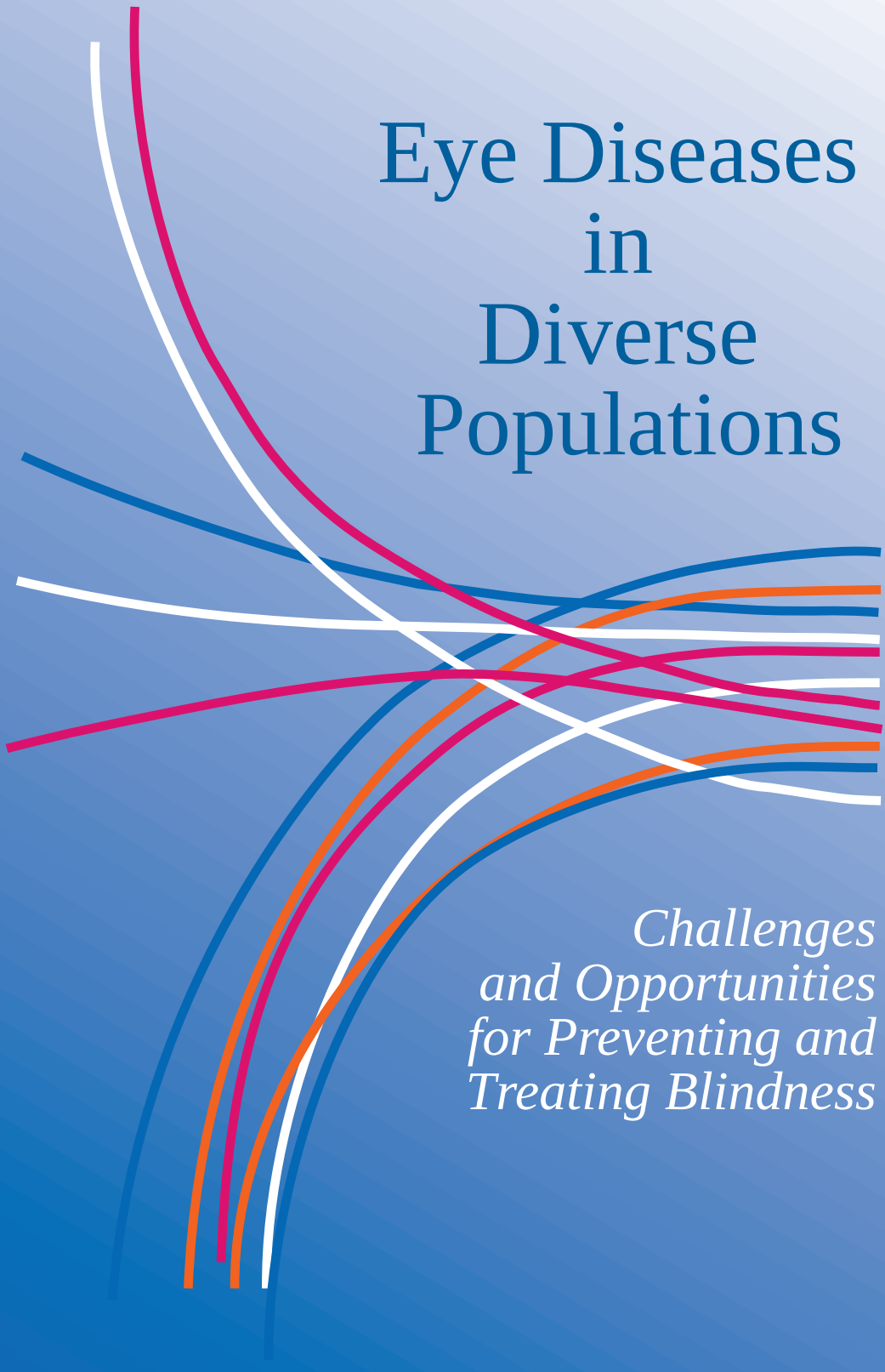
Eye Diseases in Diverse Populations

Challenges and Opportunities for Preventing and Treating Blindness



Eye Diseases in Diverse Populations

Challenges and Opportunities for Preventing and Treating Blindness

June 12–14, 2005
Rancho Valencia, California

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Contents

Tables

Figures

Preface

The fourth in a series of symposia on accelerating the implementation of research results on eye disease was held on June 11–14, 2005, at Rancho Valencia, California. The theme of this Fourth Drabkin Eye Disease Symposium was an exploration of the special challenges and treatment prospects for dealing with the ways in which chronic blinding eye diseases present in subgroups of a heterogeneous population. The diversity of the American population with respect to ethnic and cultural ancestry provided a starting point for considering implications of a heterogeneous population for understanding and treating potentially blinding eye diseases. Many of the symposium recommendations address issues of public health and the burden of visual impairment in the United States. However, in matters of health and illness, as in so many other areas of modern life, we reside in a global village. The diversity within the U.S. population reflects our increasingly important role as one crossroads, one multicultural neighborhood, within that larger village, with its global array of peoples and cultures.

A guiding theme emerged early in the context-setting presentations that opened the symposium and resonated through to its closing discussions. For complex diseases of the eye, the diversity of the American people presents clinical medicine with challenges for which evidence-based practice will need the research opportunities available in the worldwide diversity of genetic, environmental, cultural, and personal lifestyle factors. In this context, progress in American public health depends on the efficacy of partnering across national borders.

The 19 symposium participants (listed in appendix A) were selected to provide crosscutting expertise on four complex ocular diseases for

which population diversity presents acknowledged challenges: glaucoma, diabetic retinopathy, degenerative diseases of the macula, and myopia. Within each of the four subsequent sessions devoted to a specific ocular disease, the presenters focused on disease epidemiology, pathophysiology, or current practice and future trends in clinical management of the disease. In addition, three participants provided context-setting presentations on the broad topic of ethnic differences in eye diseases worldwide and within the United States. (The symposium agenda is in appendix B.) Each session included ample time for discussion of the presentations in these three areas.

On the final morning of the symposium, each session group proposed conclusions and recommendations for consideration by the participants. The results of that discussion provided the basis for the 24 conclusions listed in table 1 (pp. 5–8); supporting discussion and detailed suggestions for each of these principal conclusions follow the table.

Like the prior symposia on glaucoma, age-related macular degeneration, and emerging therapies for diseases of the retina and optic nerve **[1, 2, 3]**, this symposium was made possible by the endeavors of Mr. Robert Drabkin of Los Angeles, California, and supported by the University of California, Los Angeles, Support Group of the Jules Stein Eye Institute. It was organized and conducted by the Washington Advisory Group. This report was prepared with the guidance and supervision of the symposium co-chairs, who are responsible for its technical content.

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Acronyms

ACG	angle closure glaucoma
AGE	advanced glycation endproducts
AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
BDNF	brain-derived neurotrophic factor
CDC	Centers for Disease Control and Prevention
CNV	choroidal neovascularization
DCCT	Diabetes Control and Complications Trial
DRCR.net	Diabetic Retinopathy Clinical Research Network
ETDRS	Early Treatment Diabetic Retinopathy Study
FDM	form deprivation myopia
ICG	indocyanine green [a fluorescent dye used for angiography]
IOP	intraocular pressure
NEHEP	National Eye Health Education Program
NHANES	National Health and Nutrition Examination Survey
NIH	National Institutes of Health
NPDR	nonproliferative diabetic retinopathy
OCT	optical coherence tomography
PCV	polypoidal choroidal vasculopathy
PDR	proliferative diabetic retinopathy
PEDF	pigment epithelium-derived factor
POAG	primary open angle glaucoma
RESC	Refractive Error Study in Children
RPE	retinal pigment epithelium
TIMP	tissue inhibitor of metalloproteinases
UKPDS	United Kingdom Prospective Diabetes Study
VEGF	vascular endothelial growth factor
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO	World Health Organization

Executive Summary

Many serious and relatively common diseases for which straightforward cures are lacking are *multifactorial*, meaning that a number of genetic and environmental factors affect their onset and progression. Both anecdotal reports and bone fide epidemiologic studies indicate that these diseases vary in at least some characteristics within diverse populations. For multifactorial diseases of the eye, the evidence, although incomplete, indicates some substantial differences exist in how these potentially blinding diseases present in groups that differ in ethnic, socioeconomic, or other measurable parameters. These differences hold important general lessons for American health care, as well as engendering both challenges and opportunities for translating new research more quickly into effective treatments for potentially blinding diseases.

The first 10 conclusions in table 1 convey general lessons drawn by the 19 participants in the Fourth Drabkin Eye Disease Symposium. Table 1 also lists 14 conclusions the participants reached on major vision-threatening diseases: glaucoma, diabetic retinopathy, retinal neovascularization and macular diseases, myopia, and cataract.

Glaucoma

Worldwide, glaucoma is a common cause of irreversible vision loss. It is the second most common cause of irreversible vision loss in the United States and the most common cause among African Americans. The most common form of glaucoma in the United States is primary open angle glaucoma. Glaucoma prevalence in Americans of predominantly European ancestry (European Americans) is about 2 percent for adults over 40 years of age. By comparison, Americans of African ancestry

may have as much as five times that risk. The risk for Hispanic populations is also greater than that observed in populations of predominantly European ancestry. The data are inadequate to estimate risk in Asian Americans. No basis has yet been identified for the observed differences among African, Hispanic, and European Americans. Prevalence increases with age; for those 75 years of age or older, prevalence increases to 5 percent in people of European ancestry, to 10–12 percent in African Americans, and to 20–25 percent in those of Caribbean and African ancestry. Angle closure glaucoma is more common in many Asian populations than in populations of predominantly European or African ancestry. If, as current data suggest, specific groups have far higher susceptibility to glaucoma (or to different forms of glaucoma) than does the American population in general, then different emphases in diagnosis, prevention, and treatment may be necessary for effective management of this public health menace.

Diabetic Retinopathy

Diabetic retinopathy is the leading cause of poor vision in young adults. The causes are complex, but the risk is directly proportional to control of blood sugar and, to a lesser extent, blood pressure (established only for type 2 diabetes). As with glaucoma, persons with diabetes who are of African or Hispanic ancestry are at increased risk for severe vision loss and blindness compared with Americans of predominantly European ancestry. At least part of this elevated risk can be attributed to differences in health care among the groups with respect to risk factors such as glycemia and blood pressure. However, genetic factors and environmental/lifestyle factors such as diet (particularly in type 2 diabetes) require further detailed evaluation of factor interactions. Comparative studies are needed to ensure that high-quality care can be focused and tailored to decrease risk in specific population groups.

Degenerative Diseases of the Macula

Age-related macular degeneration (AMD) is the leading cause of severe loss of vision in Americans 65 years of age or older, particularly those

of European ancestry. It appears that African Americans and Hispanic Americans may be at lower risk for the more severe forms of this disease. However, the data for these groups are sparse, and even less is known about the risk for Asian Americans. Given the social, financial, and quality-of-life ramifications of this trend, comparative data for the major subgroups within the U.S. population will be essential to a cost-effective public health strategy.

Another disease of the macula characterized by neovascularization, leakage, and scarring is polypoidal choroidal vasculopathy (PCV). This disease has been studied primarily in Asian populations, but its prevalence among Asian Americans and other U.S. population subgroups is unknown.

Myopia

The prevalence of myopia is high and increasing in parts of East Asia. Still unknown is whether this high prevalence reflects primarily genetic factors or a more complex response to intense environmental stimulation (such as extended periods of visual concentration on details within an arm's distance, called *near work*) occurring on a susceptible genetic/ethnic background. This East Asian experience has potentially serious implications for lifetime visual impairment in the more diverse population of American youth and also for adults of all ethnic backgrounds. To assess these implications, a concerted effort is needed to determine whether the same causal factors related to the high-prevalence East Asian groups are present in groups within the U.S. population.

Summary

In any disease, each patient must be evaluated as an individual. However, useful clues for this evaluation can be found in the ethnic and cultural heritage of the patient because of the agglomeration of genetic, cultural, and environmental conditions that underlie shared heritages. Ultimately, it is these still unknown (or just emerging) factors that affect the outcome of multifactorial diseases. There are ethnic and cultural dif-

ferences in the frequencies of several vision-threatening conditions that affect millions of Americans and millions more in other countries around the world. Studies can now be designed to yield definitive data to help health care planners provide accessible and affordable diagnostic and treatment modalities for these vision-impaired patients.

Table 1. Principal Conclusions of the Fourth Drabkin Symposium

Overarching Conclusions
1. Epidemiological research into the prevalence, incidence, risk factors and determinants, treatment, and outcomes of eye disease in diverse populations continues to be a valuable and necessary endeavor. There is now an urgent need to identify and document the differences in how ophthalmic disorders present in the diverse American population and to understand which potentially relevant factors (genetic, cultural, environmental) influence these differences. Worldwide, the major causes of blindness in many countries vary by degree of socioeconomic factors, as well as by customary ethnic designations. Understanding the causal factors underlying these observable markers of population diversity can improve effective delivery of preventive and therapeutic health care to high-risk groups within the diverse U.S. population.
2. To guide intervention strategies, further research into these underlying factors can make use of evidence on disease disparities among population groups.
3. The eye diseases on which this symposium focused have genetic components. In studying population differences to identify and understand these genetic factors, one cannot assume that the standard demographic categories for ethnicity define populations with relevantly similar genetic characteristics. In short, the common ethnic categories should not be assumed to be adequate markers for disease phenotypes and their underlying disease genotypes.
4. Studies that target populations both inside and outside the United States may cost-effectively increase the value of results directly applicable to specific American groups. Inclusion of study populations from outside the United States can be a feasible way to collect the data needed to answer both basic scientific and clinical research questions about the contributions of and interactions among environmental and genetic factors.
General Implementation Actions for Ocular Disease
5. Standard definitions and terminologies for the major blinding eye diseases should be agreed on and used by major ophthalmology centers. These standards should include clinical signs for diagnosis, disease stages, and measurement techniques.

6. An economic plan for progress in cost-effective treatment (a "roadmap to a cure") should be constructed for each of the major eye diseases considered in this report.
7. For all the diseases considered in this symposium, prevention or delay of disease progression should be a priority for research and clinical management. An emphasis for future treatments, once a disease condition is present, should be on delivering the active agent to the target site.
Public Education and Outreach
8. Increased support is warranted for research into public outreach on eye health that is tailored for diverse populations. Support for public health education on eye care has a high ratio of societal benefit to cost. Improving the effective delivery of known prevention and treatment strategies, particularly to underserved populations at increased risk, is likely to increase the returns for society, measured in the economic value of health benefits to both individuals and the public good.
9. A coordinated approach is essential to public education about disease prevention strategies. Public health education should be coordinated for all diseases, not just those of the eye. This coordinated approach should include messages and outreach activities specifically tailored for population groups that are not yet being effectively treated.
10. Training for eye care professionals should reflect the growing diversity of the U.S. population. A cost-effective way to combine this training with the need for research on diverse populations is to foster the international exchange of U.S.-based and foreign-based eye care professionals.
Glaucoma
11. Research is needed into effective methods for identification of glaucoma in high-risk populations. As the U.S. population ages, early diagnosis of all forms of glaucoma will help to preserve vision. Treatments such as medical and surgical options to lower intraocular pressure are available for most forms of glaucoma, if the disease process is identified and treated early enough.
12. A better understanding is needed of the differences in glaucoma pathophysiology within and between population groups. Mechanisms may differ within and between population groups defined by customary demographic or cultural criteria.
13. Opportunities exist for improved glaucoma treatments in the future, but stronger support is needed to bridge the gaps in research necessary to develop and test them.

Diabetic Retinopathy
14. Prevention is the most important strategy for dealing with diabetic retinopathy. The principal prevention goal is to maintain normal, or at least near-normal, glycemic levels. Other prevention goals include maintaining normal blood pressure and serum lipid levels.
15. Population studies for diabetic retinopathy should be designed to: (1) ensure that results can be generalized to populations at elevated risk; (2) allow meaningful comparisons across studies; and (3) make use of results from current population studies, particularly those in which DNA sampling allows for analyses that support genotype characterization.
16. Innovative approaches are needed for improving compliance—and patients' understanding of their disease, on which compliance depends—across ethnocultural boundaries. Patient compliance is the single biggest driver in determining the outcome of known prevention strategies.
Degenerative Diseases of the Macula
17. Future epidemiological studies of macular disease—including polypoidal choroidal vascularization (PCV) as well as the wet and dry forms of age-related macular degeneration (AMD) and precursor conditions—need a common basis for interstudy comparisons based on uniform definition and classification. This standardization should reflect the need to match phenotypes with genotypes of macular disease.
18. More population-based studies are needed that are carefully designed to test specific hypotheses regarding the roles of genetic and environmental factors in AMD and PCV initiation and progression.
19. Better treatments and therapeutic agents for neovascularization affecting the macula are needed. Treatments are also needed for dry AMD. A better understanding of AMD progression is needed, on which to base decisions and techniques for treating early precursor stages of AMD.
20. Population-based studies, such as the Beaver Dam Study and the Rotterdam Eye Study, have found that smoking is a risk factor for AMD. Two major studies have reported association of dietary supplements, including antioxidant vitamins and zinc, with reduced incidence of AMD in the elderly and reduced rate of progression to advanced AMD. Further study is needed on these factors (e.g., mechanisms of action), as well as on additional risk factors and protective factors for degenerative diseases of the macula.

