RPE cells in a flat-mounted APOE4 mouse retina. (E) Automatically segmented AO-SLO image of the cone photoreceptors in a healthy human subject.

reverse early AMD and GA. The new imaging, automated segmentation, and advances in visual function testing are directly impacting the great unmet need for devising therapeutic strategies for early AMD, which has been plagued by a lack of understanding of how to sub-classify types of early stage disease based on initial presentation and subtle changes over time. These new and evolving technologies are, for example, simplifying imaging and quantifying drusen (Figs. 4C, 4D) and should allow us to test whether changes in appearance of drusen (e.g., appearance and disappearance) can be correlated with vision effects and whether these are predictors of rates of progression. These advances will also have a large impact on the success of clinical trials as they will facilitate sub-stratification of early, intermediate and late AMD patients, by prediction of progression rates and appearance as well as refine quantifiable outcome measures of visual function changes and recovery. While there are many challenges and unmet needs in understanding and treating early and atrophic AMD this is an exciting time to be working in this area due to the convergence of advances in understanding retinal physiology, genetics, and technology.

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Effects of Diabetes on the Eye

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Hyperglycemia has toxic effects on almost all cells in the body. Ophthalmic complications of hyperglycemia are most profound in cornea and retina. Seventy percent of diabetics suffer from corneal complications, collectively called diabetic keratopathy, which includes recurrent erosions, delayed wound healing, ulcers, and edema. Confocal microscopy has permitted in vivo imaging of corneal nerves, which are also affected in diabetic subjects. Gene therapies upregulating MNNG HOS transforming gene (cMet) and/or downregulating MMP10 and cathepsin S are potential future therapies for diabetic keratopathy.

Diabetic retinopathy (DR) is the most common cause of blindness in people over the age of 50. There is accumulating evidence that DR is an inflammatory disease. The initial events in animal models of DR are increased vascular permeability and leukostasis. This binding of leukocytes to the endothelium results from an increase in intracellular adhesion molecule-1 (ICAM-1) on the retinal capillary endothelium (EC) and expression of CD11/CD18 on the surface of the activated leukocyte. We have observed polymorphonuclear leukocytes (PMNs) at sites of EC vascular dysfunction in diabetic retinas as well as choroid. Anti-inflammatory drugs like etanercept, aspirin, or meloxicam reduce leukostasis and EC death. Future therapies may include repopulation of the acellular capillaries after EC and pericyte death with vascular progenitors made from the patient’s own blood cells.

Keywords: diabetes, retinopathy, choroidopathy, cornea, inflammation
same gene therapy at the limbus only normalizes wound healing at the limbus.

**EARLY CHANGES IN DIABETIC RETINA**

Diabetic retinopathy (DR) is a microvasculopathy in that the microvasculature leaks serum, increased vascular permeability, and capillaries are lost early in the disease. Hyperglycemia and mitochondrial and extracellular reactive oxygen species (ROS) are toxic to endothelial cells (ECs), pericytes, and neurons, resulting in their death early in DR. There is accumulating evidence that low-grade inflammation underlies the vascular complications of DR. Inflammation is a nonspecific response of the body to tissue injury in which leukocytes are recruited to the inflamed tissue. Diabetic retinopathy is categorized best as a chronic low-level inflammation in which there are elevated systemic cytokines like TNF-α and IL-1β and elevated numbers of circulating activated leukocytes.

Nishiwaki and associates observed “leukostasis,” sticking and retention of leukocytes labeled with acridine orange, in real time within the microvasculature of diabetic rats. Leukostasis was observed as early as 2 weeks after induction of diabetes by STZ. This is approximately the same time frame as for leakage of the inner blood-retinal barrier (BRB) in rats, which has been observed as early as 1 week after induction of diabetes. These two events appear to be the earliest changes that occur in the STZ diabetic rodent retina. The extent of leukostasis was the same at 1 month as it was at 11 months in diabetic mice, suggesting that leukostasis is chronic, like other diabetic pathologic processes.

There are three possible mechanisms for leukostasis. One mechanism could be decreased retinal blood flow and perfusion pressure. There is little agreement on blood flow or perfusion pressure in diabetic retina, perhaps because different instruments were used and patients of different cohorts were at different stages of DR. The number of static leukocytes increases in STZ-induced diabetic rats compared to...
nondiabetics, whereas the leukocyte velocity is not different from that in controls, so blood flow does not seem to contribute to leukostasis.

A second mechanism could be the narrowing of capillary lumens during diabetes. There is an increase in the potent vasoconstrictor endothelin in diabetic retina, and increased expression of endothelin receptors (ET-R) has been reported on diabetic retinal pericytes. ET-1 (endothelin-1) is also elevated in the plasma of diabetic patients. Furthermore, ET-R agonists reduced leukostasis in diabetic rat retina. The degree of constriction in the human diabetic (nonspecific esterase) retina and its role in leukostasis are still undetermined.

The final mechanism is increased leukocyte-endothelial adhesion in retinal blood vessels. Leukocytes from diabetic patients have increased levels of CD11a, CD11b, and CD18. Increased numbers of activated polymorphonuclear leukocytes (PMNs), which express CD11b and CD18 on their surface, circulate in diabetics compared to controls. Diabetic PMNs are larger and more rigid than normal PMNs and must be compressed to fit through normal retinal capillaries. We have observed PMNs at sites of endothelial cell dysfunction (loss of adenosine diphosphatase [ADPase] activity) in human diabetic retina (Fukushima I and Lutty G, unpublished data, 1997) and in the retinas of spontaneously diabetic monkeys. In diabetic monkeys, increased number of PMNs was related to dyslipidemia and hypertension. Increased leukostasis also occurs in the Tokushima Fatty rats (OLTEF), which also has dyslipidemia as well. The oxidative burst of a PMN can injure or kill ECs.

In addition to increased activated leukocytes circulating in diabetics, the levels of leukocyte adhesion molecules are elevated in diabetics. We observed elevated ICAM-1, which is associated with firm adherence of activated leukocytes, in human diabetic retina compared to controls. A similar elevation in ICAM-1 was observed in ECs of the diabetic rat retina. Leukostasis in diabetic rats was inhibited by intravenous administration of an antibody against ICAM-1. Leukostasis can also be inhibited by blocking the counterreceptor for ICAM-1 on the leukocytes, CD18. Increased leukostasis does not occur in retina when diabetes is induced in ICAM-1- or CD18-deficient mice.

**DIABETIC RETINOPATHY**

Endothelial cell death from hyperglycemia or leukocyte oxidative burst and subsequent increased vascular permeability appear to occur before pericyte dropout occurs. Once pericyte death occurs, all that remains are acellular capillaries that are basically collagenous tubes. There is no blood flow in the collagenous tubes, so the sensory retina adjacent becomes hypoxic. This hypoxic environment upregulates VEGF, which stimulates further elevated vascular permeability, increased expression of ICAM-1, and EC proliferation. Increased permeability of fluid and protein can result in diabetic macular edema (DME). Diabetic macular edema is the common cause of visual function loss in both nonproliferative and proliferative DR. Increased proliferation of ECs initially causes intraretinal microvascular abnormalities (IRMA), small abnormal vascular formations in areas lacking viable capillaries. Increased EC proliferation is probably also responsible for formation of microaneurysms in which ECs proliferate in the absence of pericytes, the cell type that normally keeps ECs quiescent. Finally, EC proliferation and migration from veins and venules can result in the formation of preretal neovascularization, the hallmark of proliferative retinopathy.