Myopia
21. Epidemiologic data from different countries with diverse populations indicate that both environmental and genetic risk factors influence the development of myopia and of ocular morbidity associated with childhood myopia. Understanding the respective roles and interactions among these factors is essential to cost-effective intervention strategies. Thus, population-based studies are needed to identify these risk factors and their interactions.
22. A better understanding of the pathophysiology of myopia as a disease of eye growth and refractive development will complement the effort to resolve the genetic and environmental factors through population-based studies.
23. Prospective population-based studies are needed to determine the predictors for progression of juvenile myopia and to identify future treatment opportunities.
Cataract
24. A high priority for further research on cataract should be to understand the disparities among populations worldwide in patient access to and outcomes of cataract surgery. Although surgery is a cost-effective intervention worldwide for visual loss due to cataract, research to understand population disparities in cataract onset may aid in preventing or delaying this disease, which blinds more than a million people each year.

Conclusions and Recommendations

The June 2005 Drabkin Eye Disease Symposium began with two days of presentations from the participating medical research scientists and clinical physicians. (The meeting agenda is in appendix B.) An opening session of high-level views on ethnic differences in eye diseases was followed by sessions focusing on one eye disease for which population diversity presents special challenges. On the morning of the third day, the presenters for each session proposed major conclusions and recommendations for all the symposium participants to consider. The conclusions listed in table 1 are based on the results of those lively discussions. This chapter presents key arguments and reasons, drawn from the symposium discussions, supporting the principal conclusions.

Overarching Conclusions

1. **Epidemiological research into the prevalence, incidence, risk factors and determinants, treatment, and outcomes of eye disease in diverse populations continues to be a valuable and necessary endeavor. There is now an urgent need to identify and document the differences in how ophthalmic disorders present in the diverse American population and to understand which potentially relevant factors (genetic, cultural, environmental) influence these differences. Worldwide, the major causes of blindness in many countries vary by degree of socioeconomic factors, as well as by customary ethnic designations. Understanding the causal factors underlying these observable markers of population diversity can improve effective delivery of preventive and therapeutic health care to high-risk groups within the diverse U.S. population.**

Many chronic diseases for which we lack straightforward cures are thought to be *multifactorial:* they are influenced by a number of genetic and environmental factors. For most of these complex diseases, both anecdotal reports and epidemiologic studies indicate that disease prevalence, incidence, and other characteristics vary within diverse populations. In particular, for complex diseases of the eye, much tantalizing but incomplete evidence suggests that substantial differences exist in how these diseases present in groups that differ on the basis of ethnic, environmental, or cultural factors.

These differences in how a complex eye disease presents in diverse populations confront the practical arts of medicine and public health with both a challenge and an opportunity. Until we understand the *how* and *why* of a complex disease—its etiology and pathophysiology—we cannot be sure that what is known about its behavior in one group will be equally valid for a different group. Indeed, mounting evidence shows that substantial differences do exist for several important eye diseases in diverse groups of Americans. Thus, we must be careful in presuming that what has been learned or proven in the context of a general, or "generic," population will apply to a subgroup whose ethnic, environmental, or cultural characteristics diverge from the norms of the larger population. Which differences *are* relevant, which of them *may be* relevant, and which can be ignored? This is the challenge in preventing or treating complex diseases in a diverse population.

2. To guide intervention strategies, further research into these underlying factors can make use of evidence on disease disparities among population groups.

The opportunity comes from the potential value of differences in disease characteristics among diverse populations to help us unravel the multifactorial nature of a complex disease. Carefully documented population differences provide an acceptable surrogate for the kinds of controlled experimentation that we cannot ethically perform on human subjects. When faced with an outcome for which there appears to be multiple causal factors, the scientific approach is to study what happens when one or more of these factors are varied in a systematic way, while all the

others are held constant. However, ethical medical scientists cannot do this. For example, they cannot create genetic strains or "knockout" models of humans to test for a genetic factor. They cannot deliberately expose human subjects to long-term environmental or lifestyle conditions if there is evidence that those conditions may be harmful, just for the sake of a controlled experiment. Faced with multifactorial diseases, medical research requires scientifically sound study methods, such as those provided by epidemiology, to detect putative factors without violating the canons of medical ethics. Epidemiological studies of diverse populations from around the world may permit further inferences regarding relationships of genetic and environmental risk factors to diseases. Where population groups with well-documented differences in factors suspected of causing or influencing a complex disease can be identified, the epidemiologist, geneticist, and biomedical scientist can cooperate to conduct appropriate studies. Population diversity thus provides an opportunity for research not otherwise feasible.

The need to identify and document differences in how ophthalmic disorders present in diverse populations is rooted in both the challenge and the opportunity posed by complex diseases of the eye. For example, there is suggestive evidence that African and Hispanic Americans may be at greater risk for glaucoma and diabetic retinopathy than are Americans of predominantly European ancestry.[1] How large is the risk differential, and what factors account for it? What are the cost-effective public health responses to address these risks, if they exist? Are Asian Americans more susceptible to angle closure glaucoma (ACG) and high (severe) myopia than are Americans of predominantly European ancestry? Is polypoidal choroidal vasculopathy (PCV) a greater risk for African and Asian Americans than for Americans of other ancestry, and if so, what factors are responsible? These are just a few of the challenges

[1]For purposes of this report, African Americans are U.S. citizens with African ancestry and Asian Americans are U.S. citizens with Asian ancestry. Hispanic Americans are U.S. citizens whose ancestry traces to Mexico, Central or South America, or the Spanish-speaking islands of the Caribbean. These categories, along with "European American," are not mutually exclusive; a large and growing number of Americans have ancestors from several of these locations.

related to reducing the risk of visual impairment from eye diseases in the diverse U.S. population. On the opportunity side, sorting out genetic versus environmental and lifestyle differences may be difficult for diseases that occur relatively infrequently, if the study populations are limited to the United States only. Data regarding incidence and risk factors derived from well-designed studies using carefully selected populations outside our national boundaries may be beneficial to understanding and preventing loss of vision in U.S. citizens. Specific instances of this opportunity are included in the symposium's conclusions for specific eye diseases. Given current knowledge about these diseases, such studies may facilitate learning which factors are relevant to future prevention and treatment.

Studies of the prevalence, incidence, treatment, and outcomes of eye diseases in diverse populations from around the world, as well as from our own diverse American population, can enhance our ability to prevent and treat these potentially blinding diseases. That is the principal, overarching theme on which the Drabkin Symposium participants agreed. However, even beyond their relevance to complex diseases of the eye, the above arguments on the challenge and opportunity in population diversity apply as well to other similarly complex diseases such as cardiovascular disease and cancer. The illustrations given below for specific eye diseases thus contain significant general lessons for American health care.

3. The eye diseases on which this symposium focused have genetic components. In studying population differences to identify and understand these genetic factors, one cannot assume that the standard demographic categories for ethnicity define populations with relevantly similar genetic characteristics. In short, the common ethnic categories should not be assumed to be adequate markers for disease phenotypes and their underlying disease genotypes.

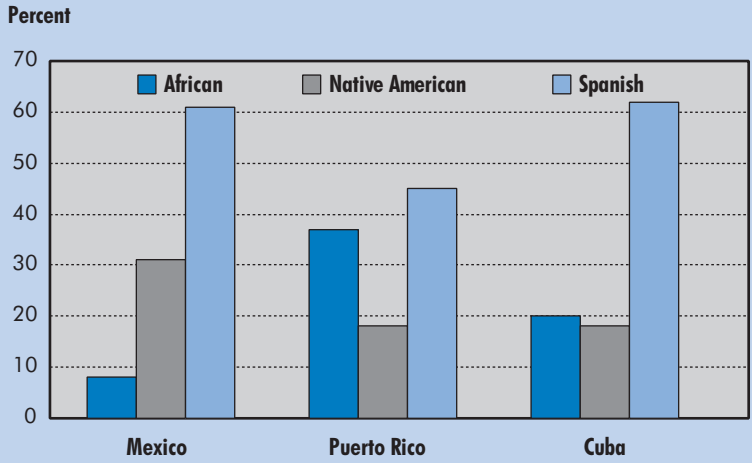
One of these general lessons for health care is that the classic measures of diversity used by demographers—ethnicity, age, and gender, for instance—are not reliable markers for disease risk factors. A demographic category such as Hispanic American or African American covers

a wide range of potentially relevant environmental, sociocultural, and economic factors, as well as genetic factors. Age and gender differences can reflect lifestyle differences, which are influenced by social factors.

For example, the Hispanic population in the United States is particularly likely to be genetically heterogeneous because this culturally defined group consists of individuals whose ancestors typically came from diverse populations in widely separated regions (Native Americans from South and Central America, Spanish and Portuguese immigrants from the Iberian Peninsula, Africans transported to the New World as slaves, and other Europeans who emigrated in response to famine or wars). Figure 1 illustrates the gene pool diversity among Hispanic Americans who emigrated from three areas: Mexico, Puerto Rico, and Cuba.

A similar caveat about genetic diversity applies to African Americans, many of whom have some European ancestry and whose African ancestors may have come from different areas of Africa. Caribbean populations of African descent often have ancestors from different areas within Africa than do many African Americans.

Figure 1. Gene Pool Ancestry for Hispanic Americans



Source: [4].

Great caution must therefore be exercised when making inferences from data for any customary demographic category to the specific factors underlying the disease experience of that population group. If, for example, Hispanic Americans have a different prevalence of a disease from the general population (e.g., open angle glaucoma or late-stage macular disease), one cannot simply assume that a genetic (or cultural, or environmental) factor is responsible for the difference. In the population geneticist's language of disease *genotypes* and *phenotypes* (see box), one must be cautious about assuming that commonly used "racial" or "ethnic" categories, even those used in demographic studies, are accurate, fully representative phenotypes of a disease genotype.

In addition to this genetic heterogeneity in a demographically defined group, one must also consider the complicating role of susceptibility genes (both their presence and absence), gene-environment interactions, gene-gene interactions, and non–gene-based regulation of

Genotypes and Phenotypes of a Complex Disease

A genotype is the genetic constitution of an organism, usually in reference to one or a few genes relevant to a specific context. In discussing multifactorial diseases, a disease genotype consists of the specific gene or set of genes (along with other non-gene genetic components) associated with one variant of the disease condition. The disease conditions diagnosed as glaucoma, for example, can arise from different genotypes. Macular degeneration and probably the other ocular diseases discussed in this report are similarly complex in genetic constitution.

The phenotype of an organism is the set of observable characteristics that depend on a genotype of the organism in interaction with its environment. Similar observable characteristics need not reflect the same genotype. Culturally significant characteristics, such as skin color or facial features, are unreliable as markers for phenotypes of a disease. Even clinically observed differences in disease conditions may not correspond to different disease genotypes and therefore may not represent distinct disease phenotypes.

gene expression. Much additional research on these underlying factors is needed so that differences with respect to probable causal factors can be scientifically established through population studies. The good news is that this work of identifying risk factors for development of any of the eye diseases is likely to produce results applicable to multiple diseases and health-related conditions and issues—not just with respect to the eye and vision but also relevant to other areas of public health and clinical medicine.

A second general lesson is that population-based research can benefit from the comparability across studies provided by judicious oversight and guidance from cognizant national and international authorities. At the national level, these authorities include the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). At the international level, an obvious example is the World Health Organization. Consultation with national and international professional societies with relevant expertise may also be of benefit in conducting such research. Especially important is oversight for longitudinal studies, to ensure optimal use of data from each study to gain insights into the underlying factors—whether genetic, environmental, or cultural—and to ensure comparability across studies. With respect to interventions, surveillance of the population's health by population-based surveys and objective measurements sponsored by the CDC or NIH—for example, the National Health and Nutrition Examination Survey—are important to determine whether *practice differences* introduced to address presumed genetic, cultural, or socioeconomic (environmental) differences in fact have the desired impact on patient outcomes in the population groups to which these differential practices are targeted. For example, does introduction of a new treatment or preventive therapy in fact reduce the frequency of functional loss from the treated condition? Does it improve patients' quality of life? In the United States, the National Center for Health Statistics, a branch of the CDC, has conducted such surveys over time. The National Eye Institute has fostered population-based studies through its funding priorities.

These general lessons for American health care can be illustrated with specifics of the chronic, vision-threatening diseases considered at

the Drabkin Symposium. As mentioned above, it is generally accepted that the prevalence of glaucoma is higher for African Americans and Hispanic Americans than for Americans of non-Hispanic European ancestry. However, data from these populations are inadequate to detect the risk factors explaining the higher prevalence rates for glaucoma. Variations among studies notwithstanding, results from studies such as the Baltimore Eye Study do show that prevalence in all population groups increases with age and with increased intraocular pressure (IOP). Beyond these fundamental risk factors, close comparison of groups for which genetic, environmental, and cultural differences are known and quantified becomes difficult, even speculative.

4. **Studies that target populations both inside and outside the United States may cost-effectively increase the value of results directly applicable to specific American groups. Inclusion of study populations from outside the United States can be a feasible way to collect the data needed to answer both basic scientific and clinical research questions about the contributions of and interactions among environmental and genetic factors.**

Conclusion 4 expands on the general point made above that studies targeting specific populations outside the United States may provide data relevant to understanding ocular disease in the diverse U.S. population. Studies of complex eye diseases need large enough numbers of subjects experiencing the underlying candidate causal factors to yield observable differences that are statistically significant. The more individual factors and combinations of factors to be compared, the larger the target population must be to have sufficient numbers of subjects with different exposures. Ideally, those designing such studies will want to select a population that will maximize the diversity with respect to potential risk factors. Going across national borders to select a study population may increase the number of participants in treatment groups of interest, compared with relying on subpopulations within the larger general population of a single country. One reason is that populations in other countries may be more homogeneous with respect to one or more risk factors of interest than the highly heterogeneous American population, even

within a demographic "ethnic" category. A second reason is that groups in different countries but with similar ancestry may differ with respect to potential environmental and cultural risk factors.

To return to an example already mentioned, Hispanic Americans have a broad range of ancestry in terms of relative amounts of Hispanic and non-Hispanic European ancestry, Native American ancestry, and African ancestry. To understand the interplay among genetic and cultural/environmental factors in the incidence of glaucoma among Hispanic Americans, a study that examines selected participants from specific areas in the United States and from targeted areas in Latin American countries may be more cost-effective. A similar situation holds for studying the higher incidence of glaucoma in African Americans than in the general population. In some circumstances, a smaller study population, but with higher proportions of risk factors of interest, might provide the same statistical power for some questions as a larger but more heterogeneous study population. To test some questions, such as on interactions among potential risk factors, the only feasible way to enroll enough participants with the relevant combinations of characteristics may be to include subjects from outside the United States.

Americans of Asian ancestry provide a third example. This rapidly growing segment of the U.S. population includes persons with ancestry from East Asia (China, Japan, Korea, etc.), South Asia (India, Pakistan, Bangladesh, etc.) and Southeast Asia (Vietnam, Indonesia, Thailand, etc.). Considering the diversity of the history and peoples indigenous to these areas of Asia, one can expect a great deal of genetic diversity within their American-dwelling descendents, as well as divergences between these Americans and others of primarily European or African ancestry. However, there have been few Asian American populations studied to date. There is evidence, for example, of an increase in the incidence of high myopia and of angle closure glaucoma in East Asian countries, but data on Americans of East Asian ancestry are nonexistent. Studies of myopia in Asians living in their ancestral country of origin need to be compared with studies of Americans with ancestry from these same origins. To make such comparisons, the studies must use similar methods and definitions. Multi-nation studies could provide

valuable information for understanding the risk factors of a disease for all populations, much as has already resulted from studies comparing cardiovascular disease in Japanese living in Japan with Japanese Americans. Differences (or similarities) in myopia among Asians living in Asia and in America could similarly shed light on risk factors for all populations.

General Implementation Actions for Ocular Disease

Given the challenges and the opportunities posed by the presence of complex ocular diseases in a diverse population, what should be done to overcome the former and embrace the latter? The three conclusions in this section describe actions relevant across most or all of the diseases discussed at the symposium. In many instances, detailed recommendations made in later sections of this summary for a specific disease are extensions and refinements of the broad actions advocated here.

5. Standard definitions and terminologies for the major blinding eye diseases should be agreed on and used by major ophthalmology centers. These standards should include clinical signs for diagnosis, disease stages, and measurement techniques.

To have precise, objective, and reproducible data on differences in eye disease characteristics in a diverse population (whether the target population resides in one country or geographical region, or comes from several), researchers should use the same disease descriptors. This methodological requirement is routinely solved within individual studies, but the lack of standard definitions and terminologies hampers comparisons across studies. Standardization in the areas of clinical signs for diagnosis, disease stages, and measurement techniques will enable comparative assessments of patient populations by both the public sector (government entities) and the private sector (e.g., pharmaceutical companies). Definitions, diagnostic criteria, and diagnostic methods for the different forms of glaucoma, for example, should be standardized, where possible, to enable valid comparisons of prevalence and incidence across multiple studies.