**DIABETIC CHOROIDOPATHY**

We have reported changes similar to DR in diabetic choroid. We observed dropout of choriocapillaris in diabetic choroid (Fig. 2), and there was a direct correlation between PMN number and area of choriocapillaris (CC) dropout (Fig. 1).
There was a 4-fold greater area of acellular capillaries in diabetic choroid compared with aged control subjects. Although the CC constitutively expresses ICAM-1, the relative level was increased in CC and was present in all choroidal blood vessels of diabetics. We also observed upregulation of P-selectin in diabetic choroidal blood vessels. The severity of CC dropout was related to the thickness of Bruch’s membrane deposits in diabetic choroid; the thickest deposits were present over areas of complete CC loss (Fig. 2D), suggesting that the deposits were related to loss of CC transport. Other features of diabetic choroidopathy were intrachoroidal and extrachoroidal neovascularization. The intrachoroidal neovascularization consisted of capillary networks deep in choroid near the lamina fusca, the border of choroid and sclera. Extrachoroidal neovascularization was observed within Bruch’s membrane and between Bruch’s membrane and RPE. Both forms of neovascularization were mostly at the equator or more peripheral in choroid. The extrachoroidal neovascularization was often autoinfarcted; that is, only collagenous tubes remained.

**Future Therapies for Diabetic Retinopathy and Choroidopathy**

Experimental work by Antonia Joussen and Anthony Adamis demonstrated that death of ECs related to leukostasis can be prevented by blocking or genetically eliminating either ICAM-1...
Effects of Diabetes on the Eye

CONCLUSIONS

In conclusion, hyperglycemia has far-reaching effects on the eye. In cornea, it causes diabetic keratopathy, and in retina and choroid, directly or indirectly, it kills vascular and neuronal cells. The obvious therapy is maintenance of normoglycemia or compliance by the patient. Once the eye has been exposed to hyperglycemia long-term, basement membranes have accumulated toxic advanced glycosylation end products and cell death has occurred. Future therapies for diabetic keratopathy could involve gene therapy to upregulate c-Met and/or downregulate cathepsin S and MMP10. The cornea is a desirable site for gene therapy because it could be given topically and remain local in its effects.

The retinal and choroidal damage from hyperglycemia appears related to local inflammation. VEGF, IL-1β, and TNF-α are elevated in serum and in the local milieu (Fig. 4). TNF-α can activate nuclear factor-κB (NF-κB) light-chain-enhancer of activated B cells), which upregulates genes involved in inflammation and ROS production. This causes upregulation of ICAM-1, which binds activated leukocytes in diabetes (Fig. 4). Leukocyte oxidative burst injures ECs so that vascular leakage occurs at these sites. The sites may be repaired by adjacent cells but may also be the site of repeated occlusive events. Since a PMN is so large and rigid in diabetics, it fills the lumen when firmly adherent. A PMN’s life is short, so repeated occlusion and then PMN death mean a local ischemia/reperfusion (I/R) event each time a PMN binds to the site, creating a continuum of small I/R events in the capillary segment. If extracellular matrix is exposed, platelet fibrin thrombi will form, which can signal the end of flow in that vascular segment (Fig. 4). This also occurs in diabetic choriocapillaris. The acellular capillaries are sites where autologous vascular progenitors could be used to repopulate the ECs as well as pericyte niches.

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Age-Related Psychophysical Changes and Low Vision

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Aging has a profound impact on human visual function. Not only does it affect the structures and function of the eye itself, as shown in articles throughout this special issue, but it also changes the functionality of many structures in the central nervous system that support visual perception and performance, visually-guided activities of daily living, and vision-related cognitive abilities. Thus, in aging individuals, the effects of pathologic changes in the eye and along the visual pathway are exacerbated by these “normal” age-related systemic and sensory changes, and by other comorbidities. Conversely, the self-care required to manage those changes and comorbidities may become too burdensome for an elderly person whose vision is affected by age or age-related disease. Here, we summarized the normal and pathologic changes in vision among the elderly population, and examined to what extent the impact of such changes can be mitigated at present, and what future improvements could be effected in this area.

Vision in aging populations has been reported in the context of major population-based longitudinal studies, some now spanning several decades of follow-up. The Beaver Dam, Blue Mountains, and Rotterdam eye studies sought to improve the knowledge of eye disease and visual impairment (VI) in a representative sample of the local population, as part of a broader epidemiologic inventory, while the Salisbury Eye Evaluation (SEE) and Smith Kettlewell Institute (SKI) studies sought to enroll the entire qualifying local population, and specifically targeted eye diseases. In the SKI study, with participants aged 58 to 102 at initial presentation, all available individuals in the oldest age cohorts, were enrolled and younger cohorts sampled proportionally to obtain a roughly flat distribution across ages. In the SEE study, all available individuals of African-American descent over age 65 (18% of this population segment) were recruited, with 61% and 56% random samples from the white population aged 75 and older, and 65 to 74, respectively. Both strategies resulted in maximizing statistical power by increased recruitment from otherwise underrepresented population segments.

While these population-based studies all collected information on important vision measures, such as refraction, cataract status, visual acuity (VA), and screening visual fields, the SKI and SEE studies made an effort to collect a broad range of additional measures related to vision, albeit with somewhat different emphases. The SKI study collected additional measures of contrast sensitivity, glare sensitivity, low contrast VA, stereopsis, color vision, and dark adaptation, all of which can be classified as visual function measures, whereas the SEE study concentrated on measured and self-reported performance in activities of daily living and, more recently, complex visually guided activities, such as driving.

In the following sections we summarized the findings regarding vision changes in normal aging, followed by those due to prevalent eye disease, and their impact on quality of life and functional independence. We concluded this overview with potential improvements in intervention and care to maximize the use of patients’ remaining vision.

VISION CHANGES IN NORMAL AGING

Vision changes in normal aging have been studied by a number of research groups; an excellent summary can be found in the 2011 review in Vision Research by Owsley. Normal aging brings about changes in the intraocular transmission and scatter of light, density of photoreceptors, efficacy of phototransduction and photopigment regeneration, and quality of synaptic transmission and signal processing in the retina and beyond. Most studies of vision and aging have examined a limited set of vision measures in small groups of older individuals, and compared these to normal adult values. The largest sample of very old individuals followed longitudinally can be found in the SKI study, and one of its most important findings is summarized in Figure 1, drafted using SKI study data kindly provided by G. Haeagerstrom-Portnoy for this paper; VA and contrast sensitivity data from that study have been published previously. Figure 1 shows, on a logarithmic scale, how the thresholds for a variety of vision measures change with age, compared to the normal adult value. As indicated by these regression lines, thresholds increase proportionally from year to year, starting at the age...
where the line intersects the horizontal axis. The age of onset and the annual rate of change appear to vary markedly, depending on the measure of interest. The review by Owsley\textsuperscript{7} cites several studies that have hypothesized that the detection of second order visual stimuli (those thought to require the involvement of multiple detection mechanisms in visual cortex) are more severely affected by aging than simple stimuli, such as flicker detection (temporal contrast sensitivity \[TCS\] in Fig. 1), and this certainly could explain why TCS has the shallowest increase with age. Other measures in Figure 1, such as color vision and stereoacuity, may have artificially steep regression lines due to the poor discrimination abilities of the stereo cards and D-15 test used to measure them. What seems clear from this Figure is that the rise of high contrast VA starts close to a decade later than other measures, possibly because it is less affected by optical factors, such as yellowing of the lens and scatter in the intraocular media.

A secondary effect of aging, not visible in Figure 1, but widely reported in studies of visual function in the elderly, is the increased range of values. While some elderly individuals appear to have the vision of a 30-year-old, others have markedly increased thresholds, even in the absence of overt pathology. In an analysis of psychophysical and electrophysiologic measures taken from a range of peer-reviewed papers, Johnson and Choy\textsuperscript{8} concluded that increasing variability with age may account for an important fraction of the overall average threshold increase seen in the population. They speculated that this may be due to latent pathology in many elderly individuals or to natural variability of the aging process.

One might expect a high degree of correlation between changes in different visual function measures within a single person, and, thus, hypothesize that elderly patients with good visual acuities would not show large changes in other measures. To test this hypothesis, Haegerstrom-Portnoy et al.\textsuperscript{5} performed a separate analysis limited to participants with best-corrected VA better than 20/40, that is, near normal, and determined the number of these near-normally sighted individuals showing a 10-fold worsening in other visual function measures increased rapidly with age, for almost every measure tested. This finding supports the notion that large changes in most of the vision measures shown in Figure 1 are part of normal aging rather than caused by undiagnosed eye pathology.