However, flexibility to respond to new medical knowledge must be built into the definitions. Care must be taken that standard definitions and measurements do not become obstacles to new research and insights that advance older approaches. As new knowledge is acquired on such topics as genetic mutations and the role of environmental and cultural factors, the definitions must allow for incorporation of that new knowledge.

Population studies on age-related macular degeneration (AMD) are another area where additional standardization and test method evaluation are warranted. Internationally accepted standardized protocols have been adopted for defining and grading AMD stages. These protocols have been successfully used in large population-based studies. Although severity scales such as the one used in the Age-Related Eye Disease Study (AREDS) have been based on these standard protocols, they are qualitative classifications and are relatively insensitive for tracking changes in the location and extent of macular lesions over time. A quantitative grading system is needed, which could be adapted to computer-based grading for scoring disease progression from early to late stages. Standard definitions for the earliest stages of AMD are needed, coupled with detection methods that make application of the definitions feasible and practical in population studies. The feasibility of using newer detection and monitoring technologies, such as optical coherence tomography or autofluorescent imaging, should be evaluated.

In the United States, federal funding agencies should support and work with representative bodies from the clinical and research communities to produce newer grading standards that could be implemented as computer-assisted approaches for scoring severity and progression for AMD and other complex ocular diseases. The standards should be widely circulated and readily accessible. For example, they should be available on the public Internet website of the National Eye Institute.

6. An economic plan for progress in cost-effective treatment (a "roadmap to a cure") should be constructed for each of the major eye diseases considered in this report.

The symposium participants agreed that having an economic plan for making progress in cost-effective treatment was essential for the major,

complex eye diseases discussed at the Drabkin Symposium. The complexity of each disease is too great to expect a "magic bullet" or easy solution to emerge from an undirected process. The aim of this planning or roadmapping approach should be to enhance public health. It should also focus research and clinical intervention programs on the most effective prevention and treatment options for a diverse U.S. population, including targeted delivery to higher-risk groups. The economic roadmap to a cure for a given disease should show the expected societal benefit from proposed studies or treatment approaches. The benefits should be sufficient to justify the cost of those studies, including the clinical trials necessary to demonstrate treatment proof of principle, safety, and efficacy.

7. For all the diseases considered in this symposium, prevention or delay of disease progression should be a priority for research and clinical management. An emphasis for future treatments, once a disease condition is present, should be on delivering the active agent to the target site.

The first priority for eye health care must be on primary prevention of the disease process—for example, prevention of diabetes on a systemic level. The second line of eye care treatment for disease conditions, such as diabetes, that have systemic origins and systemic treatment regimens, is prevention of ocular manifestations of the disease, such as diabetic retinopathy. As an example, normalization of blood glucose levels can slow or halt diabetic retinopathy (secondary prevention), as well as other consequences of the underlying diabetic condition. Once a disease condition is present in the eye itself, efficient and effective delivery of an active agent to the ocular target should be the preferred third line of treatment. In the case of diabetic retinopathy, this might be intravitreal injection of agents that prevent bleeding (tertiary level of prevention).

For glaucoma treatment strategies focusing on preventing the permanent loss of retinal ganglion cells (neuroprotection and neural rescue strategies), as well as for other diseases of the retina and choroid, conclusion 7 means delivering therapeutic agent to the back of the eye. Even more precisely, the active agent should be targeted to specific tissues and cell types in the posterior segment of the eye. With respect to diabetes,

medical research should continue to target the local mechanisms that make ocular tissues such as the retina so susceptible to diabetic damage, as well as continuing the search for improved treatment of developing or progressive diabetic retinopathy. For glaucoma, this principle should be applied to mechanical (e.g., surgical), biological, and pharmacological interventions. Fundamental disease mechanisms, such as inflammation and neovascularization, may be more successfully targeted locally (at the site of ocular damage), rather than systemically. The symposium presentations and discussions included numerous examples of this principle for a range of treatment prospects: pharmacological and biological suppression or blocking of vascular endothelial growth factor (VEGF), suppression of retinal neovascularization with agents such as pigment epithelium-derived factor (PEDF), antioxidants to reduce oxidative damage in retinal tissue, neuroprotectants, laser treatment of vascularization on the retinal surface, treatments combining laser photocoagulation with anti-neovascularization drugs, and drug combinations (drug "cocktails").

Public Education and Outreach

This Drabkin Symposium, like the three preceding it, sought ways to improve the transition of research results into positive consequences for patients and those at risk for developing a complex ocular disease. The participants' attention to the interplay of environmental and cultural factors in these complex diseases led to three general action-oriented conclusions on improving public education and outreach. The symposium conclusions for individual eye diseases extend and elaborate on the crosscutting actions recommended here.

8. **Increased support is warranted for research into public outreach on eye health that is tailored for diverse populations. Support for public health education on eye care has a high ratio of societal benefit to cost. Improving the effective delivery of known prevention and treatment strategies, particularly to underserved populations at increased risk, is likely to increase the returns for society, measured in the economic value of health benefits to both individuals and the public good.**

The complex eye diseases considered at this symposium develop over time. Their progression—and in some cases their onset—often depends on risk factors that can be managed, if not absolutely controlled. For the more common forms of glaucoma, patient involvement in lowering intraocular pressure is the foundation of current treatment strategy, short of surgery. For diabetic retinopathy, maintenance of blood sugar levels within a near-normal range appears to be effective in slowing or halting onset and progression. Cultural and socioeconomic factors related to excessive *near work*—that is, extended periods of visual focus at distances typical of reading or benchwork—during childhood are suspected in the development of myopia and, in particular, the relatively high prevalence of high myopia in East Asian populations of Chinese ancestry. Changing these environmental factors to avoid extended periods of near work for young children may be necessary to deal with this disease. Smoking is a well-established environmental risk factor for AMD.

However, a vast gap exists between the medical profession's understanding of manageable risk factors and the application of that knowledge to effective patient care. Best practices for getting treatment knowledge into the hands of patients at risk must be identified and properly applied for all population groups. In particular, outreach to groups at heightened risk will be essential to educate them about the risks and what they can do to reduce them. If effective, such outreach can produce substantial societal benefits, in addition to aiding individuals at risk. The benefits of effective public education will endure even if the most promising of new therapeutic concepts prove successful beyond expectation. In fact, several participants at the symposium surmised that the practical value of putting all that we now know into effective health care regimens, maintained by patient and care provider working together, would have greater societal benefit at lower cost than can be expected from any new biomedical breakthroughs in treatment. Whether or not this surmise is literally true, it underscores the substantial benefits still unreaped from past advances in medical knowledge. Effective public education and outreach must be included in the "roadmaps to a cure" advocated by conclusion 6.

9. A coordinated approach is essential to public education about disease prevention strategies. Public health education should be coordinated for all diseases, not just those of the eye. This coordinated approach should include messages and outreach activities specifically tailored for population groups that are not yet being effectively treated.

To the participants in this symposium, the most effective way to reap the societal benefits from public education about the major eye diseases is to *communicate an integrated and consistent message*. This basic message to the public should not be about any one disease or even just about eye diseases collectively. The message should begin with the responsibility that each individual has to self and loved ones to learn about disease risks and make the effort to manage them. Beyond this unifying theme, however, the message must target detailed, practical information to those who need it. Information on risk factors and the relative risks of specific population groups must be tailored to reach those groups. The participants discussed the difficulty of effective public outreach and education, even for a condition as common and debilitating as type 2 diabetes. There have been many attempts and only limited successes in substantially improving compliance rates. One suggestion was to convene groups of health economists and others with practical and specialist knowledge to pinpoint effective practices for improving public health information delivery. Another was to compile lessons learned about how to do effective public outreach—and about what does not work—either in the general population or in specific groups. Since the time of the first warning from the U.S. Surgeon General, anti-smoking campaigns provide a case study worth exploring for both successes and obstacles in educating the public. Heart disease, hypertension, and cholesterol are other public health issues that should be studied for lessons on effective public education.

The symposium discussions of ways to improve patient compliance with risk management regimens raised several associated issues. Are there policy changes that could improve compliance? What changes to preferred practice guidelines—such as the preferred practice patterns of the American Academy of Ophthalmology—are needed to improve compliance? How do socioeconomic and cultural factors influence com-

pliance with treatment regimens in groups at increased risk from diseases such as glaucoma or diabetic retinopathy?

Rather than attempting to guess at answers to these large questions, the symposium participants agreed that systematic, concerted efforts should be directed to identifying and substantiating practical responses to them. One suggestion was to mine the data from recent and ongoing studies of diabetic retinopathy, including those funded by the National Eye Institute, for evidence of practical improvements in public outreach that could be incorporated into government policies and programs at all levels (e.g., federal, state, and local within the United States). Another suggestion was that voluntary organizations at the community level, championed by an acknowledged community leader, may be more effective in reaching disadvantaged groups than the usual "top-down" public education programs. A third suggestion was that the search for better practices in public outreach should explicitly call attention to barriers to compliance and seek the most effective ways to overcome them.

10. Training for eye care professionals should reflect the growing diversity of the U.S. population. A cost-effective way to combine this training with the need for research on diverse populations is to foster the international exchange of U.S.-based and foreign-based eye care professionals.

In addition to public education about risk factors, the symposium participants agreed that eye care professionals need more training in treating a diverse population. The increasing diversity of the U.S. population means that education about group differences in ocular disease characteristics and risks must be included in the continuing education of ophthalmologists. The rapid annual growth in new knowledge that medical professionals must assimilate is forcing a transformation at all levels of medical education. Through professional training at all stages in a physician's career, sensitivity of health care professionals to diversity in their patient population can be enhanced, while also improving their skills in communicating with this diverse population. In this area, the United States can learn from the best practices of others, as well as contributing to improved health care worldwide.

Exchange programs through which U.S. and foreign-based professionals can observe directly and participate in the practice of caring for a different population than they normally see in their home practices provide opportunities that benefit both the home and host countries. For American doctors, on-the-job training in a country where a particular disease is more prevalent than in their home practice, or presents in forms they do not often see, can sharpen diagnostic expertise and stimulate improvements in disease management. Working within the United States with a foreign specialist very familiar with a disease rare in the United States (such as PCV) and its treatment provides similar training and stimulation. The foreign-based professional visiting in the United States gains exposure to different practice patterns, new techniques, and probably a different population than she or he treats at home. Overall, recognition of the challenges presented by population diversity globally, as well as within the United States, led the symposium participants to favor support for worldwide practice patterns and guidelines, covering a core of knowledge and skills. Evidence-based practice incorporating these principles can be disseminated through guidelines and practice patterns developed by health care professionals. Innovative distance learning opportunities to disseminate these tools for professional education should be encouraged.

Another advantage of exchange programs for the American participants is the direct experience it provides in being sensitive to cultural, ethnic, and language differences, as well as broader exposure to age and gender as factors in patient diversity. Enhancing ethnic diversity among eye care professionals also can contribute to greater sensitivity to population differences. The symposium participants also saw a need to increase the public health component of medical training in the United States, as part of an even broader need to focus on prevention as a more cost-effective alternative to treating a disease only after it presents in health-threatening conditions. Alternative educational experiences, including interactive training delivered over the Internet, are an option for tackling the challenge of diagnosing and treating special population groups within the United States, particularly when those groups may present with eye disease infrequently seen by most American physicians.

Implementation actions in response to conclusion 10 can build on scientific and clinical exchanges that have already occurred or are in progress. For example, at the time of this Drabkin Symposium in June 2005, the Ministry of Science and Technology of the Republic of India and the U.S. Department of Health and Human Services were close to final approval of an agreement on Indo-U.S. Collaboration in Vision Research. The agreement, which will foster collaboration in various fields of biomedical and clinical research, grew out of workshops on U.S.-Indo Collaborative Eye Research held in three cities in India (Hyderabad, Chennai, and Madurai). The workshops were conducted by the Association for Research in Vision and Ophthalmology and funded by a grant from the National Eye Institute

Conclusions on Individual Eye Diseases

Glaucoma

The key points and recommendations on glaucoma that were discussed in both the summary session of the Drabkin Symposium and the glaucoma session on the first day are presented here in relation to three broad conclusions. Conclusion 11 addresses population issues; conclusion 12 pertains to medical research and pathophysiology; and conclusion 13 suggests directions for improving early diagnosis, prevention, and treatment.

11. Research is needed into effective methods for identification of glaucoma in high-risk populations. As the U.S. population ages, early diagnosis of all forms of glaucoma will help to preserve vision. Treatments such as medical and surgical options to lower IOP are available for most forms of glaucoma, if the disease process is identified and treated early enough.

Worldwide, glaucoma is a leading cause of irreversible vision loss. The epidemiology of glaucoma, especially open angle glaucoma, has been thoroughly explored in many adult populations of European ancestry. Despite variations in diagnostic criteria, glaucoma prevalence in these study populations is about 2 percent for adults above age 40. By comparison, persons of African ancestry may have as much as five times that

risk. The risk for Hispanic populations is also greater than that observed in populations of predominantly European ancestry. The data are inadequate to estimate risk in Asian Americans.

Although accurate and universally accepted definitions have yet to be established for the types of glaucoma, the forms generally recognized as *chronic angle closure glaucoma* and *intermittent acute angle closure glaucoma* are particularly underdiagnosed and understudied in the United States. To assess the prevalence of these forms, studies are needed that use consistent definitions, accurate classification of population groups, and adequate sample sizes. Because glaucoma appears to have a genetic component, accurate classification of a study population will require addressing the issues, highlighted in conclusion 3, about disease phenotypes and genotypes.

Glaucoma is the second most common cause of irreversible vision loss in the United States and the most common cause among African Americans. The most common form of glaucoma in the United States is primary open angle glaucoma (POAG). Because the limited data available show a much higher prevalence of glaucoma among African Americans than among European Americans, and indicate a higher prevalence among Hispanic Americans as well, future glaucoma trials in the United States must include sufficient representation from these groups to provide statistical significance for group-specific results.

Angle closure glaucoma is more common in many Asian populations than in populations of predominantly European or African ancestry. ACG prevalence rates of 1 to 2 percent have been found in some East Asian populations. Rates for all forms of glaucoma in European American populations are about 1 percent for ages less than 60 years, and perhaps 10 percent of these (roughly 0.1 percent overall) may be ACG. Nonetheless, POAG is probably the most common form of glaucoma in Asia except in Mongolia. Generally accepted risk factors for glaucoma include:

- IOP (the major risk factor),
- Age,
- A first-order blood relative with glaucoma,
- Central corneal thickness,

- Diabetes mellitus (a particular concern for Hispanics, given the high prevalence of type 2 diabetes in this group),
- High blood pressure, and
- Refractive error (with qualifications: the association is clear for high myopia—refractive error greater than 6 diopters—less clear for 3–6 diopters of myopia; hyperopia has been associated with ACG).

For open angle glaucoma in populations of European ancestry, no difference in risk by gender has been generally established. (However, the Rotterdam Eye Study has found that glaucoma in that study population has a higher prevalence in men than women [5].) ACG, by contrast, appears more prevalent in Asian women than Asian men. For all populations studied, glaucoma prevalence increases with age. For populations at increased risk, the age effect is dramatic. Prevalence in African Americans at 65–69 years of age rises to 6 percent for women and 8 percent for men, from rates of less than 2 percent for either gender at 40–49 years of age.

12. A better understanding is needed of the differences in glaucoma pathophysiology within and between population groups. Mechanisms may differ within and between population groups defined by customary demographic or cultural criteria.

No explanations have been confirmed for the observed differences among African, Hispanic, and European Americans. Cultural and environmental factors could be involved, as well as currently unknown genetic factors. Given the range of forms of glaucoma, another consideration is that there are likely to be multiple pathways or mechanisms that lead to damage to the optic nerve head, the defining characteristic of visual impairment from glaucoma. Different pathways may predominate in different populations or groups. For example, although current data show glaucoma to be more prevalent among African Americans than among European Americans, are the causal factors and disease progression homogeneous across subgroups whose ancestors came from different regions within Africa? Some evidence exists that glaucoma in

Caribbean groups of African descent differs in prevalence and perhaps other characteristics from glaucoma in urban Americans of African ancestry. If these differences are substantiated, will they reflect underlying genetic differences, divergent environmental/cultural differences, or some combination?

For these and other reasons (such as effective treatment for normal pressure glaucoma, as well as better treatment options for advancing POAG), the mechanisms of glaucoma must be understood far better than at present. Among the mechanisms of this complex family of related disease forms that should be better explored are the following:

- **Optic neuropathy of glaucoma.** What are the relationships among disc cupping, changes in the nerve fiber layer, and visual field defects?
- **Retinal ganglion cell death.** What is the biochemical cascade leading to apoptosis? Is the ganglion cell axon or the cell body the target of the mechanism that initiates cell death?
- **Dependence of glaucoma optic neuropathy on elevated IOP and the evidence for elevated IOP as a continuous and causal risk factor.** Why does reduction of IOP slow progression of optical neuropathy at all IOP levels? Is IOP elevation always caused by outflow abnormalities (e.g., increased resistance to flow through the trabecular meshwork), rather than excess formation of aqueous humor?
- **Angle closure glaucoma:** Is this a disease pathology of smaller eyes? Do abnormalities of function in the anterior portion of the eye play a role?