While the measures in Figure 1 all refer to basic psychophysical visual functions, changes with age in the performance of activities of daily living (ADL) have been studied in the SKI and SEE studies as well, in addition to smaller studies by other groups. As part of the SKI study, Lott et al.\textsuperscript{9} measured the distance, as a function of age, at which participants could recognize faces and/or facial expressions, and also asked the participants how often in daily life they had difficulty recognizing familiar faces from across a room or in dim light. They found a high correlation between the self reports and test data, and a steady decline of these abilities after age 65, with more pronounced losses after age 80.

Driving is another visual ADL that has been studied extensively in the last decade, both in simulators and on the open road, in the latter case with either a driving instructor in the vehicle, or with multiple camcorders set up to record the drivers actions, and the relation of the vehicle to other traffic, and to road markers and signals. Most vision studies find correlations between driving performance and driver age, but the role of vision is uncertain. In the Salisbury Eye Evaluation Driving Study (SEEDS), an increase in visual field defects was associated with increased wait times at stop signs in urban drivers\textsuperscript{10} and with self-restrictions in night driving,\textsuperscript{11} which also correlated with reduced contrast sensitivity; running red lights correlated with a reduction in attentional visual field.\textsuperscript{12} These and other aberrant driving behaviors, such as running stop signs or making unsafe lane changes, were correlated primarily with cognitive factors, suggesting that vision changes have a relatively minor role in accounting for age-related
worsening in the performance of complex tasks, such as driving.

Considering these findings in normally sighted elderly populations, it becomes clear that the effects of vision loss due to eye disease in the elderly can be understood and addressed only in the context of the many changes associated with aging, including nonvisual disabilities and comorbidities that affect many elderly individuals.

VISION CHANGES IN LOW VISION

The condition of VI, defined as best-corrected VA 20/40 or worse in the better-seeing eye, affects millions of Americans. The actual prevalence of VI is unknown, but numbers ranging from 3 to 6 million are cited commonly. Based on the 1999 to 2002 National Health and Nutrition Examination Survey (NHANES) data, Vitale et al. estimated that, of the approximately 11 million Americans over age 12 with uncorrected VA worse than 20/40, fewer than 3 million could not be corrected to better than 20/40 in the better eye, and only these should be considered to be visually impaired. That still is a respectable number, and it is bound to increase as the population ages. The reason for this is seen easily in Figure 2, in which data from the report of Goldstein et al., showing the age distribution of 764 participants in the Low Vision Rehabilitation Network (LOVRNet) study, are plotted along with the age distribution of the patients enrolled for low vision rehabilitation at 28 centers participating in the Low LoVRNet study. Symbols: age distribution of the US population over age 20, in the years 2000 (Census data) and 2030 (projected), illustrating the expected doubling of demand for low vision services by 2030, compared to the beginning of the century.

The condition of VI is strongly age-dependent, with 7.3% of the patients enrolled in the LoVRNet study over age 65. In that study, female sex also was overrepresented (66%), which may in part be due to greater willingness among women than men to seek care. Age and sex are not the only factors affecting VI prevalence in population-based studies. Entering VAs of participants in the SEE study showed the prevalence of VI among blacks being almost twice that among whites (10.4% vs. 5.6%). This matched previous reports in the Baltimore Eye Survey, where it was attributed to differences in racial prevalence of diabetic retinopathy and glaucoma, which are found predominantly in blacks, and of age-related macular degeneration (AMD), predominantly found in whites. A substantial percentage of VI in the Baltimore Eye Survey was found to be correctible through surgery (e.g., 36% was due to cataract) and other treatments. Similar percentages have been found in other population-based studies, an indication that lack of access to eye care may be an important cause of VI, even in the developed world.

Data regarding cause-specific VI based on VA alone have been published for most of the population-based studies, but such data are harder to find for other types of VI, such as loss of contrast sensitivity, peripheral visual field, or patches of vision close to fixation (paracentral scotomas), dark adaptation, and glare recovery. Studies of low vision populations have been more diligent collecting such information, but even for those studies the information is incomplete. In the LoVRNet study, over half of the individuals seeking care suffered from conditions affecting the macula, and another 20% had other retinal conditions limiting their vision, as shown in Figure 3. As would be expected with this high prevalence of macular pathology, reduced VA was the primary cause of VI among these patients: using their habitual correction, 25% had VA < 20/200, and another 38% had VA of 20/70. Of the remaining 37%, just over one fifth (22%) had moderate or severe contrast sensitivity loss.

The effects of different types of VI on daily life can vary widely, and low vision rehabilitation programs will need to address the specific type of impairment, tailoring the intervention to each patient’s unique situation. Loss of VA may cause...
difficulties with many activities of daily living that require seeing fine detail, including reading, completing a form, setting the dial of a thermostat, or using small tools. Loss of contrast sensitivity is more likely to affect activities that require the distinction of hue or gray scale, such as face recognition, seeing curbs and other drop-offs, and matching clothes and accessories. Loss of peripheral field leads to difficulties detecting obstacles, avoiding collisions while walking or driving, and orienting oneself relative to others, while paracentral scotomas in macular disease lead to distortions, metamorphopsias, and objects or text simply “disappearing.” Dark adaptation problems not only affect the ability to see at night, but also the ability to find a seat when entering a dimly lit restaurant or a dark movie theater, and the temporary vision loss one experiences on a bright day when driving into or out of a tunnel. Glare disability is the loss of vision one experiences when a bright light source illuminates the eye while viewing a much dimmer target, such as a traffic light with the sun low in the sky, or road signs and pavement markings against oncoming headlights at night.

**ROLE OF LOW VISION REHABILITATION**

In the medical model of low vision care, patients with an indication of low vision are evaluated for possible deficits in their use of vision during the performance of daily activities. If confirmed, a treatment plan is formulated that then is implemented by one or more rehabilitation specialists. The goal of low vision rehabilitation is to reduce the impact of VI and minimize disability, through one or more concurrent approaches: prescription of assistive devices and training in their use, adaptations to the environment to reduce visual demand, and instruction as needed, and referral for the management of comorbidities that interact with VI.

Assistive devices have been revolutionized by improved optics, development and miniaturization of optoelectronics, the advent of digital technology, and the development of bioengineering applications. As recently as a generation ago, magnifying glasses and optical telescopes were the only assistive tools available to patients with vision loss. In the 1980s and 1990s, closed circuit television (CCTV) readers and a few head-mounted video magnifiers offered the potential of variable magnification and contrast enhancement/inversion, at substantial cost. Besides these devices, which were limited to making visual information more visible, nonoptical aids, such as signature guides, tactile markings on stove dials, and telephone news reading services, were developed to allow access for those whose visual deficit could not be remedied by optical means. The advent of text-to-speech conversion, mobile technology from small electronic magnifiers to cell phone cameras, and, most recently, a wide variety of mobile applications (apps) have greatly magnified the power and versatility, and reduced the cost of assistive technology. Most recently, an implantable telescope, electronic retinal implants, and advanced sensory substitution devices, such as the Brainport, have added new technologies to the field of low vision rehabilitation. The addition of such technological innovations has moved, and in a sense almost removed, the boundary between low vision rehab and blind rehab, since several of these technologies now are shared by the partially sighted and the functionally blind.

Adaptation of the environment has traditionally been limited to improving lighting, adding tactile bumps and audible signals at crosswalks, increasing visibility of obstacles and drop-offs, and substituting high- for low-contrast items. In recent years, this field also has been enhanced by testing the use of radio frequency identification (RFID) tags and other “smart elements” in the environment. These developments are likely to become more prominent as new and more affordable tools are being developed, especially if such technology is “dual use,” that is, can be grafted upon platforms that are used widely by consumers and, therefore, is affordable, such as the smartphone, and has utility to able-bodied users, such as speech output from a GPS route planner.