For some aspects of this research, animal models are extremely valuable for testing intervention hypotheses. The results from studies using these animal models provide important clues to pathophysiology and candidate therapeutic approaches.

13. Opportunities exist for improved glaucoma treatments in the future, but stronger support is needed to bridge the gaps in research necessary to develop and test them.

As discussed under conclusion 11, some of the gaps in what we know about glaucoma are particularly glaring when population diversity is considered. If, as current data suggest, specific groups have far higher susceptibility to glaucoma (or to different forms of glaucoma) than does the American population in general, then different emphases in diagnosis, prevention, and treatment may be necessary.

From a public health perspective, earlier diagnosis of glaucoma and its precursor conditions is more cost-effective (and reduces the risk of visual impairment), compared with later diagnosis. The current screening approach is to monitor for elevated IOP. If a patient has elevated IOP, a hierarchy of treatment options aimed at reducing IOP is brought to bear: IOP-lowering medications, laser trabeculoplasty, incisional surgery including drainage shunts, and cyclophotocoagulation. This hierarchy of treatment applies once it is established that a person has the disease, even if IOP is not elevated. Increased IOP is not the disease; glaucoma is an optic neuropathy. Newer approaches in development for reducing IOP include "mending" the trabecular pathway at the histologic level to increase outflow (for example, with agents that relax the cytoskeleton of cells forming the meshwork) or increasing outflow through the alternative uveoscleral pathway (for example, by targeting biochemical pathways such as the regulation by prostaglandin–matrix metalloproteinases of flow through the uveoscleral matrix). Another approach under study is to provide continuous monitoring of IOP as the basis for more effectively avoiding fluctuations in IOP as a glaucoma risk factor.

Another broad area of opportunity for new preventive and therapeutic approaches includes neuroprotection, neural rescue, or neural regeneration to combat the visual impairment mechanisms in the posterior region of the eye. In some novel neuroprotection approaches being studied, the axon, rather than the cell body, of retinal ganglion cells is the target for protection. In others, the protective strategy focuses on laminar glial cells, which normally feed and sustain the retinal ganglion cells. For each of these targets for protection, there are multiple biochemical molecules that are potential candidates for medical interventions. The local circulation for the cells in the optic nerve head is another route being studied for protection and rescue of nerve cells.

Among the neural regeneration approaches to treatment of advanced glaucoma, changes in the central nervous system from glaucoma are under study. Research on stem cell therapy for glaucoma has the aim of replacing lost retinal ganglion cells or other cells in the optic nerve head. Because of the specific type of cell lost in glaucoma (retinal ganglion cells), this replacement strategy has a good chance of succeeding, even though research is now at an early stage.

At present, gene therapy approaches under consideration for treating glaucoma aim at altering a target cell to do something physiologically useful in blocking or ameliorating glaucoma-related effects, not at correcting a defect in a single gene. An example of this potential approach is gene-based pharmaceutical therapy, through which a gene for a protein regulator of neural function (a neurotrophic agent) could be supplied to cells within the eye such as retinal ganglion cells. The premise of this approach is that increasing the supply of the neurotrophic agent will increase the survival rate of retinal ganglion cells, slowing the loss of visual function. For neuroprotection and gene therapy approaches to glaucoma, which are also still in the early research stage, a major objective is delivering the drug or active agent to the target site in the rear of the eye, as noted in conclusion 7.

Technology and techniques to aid in understanding and monitoring the physiopathology of glaucoma provide another area of active and promising research. Visualization of retinal ganglion cell death in a patient (in vivo visualization) would allow this aspect of glaucoma neuropathy to be followed directly in patients. For structural imaging and functional testing of the anterior chamber to understand the mechanisms of IOP elevation and control, in vivo visualization could be applied to the cellular ultrastructure of the trabecular meshwork and related histologic features. These visualization techniques may in the future aid in finding better functional tests for signs of early indications of glaucoma. Another application for visualization technologies, particularly germane to this report, is for research on the physiological and biochemical causes of the differences in response to a particular therapeutic approach for diverse patient populations.

Thus, there are many solid opportunities for future improvements in both the diagnosis and treatment of glaucoma, which could be incorporated into public health programs for early detection of ocular disease and prevention of blindness. Increased support for any number of these promising prospects will greatly increase the likelihood of further improvements in treatment.

Diabetic Retinopathy

Diabetic retinopathy is the leading cause of poor vision in young adults. The causes are complex, but the risk is directly proportional to control of blood sugar and, to a lesser extent, blood pressure. The recommendations and essential points identified during the Drabkin Symposium discussions on diabetic retinopathy are presented here under three conclusions: conclusion 14 on the primacy of prevention, conclusion 15 on population issues, and conclusion 16 on the challenges in sustaining patient compliance with long-term regimens to reduce the risk of onset or progression of diabetic retinopathy and other consequences of uncontrolled diabetes (e.g., corneal involvement).

14. Prevention is the most important strategy for dealing with diabetic retinopathy. The principal prevention goal is to maintain normal, or at least near-normal, glycemic levels. Other prevention goals include maintaining normal blood pressure and serum lipid levels.

Conclusion 14 represents the application of conclusion 7 to the specific case of diabetic retinopathy. For this ocular disease, *primary prevention* would be prevention of the diabetic condition at a systemic level. For type 2 diabetes, public education programs that encourage healthy dietary and lifestyle choices before the disease occurs are primary prevention strategies. *Secondary prevention* strategies aim to prevent the ocular manifestations of diabetes, once the underlying systemic disease condition is present. The principal secondary prevention strategy for diabetic retinopathy is to maintain glycemic levels within the near-normal range. Maintaining blood pressure and serum lipid levels within normal ranges appears to aid in preventing or slowing the development of retinopathy. *Tertiary prevention* is last-resort treatment of the serious ocular

manifestations, such as neovascularization, to prevent blindness or functional vision loss.

Public education and outreach are essential factors for the needed improvement in preventing diabetic retinopathy through maintenance of near-normal glycemic levels and, to a lesser extent, normalizing blood pressure. As discussed under conclusion 9, the symposium participants agreed that a coordinated public education campaign should address health risks collectively. The risks, including diabetic retinopathy associated with type 2 diabetes, the lifestyle risk factors associated with it, and the means available to manage the disease should be important parts, but not the sole disease focus, of this public education campaign.

15. Population studies for diabetic retinopathy should be designed to: (1) ensure that results can be generalized to populations at elevated risk; (2) allow meaningful comparisons across studies; and (3) make use of results from current population studies, particularly those in which DNA sampling allows for analyses that support genotype characterization.

Diabetes, with diabetic retinopathy as one if its potential serious consequences, is an excellent illustration of both the challenges and opportunities that population diversity poses for effective treatment of complex, multifactorial disease. As with glaucoma, persons with diabetes who are of African or Hispanic ancestry appear to be at increased risk of severe vision loss and blindness compared with those of European ancestry. At least part of this elevated risk can be attributed to the differential health care experience among these groups with respect to risk factors such as glycemia and elevated blood pressure. However, genetic factors and environmental/lifestyle factors such as diet (particularly in the case of type 2 diabetes) require further detailed evaluation of these factors and their interaction. Comparative studies are needed to ensure that high-quality care can be focused and tailored to decrease risk in specific population groups with elevated risk. As with other diseases considered at the symposium, the experience of the Asian American population with respect to diabetic retinopathy is not yet well characterized and certainly merits attention.

For Americans, significant environmental risk factors are diet and obesity linked to type 2 diabetes. Research is needed on how these environmental factors, plus the cultural and socioeconomic factors that limit effective delivery of known treatments, affect groups at increased risk for diabetes and therefore for diabetic retinopathy and other eye complications. Advances in specific technological areas that can help with these comparative studies include telemedicine, computerized reading of retinal images, and better software for recording and analyzing patient condition.

16. Innovative approaches are needed for improving compliance—and patients' understanding of their disease, on which compliance depends—across ethnocultural boundaries. Patient compliance is the single biggest driver in determining the outcome of known prevention strategies.

Much of the current knowledge about preventing or reducing the risk of progressive diabetic retinopathy has not been implemented effectively throughout the U.S. population at risk. This knowledge was acquired from authoritative studies such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy, conducted from 1980 to the present, and two randomized control trials: the Diabetes Control and Complications Trial, conducted from 1983 to 1993, and the United Kingdom Prospective Diabetes Study, conducted from 1977 to 1997. Given this limited success in implementation, even after several decades of public education efforts stressing glycemic control to manage diabetes, the symposium participants agreed that a more robust approach is necessary.

The Drabkin Symposium participants favored a prototype program that would systematically explore these issues of improving compliance and overcoming barriers. An experimental approach must be adopted for identifying, confirming, and building upon the limited public outreach successes in improving patient compliance with glycemic control strategies. Part of this approach must be recognition and removal of the barriers to communicating the message effectively enough that patients alter their behavior and sustain a healthy regimen. As a point of departure for beginning such a program, symposium participants suggested that

valuable lessons could be gleaned from the work of Dr. Paul Lee. While at the University of Southern California, Dr. Lee identified diabetic patients who had been blinded by retinopathy, even after the research conclusively establishing the benefits of a glycemic control regimen was known. He conducted focus groups with these patients, their families, and their physicians to attempt to identify obstacles to compliance. Understanding these obstacles may help in designing future compliance programs with higher success rates.

Another area that should be explored is the use of financial incentives to foster and sustain compliance. The symposium participants described circumstances in which patients or their families were paid a modest amount to have regular medical examinations and stay in compliance with a prevention regimen. This experimental program, all agreed, could yield substantial benefits to patients and to society at modest cost. It should be integrated with the larger coordinated public health education and outreach effort, as described under conclusions 8 and 9.

Macular Degenerative Diseases: AMD and PCV

The macula of the human eye is a specialized area of the retina, only about 2 to 5 mm in diameter. At its center is the fovea, just 0.3 mm in diameter, which provides high-acuity vision.[2] AMD, which is now the leading cause of blindness and serious vision impairment in older Americans, can lead to loss of visual function in the fovea and macula. Already, large numbers of Americans are affected by AMD: a 2002 study estimated 1.7 million Americans have either the wet or dry form of advanced AMD [6]. In dry AMD, photoreceptor cells of the retina (particularly in the macula) slowly die, leading to vision loss and sometimes to functional blindness. In wet AMD, bleeding from a mass of newly formed blood vessels resulting from a process known as choroidal neovascularization (CNV), leads to scarring, eventual destruction of the fovea and macula, and in many cases, acute vision loss and legal blindness.

[2]For a basic description of the human macula and the physiological structures and functions affected in the course of macular disease, see the Introduction to the summary from the February 2002 Eye Disease Symposium [2], pp. 3–4.

AMD is the most common vision-threatening disease in older Americans of European ancestry. Without effective preventive and therapeutic strategies, AMD prevalence and incidence will increase as the American population ages. Given the social, financial, and quality-of-life ramifications of this trend, comparative data for the major subgroups within the U.S. population will be essential to a cost-effective public health strategy.

This Drabkin Symposium included discussion of recent studies on another disease that predominantly affects the macula: polypoidal choroidal vasculopathy. This degenerative disease has been studied primarily in Asian populations, where it may account for more than 60 percent of patients presenting with hemorrhagic detachment of the macula. In the United States, PCV was once thought to be a disease predominantly occurring in African American women. Now it is known to occur in all population groups. Its prevalence rate among Asian Americans is not yet known, but is expected to be higher than in the general population.

The summary discussion of these macular diseases at the symposium led to specific recommendations that are presented below under four conclusions. Conclusions 17 and 18 pertain to population studies. Conclusion 19 addresses treatment and the fundamental knowledge of AMD pathophysiology on which more effective treatments depend. Conclusion 20 addresses the state of knowledge about both risk factors and protective factors for AMD progression, particularly the indications from the National Eye Institute's Age-Related Eye Disease Study that dietary supplements may be beneficial in reducing the rate of progression in advanced forms of AMD.

17. Future epidemiological studies of macular disease—including PCV as well as the wet and dry forms of AMD and precursor conditions—need a common basis for interstudy comparisons based on uniform definition and classification. This standardization should reflect the need to match phenotypes with genotypes of macular disease.

As mentioned above, AMD is the leading cause of irreversible severe loss of vision in older European Americans and Europeans. African

Americans and Hispanic Americans may be at somewhat lower risk for developing the severe lesions of advanced AMD. However, the data for these population groups are sparse, especially the data on incidence. Even less is known about the risk for AMD in Asian Americans or Native Americans.

At the global level, three large population-based studies in the United States, the Netherlands, and Australia have used similar AMD definitions and grading systems. These studies found similar prevalence and incidence of late-stage AMD in the three populations, which were largely limited to persons of European ancestry. The few studies comparing the prevalence of AMD in diverse populations have not shown conclusively that differences exist among groups defined solely by the customary demographic categories of ethnicity. But individual studies and other reports *suggest* prevalence differences based on ethnic (e.g., genetic/environmental) and gender differences. For example, a few studies have found differences, such as large drusen but little late-stage AMD, in African and Hispanic study groups, compared with groups of predominantly European ancestry. Taken together, the best-conducted population studies provide a solid foundation for AMD being a multifactorial disease, even if many of the specific factors involved continue to elude definitive confirmation. The evidence is overwhelming that AMD, as well as being multifactorial, has a strong genetic component.[3] Thus, AMD should be regarded as a "family of diseases" with potentially differing initiating events and pathogenic pathways leading to the advanced stages where functional vision is affected.

While the current qualitative grading schemes enable comparisons of AMD prevalence among populations, still lacking is a widely accepted and widely used system for quantitative scoring of the progression from early signs—the accumulation of drusen—to advanced AMD. A number of issues remain, such as how the earliest stage of AMD should be defined. These issues are important when making comparisons of AMD

[3]Dr. Peter Campochiaro reviewed the recent evidence for genetic factors in AMD, such as the connection with a polymorphism of the gene for complement factor H, in his presentation, summarized beginning on p. 141.

prevalence and incidence among diverse populations. The symposium participants agreed that the greatest needs in the area of macular disease and related CNV are for standardized quantitative measures of AMD and for the eventual identification and confirmation of disease phenotypes that truly reflect underlying genotypes (conclusion 3).[4] Further refinement of the existing severity scales and definitions should be based on these new quantitative measures (conclusion 5).

Laboratory studies with animal models will be an essential component of the larger program of identifying AMD genotypes, linking them to clinically observable phenotypes, and studying the interplay among genetic and environmental risk factors. For example, when candidate AMD-relevant genes are identified, animal models provide the means for controlled experiments to determine the role each gene plays in AMD onset and progression. Animal models will also be valuable for proof-of-principle testing of new therapies, as has been done for retinitis pigmentosa. The symposium participants thought that additional salient disease features of AMD are likely to be producible in rodent models, as has already been achieved for some characteristics, even though rodents lack a macula. Although no fully satisfactory animal model exists for all the salient features of AMD in humans, work in progress on primate models for AMD is promising. The participants thought such work should be pursued.

On the difficult problem of sorting out AMD genotypes and the factors contributing to each form of the disease, symposium participants emphasized the value of AMD tissue banks. They agreed that opportunities should be pursued for refining and clarifying AMD phenotypes/genotypes using eye tissue from tissue banks that can meet at least two criteria:

1. Donor eyes are gathered quickly enough to avoid histological and cellular changes of significance to disease pathophysiology.
2. The medical and family history of the donor is well documented.

Along with retinal tissue, patient DNA should be banked for genetic studies, as this work is an essential component in the search for genetically relevant phenotypes of AMD.

[4]Similar conclusions were reached at two preceding Drabkin Symposiums in February 2002 and October 2003. See [2], p. 5, and [3], p. 5.

18. More population-based studies are needed that are carefully designed to test specific hypotheses regarding the roles of genetic and environmental factors in AMD and PCV initiation and progression.

Conclusive studies designed to sort out the presence or absence of objectively identified genetic, environmental, and cultural/lifestyle differences in the study population are greatly needed. Within this framework, genetic and environmental differences, as well as interactions among genetic and environmental/cultural factors, need to be studied to determine the precise factors and conditions favoring or inhibiting AMD (or PCV) onset and progression. Population studies targeted to groups with specific genetic similarities (or targeted to compare groups with specific genetic differences but with other factors controlled) are important complements to laboratory research with animal models and other lines of investigation for studying genetic factors in these diseases.

Carefully designed population studies will be extremely important for identifying and studying AMD phenotype variations within and among population subgroups. Such studies can aid in differentiating the role of genetic and environmental factors, if the studies are well designed to decide between specific hypotheses. The experts on AMD at this Drabkin Symposium agreed that some useful comparisons can probably be drawn using appropriately targeted studies of groups within the U.S. population. However, given the relative scarcity of advanced AMD in any single geographic region, increased statistical power can be attained by including populations from around the world. Large populations are needed to find statistically significant associations for factors of interest that are of low frequency, while controlling for potentially confounding covariant factors. Combining data from populations outside the United States can help to achieve this.