As these assistive devices and environmental adaptations become more sophisticated, the role of low vision rehabilitation experts, that is, teachers of the visually impaired, occupational therapists with training in low vision rehab, and orientation and mobility (O&M) trainers, will become increasingly important and demanding. This is true particularly if most of their clients will be in their 70s and beyond. Even the most ergonomic and user-friendly hi-tech device will require a carefully tailored instruction and practice program if it is to be accepted by this population. For the rehab experts themselves, the availability of continuing education courses covering the newly developed devices and their optimal use already has become crucial, and this trend is only expected to accelerate.

**FIGURE 3.** Causes of VI among 675 participants in the LoVRNet study (based on Table 1 in the study of Vitale et al.14), ordered according to the affected stage along the visual pathway.
ROLE OF COMORBIDITIES

The presence of other disorders and health limitations among low vision patients is an important factor in planning their rehabilitation process, and the prevalence of such conditions should not be underestimated. Among 764 participants entering the LoVRNet study, only one-third qualified their general health as fair or poor, yet on closer questioning many of the remaining individuals considering themselves in good or even excellent health reported pain, high blood pressure, and falls in the last 2 years. When asked about their emotional state, 88% of respondents classified themselves as well-adjusted, yet with 42% reporting being frustrated, 23% anxious, and 22% depressed, among others, it appears that the qualification “well adjusted” does not tell the complete story. On detailed questioning, a wide range of physical and mental health problems was found in this study population. Successful low vision rehabilitation can happen only if the presence of these comorbid conditions is taken into account. One of the most important tasks of the low vision rehab specialist is to understand how to optimize the client’s self care of these conditions.

Having low vision has an immediate impact on the ability to manage medication use, avoid falls, and maintain independence. For this reason, it is clear that a low vision rehabilitation plan will have to take into account the presence of comorbidities, and the tools required to allow the individuals to maintain or even improve their health status. Conversely, comorbid conditions, such as limited grip strength, movement limitations, memory problems, and emotional distress, inevitably will have a negative impact on the progress and success of a low vision rehabilitation plan. Here again, the low vision rehab specialist must understand how the rehab plan can be adjusted to minimize this impact and maximize progress toward functional independence.

GAPS IN LOW VISION CARE DELIVERY

The appreciation of the need for low vision rehabilitation, and its availability and quality in the United States have made important progress over the last quarter century, especially since the acceptance of low vision care as a reimbursable form of assessment and rehabilitation under Medicare in the late 1990s. That’s the good news. The not-so-good news is that there still are large areas of the country where eye care providers do not have a sufficient appreciation of the complexities associated with chronic VI, where thorough low vision evaluations are not performed, and where no qualified low vision rehabilitation therapist or O&M specialist is available. Moreover, most third party payers limit the amount of therapy by imposing an annual cap on the number of physical and/or occupational therapy units a beneficiary can receive, and this cap encompasses low vision rehabilitation; for patients with physical comorbidities, this can form an important barrier to obtaining adequate care in a timely fashion.

In addition to the availability of accessible high-quality care, patient motivation and support are important conditions for successful initiation and completion of the low vision rehab process. Two groups can have a critical role in creating the conditions that will foster success: caregivers (including relatives and friends) and the community at large. Awareness of VI has greatly improved over the last decades, through broadcast public service announcements, public education websites, and community-based initiatives for improved accessibility. Yet, although awareness of the condition may have improved, the public at large is not well informed about the possibilities of rehabilitation. Public service organizations, such as the Lions Clubs, are playing an important role, both in bringing the availability of low vision rehabilitation to the attention of members of their communities, and by providing transportation and other support to visually impaired community members.