The symposium discussion of similarities and differences between PCV and AMD raised the general question of the extent to which at least some forms of these diseases may be largely diseases of modern (i.e., post-industrial) societies. Even if some genetic differences influence risk (either increasing it or acting as protective factors), are conditions associated with industrial or post-industrial urban living a major factor? The

participants discussed study approaches that might target selected populations to test this hypothesis. Among the challenges in studying the prevalence and incidence of either AMD or PCV in specific populations is the low frequency with which advanced stages of these diseases occur. Such studies will need large numbers of subjects to produce results with convincing levels of statistical significance and power. An added challenge for studying AMD incidence is the long duration of disease progression between early-stage or precursor conditions and the advanced stages of wet or dry AMD.

Given the broad base of evidence for AMD being multifactorial, singular causes of onset or progression appear unlikely. In genetically disparate populations, different genes and gene combinations, as well as interactions among genetic and environmental factors (e.g., smoking), are likely to be involved in AMD initiation, progression, or both. The symposium participants cited multiple sclerosis and breast cancer as analogously multifactorial diseases.

Based on the PCV presentation and discussions, the participants agreed that it appears to be a distinctly different disease from AMD. Questions not yet answered include whether PCV is (predominantly) environmental or genetic, or both. No evidence has been found to date for clustering of PCV cases within families, but the disease appears to be more common in some groups of similar ancestry, such as East Asians. The East Asian population in the United States has not been studied for PCV. Another question is whether hypertension may be a risk factor. The PCV experts at the Drabkin Symposium emphasized that further study is necessary on the PCV risk in African Americans and other populations of African ancestry, as well as on populations of East Asian ancestry in the United States and elsewhere.

19. Better treatments and therapeutic agents for neovascularization affecting the macula are needed. Treatments are also needed for dry AMD. A better understanding of AMD progression is needed, on which to base decisions and techniques for treating early precursor stages of AMD.

Surgical treatments for wet AMD have included photocoagulation, in which a laser is used to seal off and destroy the new blood vessels associ-

ated with CNV, and photodynamic therapy, which attempts to limit the damage to the surrounding retinal tissue by more closely targeting the absorption of laser energy to the new blood vessels. Both forms of laser treatment have had only modest success, in part because the conditions that induce new vessel formation remain and the CNV commonly recurs. The symposium participants thought that better visual results will probably be attainable with emerging biological approaches to controlling CNV, particularly with approaches that, by one means or another (such as limiting VEGF production or uptake), block the pathway to induction of neovascularization. Knowing more about the pathophysiological mechanisms that lead to CNV would greatly aid this search for effective biological therapies. For example, it appears that changes in or damage to Bruch's membrane and the retinal pigment epithelium are involved, but exactly what the causal sequences are continues to be a topic of much debate.[5] Understanding the pathophysiology of AMD progression will enable clinical investigators to make better-informed decisions about which antineovascular agents may be most effective for specific AMD phenotypes (once the phenotypes are identified and better defined).

20. Population-based studies, such as the Beaver Dam Study and the Rotterdam Eye Study, have found that smoking is a risk factor for AMD. Two major studies have reported association of dietary supplements, including antioxidant vitamins and zinc, with reduced incidence of AMD in the elderly and reduced rate of progression to advanced AMD. Further study is needed on these factors (e.g., mechanisms of action), as well as on additional risk factors and protective factors for degenerative diseases of the macula.

There is suggestive but not consistent evidence for AMD risk factors other than smoking and aging. The problem of identifying distinct AMD genotypes probably increases the difficulty of detecting and confirming environmental factors that may increase or decrease the risk of disease

[5]Recent hypotheses on the pathophysiology of AMD progression, the evidence for them, and the status of work to advance them are among the topics covered in the report from the second Drabkin Symposium [2].

progression for one genotype but not for another. Lumping the phenotypes of these genotypes together as AMD would result in washing out the effect of an individual factor, particularly when comparing studies that targeted diverse populations, with their greater likelihood of genotype diversity.

The part of the AREDS that constituted a controlled clinical trial for the effect of nutritional supplements on progression to advanced AMD found that a dietary supplement containing zinc and antioxidants decreased the risk for progression for specific high-risk groups from 28 percent with no supplement to 20 percent with it. These groups either had large drusen or had wet or dry AMD in the other eye already. There was no statistically significant effect of any of the supplements tested for participants who had less severe disease manifestations at the beginning of the study [75]. The Rotterdam Eye Study has reported that a high dietary intake of beta carotene, vitamins C and E, and zinc was associated with substantially reduced risk for AMD in elderly persons [97].

In addition to the clinical trial of dietary supplements, another component of AREDS was an observational study of dietary associations. Observational studies are useful for identifying hypotheses about potentially significant associations, which can then sometimes be tested in a controlled experiment. Well-designed clinical trials remain the best method to test these hypotheses in human subjects. An example of this transition from observational suggestion to controlled clinical testing is the National Eye Institute's proposed clinical trial of lutein, zeaxanthin, and omega-3 fatty acids as protective factors for AMD.

This relationship between results of observational studies or anecdotal reports and controlled experimental studies can be extended generally to the challenges and opportunities presented by population diversity. Observations of differential disease consequences in subgroups of a study population are useful for identifying associations worthy of further consideration. This further consideration, however, may require testing hypotheses with study designs and control groups that can only be established ethically by employing the global diversity of conditions in which people live, apart from their participation in the study. For complex diseases suspected of having a multifactorial genetic component, studies

that use existing diversity of living conditions may be the only way, as well as the best way, to test the most compelling hypotheses suggested from observational studies.

Myopia

In myopia, the point of sharpest focus for light entering the eye from distant objects falls in front of the retina rather than on it. A myopic person can see objects distinctly only when they are relatively near; hence, the person is "near-sighted." Although all forms of myopia represent an economic burden to families and society, the principal health concern with myopia at this Drabkin Symposium was progression to severe myopia. If early myopia progresses to a severe form, serious functional impairment or total vision loss can occur. These consequences of serious ocular morbidity were the primary myopia-related health risks of concern to the symposium participants. The relationship between milder and severe forms of myopia is uncertain.

21. Epidemiologic data from different countries with diverse populations indicate that both environmental and genetic risk factors influence the development of myopia and of ocular morbidity associated with childhood myopia. Understanding the respective roles and interactions among these factors is essential to cost-effective intervention strategies. Thus, population-based studies are needed to identify these risk factors and their interactions.

In some parts of East Asia, the prevalence of high myopia in young children is alarmingly high and appears to be increasing. Children of Chinese ancestry may be at higher risk than others, but it is still unknown whether this reflects primarily a genetic or environmental effect, or both. The environmental hypothesis is that this early myopia is a response to intense environmental stimulation in the form of extended durations of near work, beginning at an early age (three years or earlier) and continuing through adolescence. A genetic background particularly susceptible to responding to this environmental stimulus with abnormal axial growth of the young eye also appears to be a factor. Inheritance patterns and genetic studies support a genetic basis or at least a strong genetic influence. The evidence of a role for environmental factors includes

observed increases in prevalence of myopia in some study populations with increases in close visual work. There are also differences in prevalence between populations of similar ancestry of origin but currently living in differing cultural settings.

This Asian experience has several points of relevance to the diverse U.S. population. If the environmental hypothesis is correct, are American children, or some subset of them, at greater risk for progressive myopia because of cultural or scholastic performance expectations that require extended periods of near work from an early age? Are Asian Americans, or some genetic subgroup of Asian Americans, at much higher risk than their peers, even at the same levels of childhood near work? Even more generally, does the experience of Asian children make them a particularly "high exposure" group from which one can extrapolate to lesser but potentially significant response levels for all children, or even for adults? To move forward on such questions, a concerted effort is needed to determine whether the same causal factors at play in the high-prevalence Asian groups are present in other groups. If so, the next issue is whether these factors are indeed major determinants of risk for segments of the U.S. population.

Studies of refractive error in children show dramatic differences in myopia prevalence between populations of different ethnicity (which may reflect environmental as well as genetic differences). Myopia prevalence ranges from essentially no cases found in illiterate, rural areas of Nepal to 75–80 percent in urban Chinese children. In adults, prevalence estimates range from 15 percent in Australia (a population of predominantly European ancestry) to 40 percent in Singapore residents of Chinese ancestry.

As mentioned, a suspected prime risk factor is the amount of near work done by children. Abundant evidence exists for reading and other near-work activities being associated with the onset and progression of myopia. The educational environment, particularly the intensity and duration of the schooling experience (reading and other near work) differs substantially across the populations studied. Differences exist between ethnically diverse populations (e.g., Chinese versus Indian children) and between ethnically similar populations in environmentally diverse settings (e.g., urban versus rural children of Indian ancestry).

Although these and other data from different countries with diverse populations have provided invaluable information for understanding juvenile myopia, quantitative comparisons across populations have been hampered by inconsistent measurement methods, definitions, and sampling biases. The objectives of primary importance for further population-based study of myopia include:

- Impact of myopia on visual function;
- Relationship of early myopia to future complications resulting in blindness; and
- Studies to understand the impact of mild-to-moderate myopia, as well as early severe myopia.

22. A better understanding of the pathophysiology of myopia as a disease of eye growth and refractive development will complement the effort to resolve the genetic and environmental factors through population-based studies.

In many species from fish to primates, eye growth and refractive development are actively regulated by visual feedback associated with the eye's effective refractive status. Visual experience affects refractive development primarily by altering axial elongation rates. These vision-dependent mechanisms are active well into early adulthood. According to the environmental hypothesis, the effect of excessive and extended near work is to overstimulate axial growth, resulting in both high myopia in childhood and other chronic dysfunctions that contribute to progressive loss of visual function, and even blindness, later in life.

The current pharmacological (atropine, pirenzepine) and optical (progressive add lens) treatments, which appear to work by counteracting the stimulus to axial growth, have been only moderately effective. First, these treatments slow the progression of myopia but do not prevent it. Second, their benefits are short term, and the effects do not persist. Third, current treatments seem to have only a small effect on axial elongation. Fourth, they are difficult to administer and have compliance issues. Finally, some of the drugs used have multiple tissue and cell targets, so their long-term side effects are unclear.

An alternative approach being considered is to intervene more directly in targeting the physiological pathway for axial elongation. The effects of visual experience on refractive development are primarily mediated by local retinal mechanisms. The signal cascade includes multiple retinal, choroidal, and scleral components. Mechanisms that regulate this development integrate visual signals that increase and decrease axial growth in a nonlinear pattern over time. Both peripheral and central vision influence this development. Research is being done to characterize the components in the signal cascade linking visual experience with axial elongation. A near-term objective is to develop methods for quantifying visual experience that take into account the nonlinear way in which visual signals are integrated over time and the nature of the visual signals across the visual field. In the longer term, this fundamental understanding can inform selection and testing of interventions that more precisely regulate the elongation response to visual stimuli.

23. Prospective population-based studies are needed to determine the predictors for progression of juvenile myopia and to identify future treatment opportunities.

The search for better interventions in treating children at risk for severe myopia will be aided if reliable predictors for progression of the disease can be identified. Prospective studies for this purpose should include details of ocular structure and biometry, as well as measurement of refractive error. These studies should be designed to include Chinese Americans and other Asian Americans, as well as Chinese and other Asian populations in Asian countries and possibly elsewhere (Australia, Southeast Asia). Such studies could be coordinated with a program of cross-fertilizing educational exchanges, as recommended under conclusion 10. The understanding of genetic and environmental factors gained from these prospective studies should be applied to developing prevention strategies for myopia that take into account the eye's effective focus across the visual field. This improved understanding can also be applied to the search for better pharmacological interventions to prevent severe myopia.

Another issue is how to quantify near work. An accepted basis for quantifying near work should be established, in line with the general recommendations made under conclusion 5.

Future randomized clinical trials that include groups at risk from severe myopia should examine the effects of prevention or treatment strategies on ocular function, structure, and morbidity. Community-based clinical trials should be used to assess the influence of environmental and behavior modifications on outcome. There is no evidence to date of ethnic differences in response to treatment, but this null result should be confirmed using more precise characterization of genetic associations (e.g., better characterization of ancestry than customary demographic categories) and of the potential environmental and cultural factors reflected in customary ethnic categorization.

Cataract

Although cataract was not a specific focus of this symposium, it is a leading cause of blindness worldwide and, as such, was discussed during the meeting. According to the World Cataract Foundation, more than half of the blindness in the world—about 25 million individuals—is the result of cataract. The number of new cases each year is 1.5 million. The vast majority of those blind from cataract live in developing nations. The simple, safe surgery to remove cataracts and restore vision is unavailable to them because of poverty, lack of medical insurance, and inadequate access to eye care and eye surgical services.[6]

In the United States, cataract remains the second most common cause of blindness, after AMD, in the general population. For African Americans, it is still the leading cause of blindness. For all Americans, cataract remains the leading cause of low vision, accounting for about half of the total cases.[7] Although timely surgery can reverse the loss of vision from cataract in most cases, affordable and effective access to this treatment remains a major public health issue in the United States as in the developing world.

[6]From the World Cataract Foundation website: www.worldcataract.org.

[7]National Eye Institute press release, April 12, 2004, "Vision Loss from Eye Disease Will Increase as Americans Age," www.nei.nih.gov/news/pressreleases/041204.asp.

24. A high priority for further research on cataract should be to understand the disparities among populations worldwide in patient access to and outcomes of cataract surgery. Although surgery is a cost-effective intervention worldwide for visual loss due to cataract, research to understand population disparities in cataract onset may aid in preventing or delaying this disease, which blinds more than a million people each year.

There is at present no reason to suspect that outcomes of cataract surgery would differ in diverse populations because of factors intrinsic to the patient (e.g., genetic or lifestyle differences), so the reported disparities in outcomes need further investigation. Although a reasonable "null hypothesis" is that the disparities reflect differences in the local conditions of surgical treatment and/or the expertise of local health care providers, this hypothesis should be examined objectively and thoroughly. At this Drabkin Symposium, Dr. Sheila West presented findings on the disparities between African Americans and the general U.S. population with respect to cataract prevalence and treatment. Although African Americans were more likely to be visually impaired due to cataract (2.7 percent versus 1.1 percent), they were less likely to seek eye care services for their condition (odds ratio = 0.62).

The symposium participants agreed with the emphasis placed by organizations such as the World Cataract Foundation and the World Health Organization on extending the access to surgical treatment of cataract. The participants thought that a priority for further research should be to identify and address the reported disparities in outcome of surgery. They also agreed that research should continue on means of at least delaying, if not preventing, cataract development. Delaying onset by even five years could substantially reduce the impact of cataract-induced blindness on millions of individuals and social support agencies.

Session 1

Ethnic Differences in Eye Diseases

This and the remaining chapters of this report summarize the 16 presentations by participants during the first two days of the June 2005 Drabkin Eye Disease Symposium. The summaries highlight points made in each presentation that support, illustrate, or extend the conclusions and recommendations listed in table 1 and discussed in the previous chapter. Each summary has been reviewed and approved by the presenter, but it reflects the symposium chairs' perceptions of which elements in the presentation should be emphasized in the context of the major symposium themes, particularly the discussions on the final day, which are the basis for the symposium conclusions. Presenters' titles and current affiliations are listed in appendix A.

What Epidemiology Has Taught Us about Eye Diseases in Diverse Populations

Dr. Sheila West

The opening presentation addressed three context-setting issues for the entire symposium: (1) what epidemiology does; (2) what is meant by diverse populations, particularly in the context of medical epidemiology; and (3) highlights of what is known about how major ocular diseases present in diverse populations. As the scientific underpinning for the field of public health, epidemiology characterizes chronic ocular diseases with respect to group characteristics. It provides at least partial answers to questions of:

- *Who* (an identifiable subset of a population),
- *What* (the characteristics of the disease or a related health condition),
- *When* (age characteristics of the group at risk),
- *Where* (geographic location of the group at risk), and sometimes
- *Why* (risk factors and coincident conditions that suggest causal connections).

For the epidemiology of complex ocular diseases, there are questions about which characteristics represent relevant diversity in a population. From a scientific perspective, the visible characteristics typically used in demography—not only race or ethnicity but also gender and age—are at best markers for underlying factors that could account for the differences in how a disease occurs in different groups within a study population or between different study populations. Thus, a major issue is the reliability of visible (or readily observable) characteristics of individuals as markers for the underlying factors of ultimate interest. Dr. West emphasized that "race" denotes socially constructed delineations that are not scientifically valid. Although the disease epidemiologist often must begin with group variations in disease based on geographically and demographically identified groups, a scientific understanding of population diversity as a factor in public health and medical care requires identifying the underlying factors, genetic and environmental, for the differences in how diseases present.

Why, then, bother to study groups that are defined by these customary ethnic or cultural distinctions? As an example, Dr. West used the demographic category of "Latino." It designates a shared language and culture and has social and political significance, but members of this group have diverse anthropological origins. Even for a group as genetically diverse as Latinos (or Hispanic Americans), studying them as a group can identify risk factors that arise from common cultural factors, such as inadequate access to medical care or lower utilization of available services or preventive regimens. A variety of risk factors along the disease process—from onset through treatment or disease progression to endpoints—influence the observed disparities in population groups defined using ethnic categories. Environmental factors in particular may

be operative anywhere along the disease process. Therefore, even where there is little scientific basis for linking customary ethnic categories with disease genotypes, these categories can be useful in disease epidemiology.