The single most important gap in low vision care delivery in the United States is the lack of insurance coverage for assistive devices. Low vision patients who are employed or participate in vocational training, and who depend on certain devices for gainful employment are entitled to coverage of assistive devices through the mandates of the Americans with Disabilities Act and, state services for the blind and visually impaired, respectively. Similarly, the cost of assistive devices is covered for individuals with vision disabilities who qualify for Veterans Administration benefits. Unfortunately, these conditions do not apply to the great majority of visually impaired elderly individuals. The only cases in which Medicare or other third party payers have been compelled to cover assistive devices, such as a CCTV reader, through court action were those where the plaintiff successfully made the case that the assistive device functions as a prosthesis rather than the equivalent of a pair of glasses (which would exclude it from coverage under the Medicare statute). Ironically, the tendency for consumer products, such as smart phones, to be adapted as tools for the visually impaired has made it harder to claim reimbursement for them as prosthetic devices.

In a compelling study of the likely impact of a change in Medicare policy toward allowing coverage for assistive devices in cases of significant VI with good rehabilitation potential, Morse et al. estimated that the utilization cost of such a benefit would be on the order of $800 per person for approximately 40,000 Medicare beneficiaries per year, if a consistent set of qualification criteria was drafted. In other words, the cost to the Medicare program would be approximately 1% of the $5.4 billion it spends annually on cataract-related expenses.

TOWARD A REDUCTION OF THE LOW VISION BURDEN

As is clear from the population distributions in Figure 2, a significant increase in the prevalence of low vision is expected, unless its incidence can be reduced along with that of the underlying disorders, through a combination of research and public health education as advocated by other investigators in this special issue. Even if the increase can be mitigated, it is likely that a substantial burden of low vision will persist well into the future, and, therefore, we need to look at the three ways we can address this burden.

Improving the Quality of Low Vision Care

There are many excellent low vision care providers, and a substantial effort is under way to collect additional evidence and further improve the standards of successful low vision rehabilitation. Further support from the National Eye Institute, and other sponsoring agencies and foundations will be required to obtain more detailed outcomes data and develop better care delivery models. This research effort will have to be translated into training programs, fellowships, and certification standards for low vision physicians and therapists to become experts in a wide range of rehabilitative options, and to maintain their expertise as these options increase. An important part of this training will have to address the understanding of comorbidities that are prevalent among older low vision patients, and the need for comanagement of these conditions with geriatricians and other care providers.
Increasing the Availability of Low Vision Care

It is unrealistic to expect that every low vision care provider will be trained in handling the most complex cases, and that every eye care provider seeing elderly patients will need this level of expertise. Low level certification standards should be established for most eye care providers, so that they are competent to handle patients with mild VI and to recognize which patients should be referred to specialized secondary or tertiary centers, due either to their degree of impairment or to the complexity of their comorbidities. Such a tiered system also allows secondary centers to provide consultation services and initial rehabilitation, but then refer patients back to their community health centers for follow-up care. This system has been in use for many years in Sweden, where it has led to greatly improved access to low vision care. While such strictly organized multiterrific care is unlikely to become the norm in the United States, it certainly can be promoted through a system of continuing education courses and certificates for primary level low vision care providers.

Increasing the Awareness of Low Vision Care

Even with the many options for low vision rehabilitation available today, too many patients with vision loss do not visit eye care providers, or are if they do, are not referred to a low vision care provider. Improving this situation will require education of eye care professionals as well as the public at large. It is encouraging that the National Eye Institute, Lions Clubs, and many patient advocacy organizations are fully behind these education efforts, and there is reason for optimism that the awareness of low vision care will not be the rate-limiting step in reducing the burden of low vision.

Reducing the Economic Burden of VI

Finally, there needs to be a wider recognition of the economic impact of low vision loss, and of the cost effectiveness of low vision care. This not only could help make funds available for training and certification programs for low vision care providers, it also may be the best hope for low vision patients that Medicare and other third party payers will consider coverage for low vision assistive devices. It is unlikely that such a change will be adopted any time soon, but a few carefully chosen demonstration projects could address the question whether coverage of devices would lead to better outcomes and a lower overall financial burden, through greater independence of the patient and reduced cost due to medical complications.

In summary, addressing the consequences of vision loss in the aging population should be an important aspect of the research agenda for visual health in the coming years.

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