Dr. West's survey of population-based disparities in disease characteristics began with an account of research on the disparity between European and African Americans in severity of cataract (measured by lens opacity), treatment rates, and outcomes. In the Salisbury Eye Evaluation Project, for which the target population included older African Americans and European Americans, the African Americans were nearly twice as likely to have cortical opacity. For nuclear opacity, which is considered a greater threat to vision, the African American group had lower incidence than their European American counterparts. The Salisbury team investigated whether these group differences could be explained by known risk factors for cataract. Even after adjusting for gender, age, exposure to ultraviolet light, and diabetes, a 4.5-fold increased risk of cortical opacity remained for the African American group compared with the general population. Previous work had found that African Americans were 80 percent as likely to have cataract surgery as European Americans. However, when the Salisbury subjects were matched by type and initial grade (severity) of opacity, the incidence of cataract surgery was similar for the African and European Americans. The African Americans did experience more than double the rate of visual impairment due to cataract (2.7 versus 1.1 percent), and they were less likely to seek eye care services, even after adjusting for diabetes, vision, and education factors (odds ratio = 0.62). Dr. West interpreted the Salisbury results as pointing toward the interface between eye care services and the cultural or economic setting of African Americans within the U.S. population as a major factor in the observed disparities.

As her next example of how epidemiology has identified problems within diverse populations and can suggest which underlying causal factors may be involved, Dr. West discussed juvenile myopia among Asians. East Asian children have a much higher prevalence of myopia than occurs in general populations elsewhere in Asia and the rest of the world. In Singapore, the prevalence of myopia (-0.5 diopters) was 28 percent in 7-year-old children, 34 percent in 8-year-olds, and 44 percent

in 9-year-olds, compared with a prevalence of 1.4 percent in Australian 6-year-olds and 5–15 percent among Indians 5 to 15 years of age. A longitudinal study of children in Singapore found three-year incidence rates of 48 percent for 7-year-olds, 38 percent for 8-year-olds, and 32 percent for those who were age 9. The concordance rate for myopia in monozygous twins is high. The concordance is even higher for involvement in near work. When 16 percent of children have high (severe) myopia, as has been found in some locations, the public health problem is significant. Among the important questions posed by these results are "Why were the Singapore children more susceptible?" and "What can be learned from this situation that can be applied more broadly?"

The third example was progression of glaucoma in African Americans, who have higher rates of glaucoma and of blindness due to glaucoma than the general U.S. population. There is also evidence for earlier onset of glaucoma among African Americans. A dominant hypothesis for these differences has been that African Americans tend to have a more aggressive form of the disease. However, the Advanced Glaucoma Intervention Study recently reported that, if other ocular characteristics were adequately controlled, being African American rather than European American was not a risk factor for predicting progression of visual field loss.

A fourth example relates to the role of gender in disease diversity. In studies of self-reported quality of life as an indicator of disease outcome, women were more likely than men of the same age to report difficulty in activities of daily living for a wide range of diseases, including ocular diseases. This disparity is supported by Dr. West's data from the Salisbury Eye Evaluation Project. A candidate hypothesis that women more readily admit to a difficulty for the same objectively measured disease condition (dubbed the "complainer hypothesis") has been disconfirmed by a study of male and female twins. The study found that the female twin of the pair tended to have more health conditions, more "somewhat life-threatening" cardiac conditions, and more psychological symptomatology compared to the male twin. However, there was no difference by gender in self-report of health status. A second hypothesis is that women have more co-morbidities or more severe symptoms. But in various stud-

ies of cardiovascular disease, mental illness, and HIV, the gender differences in self-reported quality of life remained after severity and other clinical variables were taken into account. A third hypothesis is that gender differences in sociocultural conditions are a factor. When investigators controlled for differences in working conditions and work stress, the gender differences in reports of pain severity disappeared. These data suggest that environmental conditions not directly related to having the disease or its severity affect the response. Another hypothesis relates the difference to the higher prevalence of depression in women. Depression is an important predictor of self-reported functional status and outcomes, and there are gender differences in prevalence and incidence of mental disorders. From this example, Dr. West emphasized the medical and public health importance of seeking to understand the factors underlying gender differences in disease outcomes, as well as the factors underlying ethnic and other cultural differences. Sorting out which factors are causally involved in gender differences, rather than just adjusting study results for gender, can lead to improvements in prevention and treatment, just as discovering the factors underlying other types of population diversity can increase the effectiveness of health care for the entire population. In formulating treatments and interventions, consideration must be given to all the underlying factors—personal, environmental, genetic, and cultural—tied to disease.

The discussion immediately following Dr. West's presentation began with a question on defining disease onset, which she agreed was an important consideration for this symposium. From an epidemiologic standpoint, how one defines onset depends not only on the disease but also on conditions that can feasibly be studied in a population. Although that generally means clinically observable manifestations, which manifestations to use as a uniform, interstudy definition of onset is an issue.

To a question on how to apply results from population studies to differential treatment of a disease, Dr. West replied that it depends on the particular results, but generally epidemiologic studies serve best when included in an iterative loop with complementary laboratory studies. Epidemiologic data are needed to understand differences in treatment outcomes; for example, are they due to access to treatment or to differ-

ence in severity? In clinical trials, population-based variations in disease characteristics anywhere along the disease process can trigger further investigations, population- or laboratory-based, to understand the underlying factors. On the related issue of how to use epidemiology to ascertain the best use of limited resources to focus on the most important problems, she agreed that epidemiology can and should address such questions. A population-based perspective on diseases that coexist in a population can allow the social costs and benefits of options for treating and not treating to be estimated and weighed.

Continuing on the topic of determining cost-benefit ratios, the participants discussed whether any nonsurgical treatment for cataract was likely to compete with the proven cost-effectiveness of surgical treatment. The principal issues, Dr. Paul Kaufman suggested, relate to providing access to effective, well-performed surgical treatment. Dr. West agreed that, from the perspective of clinical success in preventing blindness, cataract surgery has the value of virtually being a "magic bullet" solution. From the broader perspective of providing health care globally, access to this surgical solution and its effective delivery remain huge issues, as are the disparities in surgical outcomes in different countries. Given the effectiveness of cataract surgery, Dr. West said, if a preventive approach were known but involved constant attention and cost over an extended time, its justification from a public health perspective would be difficult.

On the topic of factors in diversity, a participant noted that the geographical location of a target population can be a surrogate for a wide range of underlying causal factors, including environmental and cultural factors as well as possibly genetic differences. In a genetically heterogeneous population, a deep understanding of the culture and even history of the region can be important in assessing whether geographically local differences in disease characteristics may in fact reflect underlying genotype differences.

The participants then turned to a main theme throughout the symposium: the importance of uniform disease definitions. They discussed at length whether the standard definitions for glaucoma, cataract, and incident age-related macular degeneration are adequate to allow comparisons across studies of different populations and groups. This topic

led to discussion of the difference between objective measures of disease-related signs and patients' subjective perception of functional loss. Dr. West emphasized the importance of recognizing, even in the practice pattern guidelines for physicians, that perceptions of functional loss from chronic diseases such as cataract can differ from objective measures of disease status. The participants agreed that wide disparities exist among patients in their perception of the quality-of-life decrement due to a visual impairment. Many patients also unconsciously adjust and compensate for impairment, as evidenced by the surprise expressed by many cataract surgery patients at how much better they can see after surgery and how much their vision had become impaired without their awareness of the loss.

Dr. West summarized the discussion by saying that there are multiple ways to view disease and treatment outcomes. External, objective measures of function are one way, but assessing the public health impact also requires the capability to relate those measures to how individuals assess treatment and functional deficit in terms of their quality of life. The issue of self-reporting validity relates to the longitudinal trajectory by which an incremental functional deficit becomes a real disability. If self-perception of the deficit can be improved, the trajectory toward a disability outcome may be stopped or slowed. For example, patients with elevated intraocular pressure or with diabetes can decrease their risk of visual impairment by improving their compliance with preventive regimens (e.g., eye drops for elevated intraocular pressure or maintaining near-normal blood sugar for diabetic patients). Even so, further work is needed to improve the relationship of objective measures of outcome to the quality-of-life impacts on patients.

Clinical Considerations: Lessons from China and the Far East

Dr. Robert D. Yee

Over the past three decades, Dr. Yee began, American clinical ophthalmologists have been encountering more diversity in ethnic backgrounds.

In his own practice, he now sees different diseases and different forms in which they present than he saw several decades ago. Many of these differences probably reflect the diversity in diets, access to medical care, and other nongenetic factors that are evident in the medical histories of patients coming to his practice from other parts of the United States. Across East and Southeast Asia, there are similarly large variations in prevalences and types of eye diseases from one location to another. Some of this variation probably does reflect differences in genetic factors, but Dr. Yee believes much of it reflects different socioeconomic factors among and within the countries of these parts of Asia.

He described a few of the many useful recent reviews on eye disease in the region, such as the review by Keeffe, Konyama, and Taylor of vision impairment in the Pacific region [7], the series of publications from the Singapore Epidemiology of Eye Diseases Centre, and Dr. Eugene Chan's works on the history of Chinese ophthalmology. From these sources, Dr. Yee has constructed an inverse relationship between the prevalence of visual impairment from eye diseases and the level of socioeconomic development. Differences in the major causes of visual impairment also tend to differ according to level of socioeconomic development. In the underdeveloped Asian-Pacific countries, in addition to cataract, corneal disease, and refractive error, many cases of visual impairment are related to trauma, infection, and poor nutrition. In the developing countries such as China, the dominant issue is access to health care. In the developed countries such as Japan, Taiwan, and Singapore, the predominant causes of visual impairment are similar to those in the developed countries of Europe and North America.

Dr. Yee used the history of eye disease and related public health measures in Japan and China to further illustrate how the dominant eye disease issues have changed over time, as societal and economic conditions changed. Prior to passage of the Trachoma Prevention Act in the early 1900s, the prevalence of trachoma in Japan was about 25 percent.[1] After the act was passed, trachoma prevalence fell to less than 10 percent

[1]Trachoma is a chronic, contagious inflammation of the conjunctiva caused by *Chlamydia trachomatis*. It remains endemic in Africa, India, and the Middle East and is also present in the southwestern United States.

by the 1920s. During World War II, with less attention to public health measures, the prevalence increased to 20 percent. After the war, with improved public health measures and medical treatment, trachoma essentially disappeared in Japan, and the Trachoma Prevention Act was repealed in 1983. The major causes of visual impairment in Japan now are similar to those in other industrialized countries: glaucoma, cataract, macular degeneration, and diabetic retinopathy. But there are also some differences, such as higher prevalences of severe myopia and degenerations of the optic nerve, retina, and choroid.

China also provides historical illustrations of the effect of socioeconomic development on eye disease. For 2,000 years, traditional Chinese medicine was based on balancing the forces of yin and yang through applications of the five recognized elements. Most of these treatments were systemic, but some were topical. In addition to acupuncture, ancient surgical procedures included cautery for corneal ulcers, surgery for pterygium, couching of cataracts, and enucleation. A major period of outside contacts began during the Tang Dynasty, around 700 CE (Christian Era). There is mention of the use of eyeglasses during the Song Dynasty (~960 CE). When contacts with the West began in the 19th century, Christian missionaries generally made the initial attempts to introduce Western medicine. These were largely unsuccessful because they were underfunded. In 1921, the Rockefeller Foundation established the Peking Union Medical College with a $45 million endowment. This highly successful effort aimed at improving medical education. It increased the level of research publication, resulted in substantial reforms in public health, and increased the role of medical teaching.

After this bright beginning, Chinese ophthalmology and public health care for eye diseases suffered setbacks from years of war, natural disasters, and increasing poverty, until the Communist Revolution in 1949. For the next 30 years, disease prevention was emphasized over therapeutic treatment. Progress was made in public health measures such as infant and maternal mortality rates, but the disparity between rural and urban health care access continued. Modernization of medical care was set back again by the Cultural Revolution in 1965.

In 1978, the Chinese leadership decided to pursue a socialist market economy in which developing expertise and modernization would be emphasized. Medical education was modernized, and the market for providing medical care was opened to overseas investors. Despite major improvements in health care institutions and technology, problems continue. The historical inequities between urban and rural areas persist. Medical care costs are increasing rapidly; the 19 percent annual growth in cost of medical care is more than six times the rate of national revenue growth. This history graphically demonstrates the impact of socioeconomic status and related factors on disease prevalence, even when the ethnic composition of a population is stable.

The challenges for ophthalmology in China today include an aging population in which the typical eye diseases of aging are becoming far more prevalent. Effective treatment for some conditions is available but expensive. Through information sources such as the Internet and expanded contacts with foreigners, Chinese patients are increasingly aware of advanced treatments, in terms of both therapeutic drugs and surgical procedures. Although highly trained ophthalmologists can provide these services in hospitals and clinics on a fee-for-service basis, the economic barrier to better care perpetuates the disparity in health care access between urban and rural Chinese. These historical illustrations demonstrate to Dr. Yee that U.S. or Western medical care solutions cannot simply be grafted onto the Chinese situation. The social, political, and economic factors of that situation differ from U.S. or European conditions, past and present.

Another implication is that U.S. researchers and clinical ophthalmologists will need an increased awareness of, and preparation for, ocular disorders that are more prevalent in undeveloped or developing countries. Ophthalmic disorders that may present in East and Southeast Asians include severe myopia with degeneration of the retina and choroid. Narrow angle and combined mechanism glaucomas are more prevalent in East Asians than in populations of European ancestry. For example, a study of hospitalized patients in Singapore found a prevalence of acute primary angle closure glaucoma of 12.2 per 100,000 population per year for Asians [8]. This prevalence was three times higher

than the rate in other ethnic groups in Singapore. Possible, but not demonstrated, associations with acute primary angle closure glaucoma include severe myopia, differences in angle anatomy, or even increased use of computers (near work) by Singapore East Asians. With regard to the latter hypothesis, a study in Japan found that myopia and the number of hours per day working on a computer was positively correlated with visual field changes associated with glaucoma. As American ophthalmologists see more and more patients from Southeast and East Asia, or Americans with ancestry from these regions, they must bear in mind that diseases will differ based on socioeconomic as well as genetic differences.

During the discussion after his presentation, Dr. Yee said that the substantial backlog in cataract treatment in China is predominantly among the rural population. It is one aspect of the broader problem of improving medical care delivery in the rural areas. Skilled physicians do not want to practice in rural areas, which lack the infrastructure and improved living conditions available in cities. In answer to a question on differences between Han and non-Han cultural groups in China, Dr. Yee agreed that this ethnic division is probably a factor in some disease disparities, but he believes the economic differences between urban and rural populations are probably a far greater factor at present. Several participants agreed with his emphasis on the importance of medical care cost in the current situation and elaborated on the evidence for its substantial impact on Chinese public health and quality-of-life issues.

In response to a question on implications for Americans of East or Southeast Asian ancestry, Dr. Yee said that studies investigating the factors responsible, for example, for the difference in prevalence rates for forms of glaucoma have not yet produced conclusive answers. It is still unclear why some Asian groups have a higher rate of angle closure glaucoma. Dr. de Jong said that a belt of increased prevalence of angle closure glaucoma extends from Singapore across China to Alaska. On a worldwide level, he added, angle closure glaucoma appears to be more prevalent than primary open angle glaucoma, the more common form in populations of predominantly European ancestry.

Worldwide Education and Training in the Detection and Treatment of Eye Disease

Dr. Bradley R. Straatsma

In his presentation, Dr. Straatsma emphasized the power of education to influence worldwide eye care. We first need to know the extent and causes of visual impairment worldwide and in the United States, he said, then we need to apply that knowledge to education of medical professionals and the public. The world today presents extraordinary challenges in a context of extraordinary global connectedness.

The human population is not distributed evenly: only 5 percent live in North America (table 2). While the genome for this global population of 6.1 billion is 99.9 percent the same, the disparities in environmental conditions and socioeconomic opportunity are immense. Half of the world's population, 3.1 billion people, live on less than $2 a day. A quarter never have clean water to drink, and one in three are hungry every day. According to the World Health Organization, 161 million people are visually impaired (20/60 or worse in their better eye with best correction), and 37 million of these are blind (20/400 or worse in their bet-

Table 2. World Population in 2000 by Region

Region	Population		Land Area
	Millions	Percent	Percent
Asia	3,683	61	33
Africa	784	13	22
Europe	729	12	7
Latin America, Caribbean	519	9	13
North America	310	5	18
Australia, Oceania	30	<1	6

Source: [9].

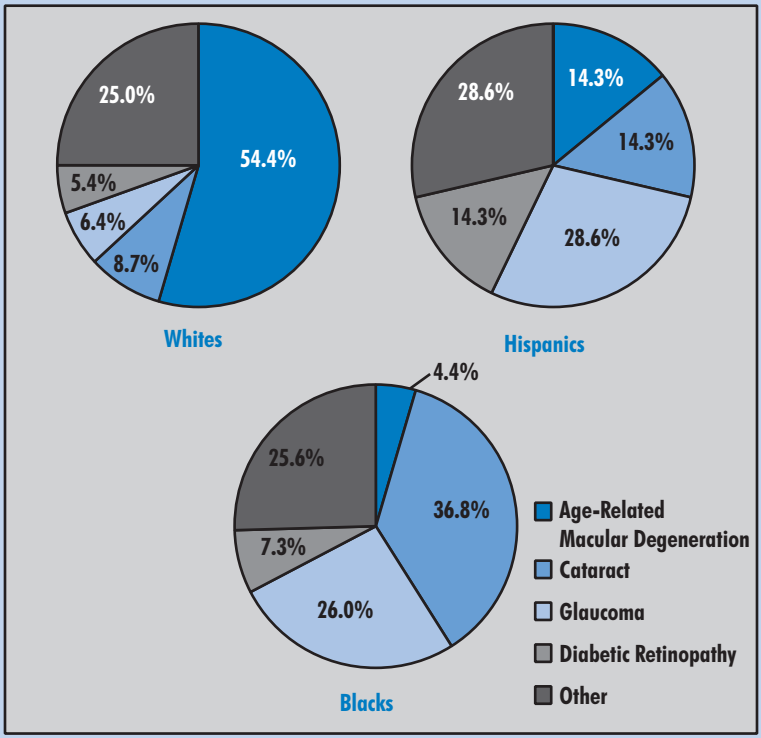
ter eye). Cataract still accounts for 48 percent of blindness, worldwide. Glaucoma is a distant second at 12 percent.

What relevance do these global eye health conditions have for the health of Americans? The United States is and will continue to be a nation of immigrants; its population is a microcosm of the world's ethnicities. Even for the three broad demographic categories of European Americans, African Americans, and Hispanic Americans, the leading cause of blindness differs among adults over 40 years of age (figure 2). Such differences indicate differences in risk factors for individual eye diseases among identifiable groups within the general population. Knowledge of these risk differences is needed to educate both medical professionals and the public. However, even the broad-based population data in figure 2 have limitations: children and young adults are not represented, impairment caused by refractive error is not included, and many of the 11 million U.S. residents who are undocumented are not represented.

During the past several decades, the amount of medical knowledge coming from biomedical applications of molecular genetics has increased enormously. Over the same period, rapid advances in medical technology have resulted from applications of physics, chemistry, and nanoscience, as well as from cell and molecular biology. For example, every child born today at the University of California, Los Angeles, Medical Center is screened at birth for 30 diseases, using a single drop of umbilical cord blood. The increasing diversity of the U.S. population, coupled with its increasing average age, will have continuing effects on societal well-being, including medical care delivery and public health issues. As one indicator of the amount of knowledge to be assimilated, the 16,000 professional journals in biology, technology, and social science now publish 1.2 million new articles a year. All of these changes are increasing the burden on both medical professionals and the general public to assimilate and apply this new knowledge.

Medical practice is among the areas feeling the stresses from this growth in fundamental scientific knowledge combined with a rapidly changing societal context. In Dr. Straatsma's view, medical education is changing at all levels—post-baccalaureate, resident physician, and practicing ophthalmologist—more dramatically, than at any time since

Figure 2. Blindness in U.S. Adults over 40 Years of Age



Note: Blindness is vision less than 20/200.

Source: **[98]**.

the Flexner report in 1910 completely reformed the medical education system. He described the increased amount of patient contact and diversity awareness, along with major curriculum realignments, that have occurred at the University of California, Los Angeles. Resident training is becoming even more intensive, with comprehensive tests to be passed in each of the three years. The American Academy of Ophthalmology course in basic and clinical science has grown from a single one-inch notebook in 1971–72 to 13 volumes comprising 5,000 pages of material on which residents are tested.

The forces changing U.S. medical education are also affecting medical education worldwide. The International Council of Ophthalmology has developed a medical student curriculum prepared by a multinational committee and evaluated in a number of countries. To the core content is added content specific to geographic regions and a mechanism for knowledge assessment. This curriculum is distributed via the Internet. Another multinational committee has developed a worldwide resident education curriculum. However, this basic training still must be adapted to the ethnicity, culture, and regional disease prevalences of different regions. The International Council of Ophthalmology also administers the Ophthalmology Knowledge Assessments as a worldwide system of specialty medical examinations. At the last administration of these examinations, 1,300 ophthalmologists participated at the various examination centers worldwide.

Within the United States, the medical profession is gradually but forcefully coming to recognize that certification at the end of a physician's initial training is not an adequate measure of continued proficiency throughout that individual's career. Since 1995, the American Board of Ophthalmology has been issuing certificates with a 10-year duration. To maintain certification beyond that time, a physician must undergo a rigorous evaluation process, which requires evidence of continued professional development. Worldwide, processes for continued professional development and evaluation are far more fragmented than in this country, with many national and specialty societies involved. A positive development is that Internet resources are providing increased access to the current scientific literature, even in the less-developed countries.

Another force for promoting a uniform, high standard of practice in ophthalmology is the distribution of eye and vision care guidelines for worldwide use. In the United States, the American Academy of Ophthalmology issues and updates preferred practice patterns. Analogous bodies in other developed countries issue similar guidelines for their practitioners. The International Council of Ophthalmology has placed eye and vision care guidelines for 19 conditions on its Internet site.

Public education on eye care is an essential component of prevention, early detection, and timely treatment of eye disease. The National

Eye Institute launched the National Eye Health Education Program (NEHEP) in 1991 to promote coordination, clarity, and accuracy of eye health information.[2] The NEHEP focuses on diseases for which early diagnosis and treatment offer substantial benefits. Another objective is to tailor messages to ethnic groups. More than 60 medical and nonmedical organizations interested in health care education now participate as partners in the NEHEP.

To address these many challenges and take fuller advantage of new scientific knowledge, Dr. Straatsma proposed the following actions to improve professional and public eye care education in the United States and worldwide:

- **Modify medical education to increase the component that addresses population-based public health education.** Even a relatively modest modification could increase the ability of physicians' groups to communicate effectively with government entities and officials. Better communication will increase physicians' influence on the design and implementation of national health and eye care systems and programs. Moreover, it would help to focus physicians' attention on prevention, early detection, and timely treatment of diseases.
- **Through professional training at all stages, further enhance the sensitivity of health care professionals to the diversity, of all kinds, in their patient population and improve their skills in communicating with a diverse patient population.** The increasing heterogeneity of the U.S. population requires even greater sensitivity to diversity from physicians and the concomitant communication skills. In this context, diversity pertains to factors such as age, gender, and language, as well as ethnocultural and socioeconomic diversity. Institutions need to be receptive to training individuals representing this population diversity.

[2]The description of NEHEP objectives in this section is from Dr. Straatsma's presentation. At present, "the focus of the NEHEP is on public and professional education programs that encourage early detection and timely treatment of glaucoma and diabetic eye disease and the appropriate treatment for low vision" (NEHEP Overview, www.nei.nih.gov/nehep/nehepov.asp).

- **Encourage evidence-based practice through adherence to eye and vision care guidelines that incorporate evidence-based results.** Adherence to evidence-based guidelines is likely to produce the best outcomes for patients, while also providing optimally effective use of resources.
- **Compensate medical and eye care professionals for their investment in their initial and continuing education.** Medical education receives relatively little direct support in the federal budget and little attention in the insurance reimbursement system. Health care consumes $5,500 per person per year in the United States, and the entire fiscal year 2006 budget of $28.6 billion proposed by President Bush for the National Institutes of Health (NIH) amounts to just $96 per person per year. However, there is no place in the budget for direct support to medical education. Rather than aid to medical schools and universities, Dr. Straatsma suggested that the cost of initial and continuing medical education to the practicing professional should be recognized in the compensation paid for service, similar to the way in which rent and equipment costs are included in overhead.
- **Upgrade public education on eye health and the prevention, early detection, and timely treatment of eye disease.** Health care messages to the public should be coordinated not only for eye health but across public health concerns. Systemic risk factors such as smoking, diet, and hypertension need to be addressed through a coordinated program covering the range of disease outcomes, rather than having multiple messages focusing on the risk for a single outcome. Accuracy and clarity need to be emphasized, as well as targeting messages to communicate effectively to diverse groups within a heterogeneous population.

At the conclusion of his presentation, Dr. Straatsma responded to a question on how society can pay for all the health care needed, whether within the United States or throughout the world. He suggested that society needs to provide a foundation of care, but not try to provide all medical care for everyone. The difference is up to the individual to provide, either through employer-based insurance or his or her own assets.

He favors a tiered system similar to that for elder care in Sweden. Government provides some support to the elderly. Private pension systems and insurance plans contribute part, and part comes from individuals' savings. The goal embedded in the U.S. Medicare system of trying to provide excellent medical care to everybody for every condition, he added, is unfortunately not sustainable.

In response to a question on the efficacy of addressing the disparity in worldwide health care delivery by training more foreign medical students and fellows in the United States, Dr. Straatsma discussed two issues: whether we are doing enough of such training and whether we are doing it sufficiently well. The approach of the International Council of Ophthalmology, which he cited as particularly successful, is to train teachers of ophthalmology in foreign countries through three-month fellowships at a medical teaching center in a developed country. To date, all of the 140 teachers who have participated in these fellowships have returned to their home countries. This program addresses the need for short, highly focused programs, in addition to other programs for the more extended two-year training of specialists. It could serve as a prototype for other programs that address disparities in health care.

As another example of successful training of foreign physicians, Dr. Yee mentioned the Orbis program in telemedicine, which pairs an ophthalmologist in a foreign country with a U.S.-based ophthalmologist. The paired physicians use the Internet to exchange information and advice on cases. Both participants in the pairing benefit. The U.S. physician gains experience with conditions that she or he might seldom see directly but which may prove relevant in treating an increasingly diverse patient population.

The symposium participants discussed barriers to effective education of foreign physicians visiting in the United States, particularly the restrictions many states impose on visiting foreign physicians participating directly in procedures on patients. Dr. Bird commented that the perception around the world is of increasing difficulty in acquiring training in the United States because of these barriers. He described the European system of temporary registration, with limitations, as an option. Dr. Straatsma added that acquiring a visa for training in the United States

has become increasingly difficult since the September 11, 2001, terrorist attacks. Dr. Kaufman agreed that the barriers are becoming higher at every level of education. In addition to regulatory barriers, funding for such training is increasingly problematic. Cross-training experiences that connect U.S.-based and foreign physicians will not happen on a significant scale, he said, without both regulatory changes and new sources of funding.

The participants also discussed the "brain drain" of young medical professionals from the developing world to the United States and other industrialized countries. Dr. de Jong described the recent practice by the Netherlands government of paying specialists industrial-country salaries to remain in practice in their home areas. To entice trained specialists to return, adequate medical facilities are needed in developing parts of the world to enable them to practice. Dr. Straatsma gave an example of the Carl Zeiss company starting a demonstration center in Nigeria, which will provide needed infrastructure and equipment for ophthalmology subspecialists to practice. Dr. West said that foreign physicians remark on the instrument-intensive nature of U.S. health care. When they return to their own countries, they face problems not only in acquiring the equipment but also with the expert maintenance necessary to keep it functioning. Dr. Straatsma noted that the demonstration center in Nigeria is training an equipment specialist to deal with that challenge.

With respect to the scale of the brain drain into the United States, Dr. Ryan commented that about 8,000 of the 24,000 interns who begin training here each year are graduates of foreign medical schools. About 8 percent of U.S. ophthalmologists received their medical degrees from foreign medical schools. Another education challenge, he said, is that the curriculum time given to ophthalmology for non-ophthalmologists varies greatly from school to school within the United States. When the curriculum undergoes change, the faculty members involved in defining the new curriculum play the major role in how the curriculum is structured. Two issues, then, are how much time is allotted to ophthalmologic training in the general curriculum and how medical students will learn about the opportunities in ophthalmology as a specialty. Dr. Straatsma added that one of the purposes of putting the basic ophthalmology cur-

riculum on the Internet was to support the argument that this content is what every physician needs to know, as a minimum standard.

Speaking from the perspective of public health education, Dr. Ronald Klein expressed concern about the inability of the health care delivery system to translate the increasing body of medical information into an effective level of care. In some American managed health care systems, a primary care physician must average no more than eight minutes per patient visit. The U.S. health care delivery system, he said, is effectively broken. Physicians can be taught the right things to do, but the delivery system does not allow them to practice that way. Dr. Klein then reiterated a point made by Dr. Straatsma, which became a recurring theme of this Drabkin Symposium. Beyond just the lack of medical insurance, an even larger problem is to remake the health care delivery system so that the available knowledge can be delivered effectively.

General Discussion on Session 1 Topics

Session 1 concluded with an open discussion of all the issues raised by the three presentations, focusing on those with broad significance to potential themes and conclusions of the symposium. Dr. Wong spoke of the importance of the "outbound" side of physician exchange initiatives. The prior discussion had focused on bringing foreign students and fellows to the United States to learn, but the spectrum of diseases here differs from that in other countries. As Dr. Yee noted, U.S. physicians will be seeing increasing numbers of patient conditions with which they are not familiar, such as polypoidal choroidal vasculopathy or angle closure glaucomas. To gain experience with these conditions, U.S.-based ophthalmologists will need to work in other countries, or at least partner with foreign-based ophthalmologists through telemedicine technology, to learn how ocular diseases present elsewhere. Dr. Chader agreed on the value of sending U.S. ophthalmologists to foreign countries to gain experience and training in diseases likely to be encountered in the growing minorities within the U.S. population. He proposed that this should be a major theme of the symposium. Dr. Straatsma extended this principle, suggesting that, as preparation to practice in a particular area, physicians

should learn how specific diseases present in that area's population and which diseases may be more prevalent there than elsewhere.

Dr. Bird noted that treatment of locally prevalent diseases in some developing countries may come from indigenous care providers who are not qualified as medical practitioners in the sense recognized by bodies such as the International Council of Ophthalmology. Examples include the health care delivered by nuns in Africa and in Mediterranean areas. As another example, Dr. Frank described the two types of ophthalmic paramedical personnel active in India. One type stays entirely in the medical centers and is trained to assist physicians in procedures and examinations. The second type serves as the primary caregiver in the community. This use of paramedical personnel for ophthalmic care varies from country to country, he said, depending on laws about medical practice. Dr. Bateman said that there are only 50 ophthalmologists in Haiti, where she recently visited, and only 25 are trained to do surgery.

Dr. Chader asked the participants for their views on major themes or issues arising from the session 1 presentations. An important theme he found relates to Dr. West's main points about differences between the customary observable characteristics of diversity and the underlying causal factors for diversity in ocular disease characteristics. That point raises two issues for improving health care and fighting these diseases. One is the challenge of getting to the underlying factors involved in the disease, which are reflected in the disparities in how the disease presents in a population. The second issue is getting to specific differences in treatment for these diseases, to reflect the reality of differences in the disease process for diverse segments within a general population.

Dr. West said that, in relation to current directions in research on diversity, NIH has recognized the importance of studying diseases of minorities within its organizational structure. Funding is allocated specifically for the study of diseases in minorities.[3] With respect to disparities

[3]An Office of Research on Minority Health was first established in 1990. The Health Revitalization Act of 1993 (Public Law 103-43) codified the Office of Research on Minority Health under the Office of the NIH Director. Ten years later, the Minority Health and Health Disparities Research and Education Act of 2000 (Public Law 106-525) established the National Center on Minority Health and Health Disparities as one of the permanent research centers within NIH. For further

in access and health care education for the public, she said, the symposium report should start by recognizing that NIH and Congress have at least seen the issues and allocated funds to address them. With respect to Dr. Chader's question, devising an approach for moving forward from that starting point should be a main objective of the symposium.

Dr. Kaufman formulated two distinct policy issues stemming from the disease disparities in a population. One question is how a nation with sufficient resources, like the United States, deals with the problems of disparity. A separate question is how the world deals with the global disparity in resources as it affects nations that lack adequate eye care. The session's discussions, he said, had raised both of these issues.

Dr. Wong saw the data on ethnic disparities as raising two issues: one of access to care and the other of the underlying etiology or pathogenesis of the disease. Addressing the second issue will require distinguishing the roles of genetic and environmental factors in disease etiology. In terms of understanding treatment effects in disparate groups, the ophthalmologic data on populations are too sparse to identify which disparities reflect differences in ancestry and which are environmental. For the near term—four to six years—he suggested that the epidemiology of ophthalmologic diseases focus on identifying differences in disease rates between groups of differing ancestry, to establish a basis for differences in clinical treatment.

Partly in response to Dr. Wong's suggestion, Dr. Ronald Klein noted that, for some health factors such as hypertension, differences in response to treatment between ethnic groups are well established. Examples are the differences in response to acetylcholine esterase inhibitors and diuretics. He expects that continued study of glaucoma and other ocular diseases in the U.S. population will establish ethnic differences in the response to medical treatments. Individual differences in response to medical agents will be investigated as part of the emerging field of pharmacogenetics. His principal concern was whether, for example, effective treatment for age-related macular degeneration will be affordable on a

information, see the center's website, http://ncmdh.nih.gov, and its organizational history at www.nih.gov/about/almanac/organization/NCMHD.htm.

societal scale. A question often raised is the ability of the economy to pay for such treatment and still pay for other highly cost-effective programs such as immunizations for infectious diseases of childhood. Current treatment disparities even within the United States raise the issue of tiered care that Dr. Straatsma had introduced in his presentation.

Dr. Campochiaro agreed with Dr. Klein's comment on the ability to document individual differences in treatment response using pharmacogenetics. The pharmaceutical companies are now collecting DNA samples from participants in clinical trials. What is still needed is the ability to link trial data to genetic profiles. Although much of the session's discussion focused on public health issues related to diversity, Dr. Campochiaro emphasized that a great deal can still be learned about disease pathogenesis from studying population diversity. In laboratory studies, genetic background is important even among rodent strains. Laboratory researchers learn much from doing the same experiment in different strains. An important objective for this symposium, he suggested, could be to show how studying the differences in populations can help in understanding the diseases. Dr. de Jong cited recent work on the different levels of cytochrome B in Europeans and Asians as an example of the potential application of pharmacogenetics to tracing differences in systemic levels of a medical agent in subjects receiving the same treatment (same dosage).

Dr. Chader closed the general discussion with the hope that the data on population differences will spur movement away from reliance on customary ethnic categories as the presumed phenotypes for ocular diseases and toward identifying the true genotypes involved in differing susceptibility to disease. Differential treatment of individuals should be based on true disease genotypes.

Session 2

Myopia

Quantifying Differences in Myopia Prevalence: Findings from the RESC

Dr. Leon B. Ellwein

Dr. Ellwein's presentation dealt primarily with the methodology and results from the Refractive Error Study in Children (RESC). This study has been supported by the National Eye Institute and administered through the World Health Organization (WHO). Dr. Ellwein began by describing the difficulties in comparing studies based on different criteria for myopia, different study methodologies, and selection biases. The WHO Refractive Error Working Group, after compiling and assessing 200 such studies, found that very little of the data are directly comparable. The advantage of the RESC, Dr. Ellwein emphasized, is that it provides completely comparable data on geographic and ethnic differences in children from multiple locations around the world. Its purpose is to assess the prevalence of visual impairment and refractive error in school-age children of different socioeconomic status, ethnicity, and cultural origins, using a uniform protocol and uniform examination methods.

The RESC examined population-based samples of children from 5 to 15 years of age at some locations and 7 to 15 years of age at others. For quality assurance, nearly 10 percent of the subjects were tested twice. Random cluster sampling, including door-to-door enumeration of children, was used to draw the study sample in each study location. Table 3

lists the eight completed study sites and three in which data collection is either ongoing or planned. At each site, the sample size was approximately 5,000. Dr. Ellwein noted the substantial challenges of the RESC, which required complete enumeration of children in the target age range in each area studied, achieving an adequate response rate (defined as all examinations completed), and measuring visual acuity reproducibly in young children.

Dr. Ellwein reviewed the RESC results for all locations, then focused on results for ethnic and age subgroups at several of the sites with particularly high prevalences of myopia. He presented prevalence data for visual impairment defined by two visual acuity cut points: the 20/40 cut point often used in the research literature and the 20/63 cut point used by WHO. Visual impairment data were analyzed on the basis of uncorrected vision, vision with existing refractive correction, and vision with the best possible refractive correction.

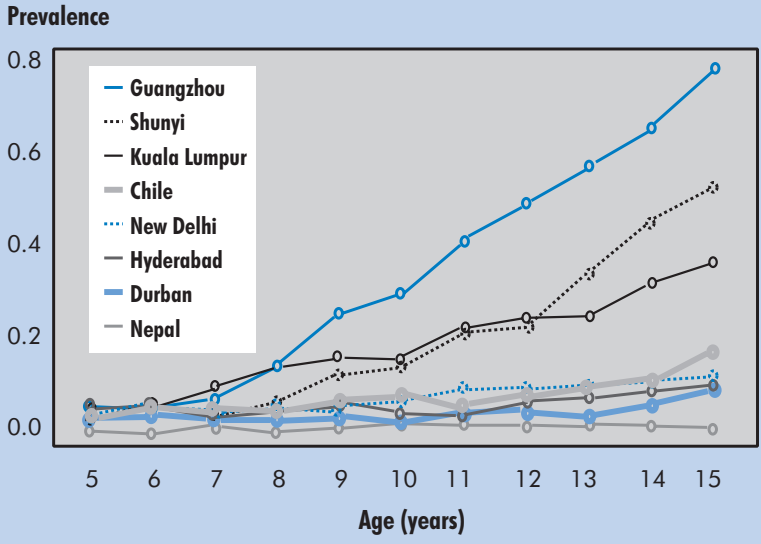
Dr. Ellwein presented results for the age-specific prevalence of myopia at each location, with myopia defined as spherical equivalent refractive error of -0.50 diopters or more. (In response to a later question, he

Table 3. Sites Involved in the RESC

Country	Location	Rural/Urban Status	Study Status
China	Shunyi District	Semi-rural	Completed
Nepal	Eastern area	Rural	Completed
Chile	Santiago area	Urban	Completed
India	Hyder abad area	Rural South	Completed
India	New Delhi area	Urban	Completed
South Africa	Durban area	Semi-urban	Completed
China	Guangzhou area	Urban	Completed
Malaysia	Kuala Lumpur area	Urban	Completed
Brazil	São Paulo area	Urban	In progress
China	Yangxi County	Rural South	In progress
South Africa	Johannesburg area	Urban	Planned

said that the RESC database allows easy computation of prevalences for any refractive error cut point.) The data show markedly higher prevalences of myopia for Guangzhou and Shunyi District in China and for Kuala Lumpur in Malaysia than for the other sites (figure 3). Whereas the Guangzhou and Shunyi study populations were entirely Chinese, the Kuala Lumpur population can be analyzed for subgroups of Chinese, Indian, or Malay ancestry. The Chinese children from the Kuala Lumpur study had substantially higher age-specific prevalences (e.g., 31 percent for 7 to 9 years of age) than either the Indian or Malay children (13 and 9 percent, respectively). These results qualitatively parallel those of a separate study of schoolchildren in Singapore, 7 to 9 years of age, in which the same three ethnic groups also occur in substantial numbers [10]. Moreover, the RESC results for urban Chinese children (Guangzhou) compared with rural Chinese (Shunyi District) and for urban Indian children (Kuala Lumpur and New Delhi) compared with their rural counterparts (Hyderabad) support a finding that an urban lifestyle

Figure 3. Myopia Prevalence by Age



Source: RESC database.

is a secondary risk factor for myopia. Dr. Ellwein believes that the higher rates of early, continuous school attendance and greater pressures on scholastic performance for the urban children are the cultural differences of causal significance.

The RESC results also allow analysis for prevalences of myopic children who (1) need correction and are appropriately corrected (with eyeglasses), (2) need correction and are undercorrected (eyeglass prescription incorrect), and (3) need correction and are uncorrected (without eyeglasses). A telling point from these data is that, at all locations, much of the refractive error is not being corrected, although it could be with proper eyeglasses. For Guangzhou, Dr. Ellwein summarized RESC data on the reasons why myopic children without eyeglasses did not have them. Both cultural and economic reasons were important for the group of parents who were aware of their child's need but had not purchased eyeglasses. This group accounted for half of the children without correction. The parents of the other half claimed to be unaware of their child's need.

In his summary, Dr. Ellwein said that the RESC results provide representation of populations from low and middle socioeconomic settings with diverse ethnic and cultural characteristics, including cultures ranging from rural to urban. Among these children, correctable refractive error accounts for essentially all of the visual impairment in the study groups. The prevalence of myopia ranged from 1 to 38 percent across the eight study sites—from 1 to 78 percent in children 15 years of age. Using the RESC ranges, one can extrapolate that roughly 115 million of the world's 1.4 billion children between the ages of 5 and 15 have visual acuity of $\leq$20/40 in both eyes because of refractive error. Children needing refractive correction represent a global public health problem, he emphasized, because more than half—roughly 60 million children—either lack corrective eyeglasses completely or do not have the appropriate prescription.

During the question period, the symposium participants asked Dr. Ellwein about the possible reasons for the disparities between rural and urban environments. As possible factors, he mentioned the later age for starting school, higher rates of illiteracy, lower rates of school attendance, and the decreased social pressure for scholastic performance in rural areas compared with urban environments. All of these factors

would decrease the amount of early childhood near work in the rural populations.

The participants also discussed at length how one could objectively establish a link between a given level of refractive error and visual impairment that resulted in a functional deficit, such as educational outcome (poorer performance in school). Dr. Wong said that Singapore is attempting to use performance on standardized tests to determine if scholastic performance is impaired. Other participants questioned whether all the potential systematic biases and confounders could be controlled (such as the counter-influence of parental and societal pressure for scholastic performance in the same environments with the highest levels of near work). Dr. Bateman noted that there are no data for the United States on the effect of uncorrected myopia on school performance. Part of the problem is the difficulty of establishing a control group, if that means the control children are denied the benefit of corrective eyeglasses for their myopia. Dr. Ellwein noted that some of the questions posed by the results, such as those raised by the participants, may only be answerable with longitudinal studies.

In response to a question on whether an association of myopia with near work at an early age has been established, Dr. Ellwein said that an association is clearly supported by pathophysiological evidence for an environmental trigger, as well as by the observed differences in groups of similar ancestry or origin but living in cultural settings with substantially different emphases on early schooling and scholastic achievement. The participants also discussed the linkage between more severe myopia and serious functional deficits from consequences such as retinal detachment or atrophy.

Pathophysiology of Myopia

Dr. Earl L. Smith, III

Dr. Smith discussed what is known about the pathogenesis of the more common forms of myopia such as juvenile onset myopia, particularly with respect to the role of visual experience in refractive development.

Many new ideas about the etiology of refractive error have emerged since the 1970s, and there is now general acceptance that both genetic and environmental factors influence refractive development. The evidence for genetic factors includes familial inheritance patterns, studies of monozygotic twins, ethnic differences in the prevalence of refractive errors, and the identification of candidate genes for forms of high (severe) myopia. The evidence for environmental influences includes epidemiologic studies of myopia prevalence and laboratory experiments on animals exposed to vision-restricted environments or to altered retinal imagery. Substantial debate continues on the relative weight of genetic versus environmental factors, but a widely accepted view is that the environmental factors act as a trigger for genesis of myopia on a background of genetic susceptibility. Dr. Smith summarized the evidence for the hypothesis that environmental feedback, primarily as optical defocus (i.e., the focal point falls in front of or behind the retina, rather than on it), regulates axial elongation of the growing eyeball. He then described what is known about the operational properties of the mechanisms involved in this feedback process and what is known about how the visual signals are transformed into biochemical signals for growth.

To set the context, Dr. Smith began with an overview of the normal process by which the newborn eye achieves emmetropia: the condition in which the eye at rest focuses parallel light rays on the retina. The broad distribution of refractive conditions in newborns, which is skewed toward hyperopia, or farsightedness, narrows over time, and most children are close to emmetropic by 4–6 years of age. The prevalence of refractive errors (myopia or hyperopia) in that age group is less than at any other age. For reasons not understood, refractive error—particularly myopia—increases after that, beginning in American children at around 8–10 years of age, earlier in Asian children. Dr. Smith's theme focused on the question, "Why does the emmetropization process begin to fail after age 6?"

For centuries, the onset of myopia has been linked temporally with the beginning of formal education. Despite decades of population-based studies, no conclusive case has been made for which factors associated with near work affect refractive development and how they influence it.

Recent laboratory work on animals has enabled the kinds of controlled experimentation that could not be done with humans. In particular, experiments with form deprivation myopia (FDM) in young primates show that visual experience of a clear retinal image is essential for normal refractive development. If a young animal is deprived of the experience of well-formed images (form deprivation), axial growth of the eye accelerates, resulting in myopia (the focal point for parallel light rays falls in front of the retina). This growth occurs largely in the area of the vitreous chamber, with little effect on the eye's main optical components: the cornea and crystalline lens. Structural changes that occur in the form-deprived eye are qualitatively and quantitatively very similar to the typical characteristics of the naturally myopic eye.

In lens compensation experiments, a lens is placed in front of the eye to artificially impose an optical error, i.e., to displace the focal point from the retina. Negative lenses, which shift the focal point behind the retina, cause the eye to elongate faster. Positive lenses, which shift the focal point in front of the retina, reduce axial growth. These results are strong evidence that the eye regulates growth through feedback from the visual experience associated with the position of the focal point relative to the retina (the eye's effective refractive status). If the added lens is removed while a test animal is still young, eye growth rates will adjust in the direction of emmetropia. The same phenomena observed in young animals occur in older animals, but to a lesser extent. However, once the cornea and crystalline lens have reached adult size, it is no longer possible to decrease the eye's optical power. Because the eye cannot shrink in size, any myopia induced after that age is permanent.

The responses to conditions like those created by FDM experiments occur in a wide range of animal species: fish, birds, and many mammals, including monkeys and humans. So the mechanisms involved in human axial growth are likely to be fundamental, from an evolutionary perspective. This similarity across animal species increases the likelihood that results from laboratory studies of animals are indeed relevant to understanding the pathogenesis of human myopia.

How might near work affect axial eye growth in humans? Myopic children accommodate (alter the curvature of the crystalline lens by

contraction of the ciliary muscle) significantly less well to near visual targets than do emmetropic children. The most common hypothesis holds that, if the natural accommodative response of the lens is inadequate to produce optimum focus when concentrating on near targets, the eye responds to the resulting defocus signal by increasing the axial growth rate of the vitreous chamber. For the natural emmetropization process, this hypothesis implies that correcting for myopia or hyperopia should prevent newborn emmetropization. The data from animal experiments confirming this implication are extensive and unequivocal. Unfortunately, the results from tests of the hypothesis in humans are at best uncertain. If this hypothesis is correct, an effective intervention strategy should be to undercorrect myopic refractive errors or to have myopia-prone children use bifocal lenses. Use of progressive lenses by such children does produce some improvement, but the effect is small. However, Chung, Mohidin, and O'Leary found that undercorrecting adolescent myopia increased myopic progression rather than decreasing it **[11]**. Atkinson and colleagues found that partially correcting high hyperopia (+4 to +5 diopters) in infants led to an initial decrease in the rate of emmetropization, but by age 3 the refractive errors were not significantly different between the untreated control groups and infants who wore corrective lenses—about +3 diopters for both **[12]**. The simple hypothesis is thus neither proven nor refuted; nor is it sufficient to account for the experimental facts.

Dr. Smith argued that the reason for this disparity is that the *operational properties* of the mechanism that mediates the effects of visual experience on eye growth are more complex than the simple hypothesis—or study designs based on it—assume. In most human studies, the visual stimuli are inadequately characterized, and the hypotheses on which predictions are based are too simple. Among the important operational properties are those involved in both the temporal and spatial integration of the visual signals that influence axial growth. Normal visual experience includes periods of hyperopic focus, myopic focus, and in-focus vision. How the signals from these disparate periods of focus are integrated over time determines how the eye will grow. This temporal integration mechanism is nonlinear with respect to how durations of

focused and defocused vision are weighted. If experimental animals fitted with form deprivation lenses are allowed even a brief period of normal visual experience during a 12-hour light cycle, the resulting myopia is greatly reduced. Animals that wear the form deprivation lenses constantly for the full duration of each 12-hour light cycle averaged -5 diopters of myopia. A single hour of normal visual experience out of the 12 hours reduces the FDM by 65 percent. At 4 hours of normal vision, the test animals have effectively the same refractive error as untreated controls. Thus, the integration mechanism appears to weight the durations of focused vision more heavily than those of unfocused vision.

In another lens compensation experiment, monkeys wore negative-powered treatment lenses that normally cause the eye to grow long and become myopic. If, however, the treatment lenses were removed for just four 14-minute periods distributed through the 12-hour light cycle, the refractive error in the test group ranged from myopic to hyperopic, but the mean refractive error for the test group was indistinguishable from the mean for controls reared with unrestricted vision. Overall, these studies indicate that the time-integrating mechanism gives less weight to periods of visual experience that would cause the eye to grow than it does to periods where the feedback signal would decrease growth. This complexity helps explain the difficulty in quantifying the relationship between near work and myopia in humans. To produce myopia consistently in a range of individuals, the stimulus from visual experience would have to be nearly constant over time.

Another operational property that has probably confounded studies of the effects of visual experience in humans is the manner in which the visual signals for eye growth are integrated across the retina. Because resolution acuity is most acute at the fovea and decreases rapidly with eccentricity, central vision was thought to dominate refractive development. Thus, most studies of humans have assumed that vision-dependent eye growth is dominated by visual experience (focus versus defocus) in the region of central vision—at the fovea. However, several lines of evidence now call this assumption into question. First, the high acuity typical of the primate fovea is not essential for emmetropization of newborns in other mammals. Second, detection acuity, which is high in the

peripheral retina, is strongly influenced by defocus. Third, in the clinical literature, diseases of the peripheral retina are frequently associated with refractive errors. Fourth, refractive error varies with eccentricity of the eye. Myopic individuals typically exhibit relative hyperopia in the periphery, whereas hyperopic individuals show relative myopia in the periphery. The visual signal from the fovea may therefore not be representative of the signal across the entire visual field. How the effects of visual experience from across the entire retina are integrated into the signal for growth of the eye is probably a major factor determining eye growth.

Recent FDM studies further show that the peripheral visual field does significantly influence eye growth, whereas the fovea is less critical than previously assumed. When monkeys were fitted with diffusers that created form deprivation in the peripheral retina but retained normal vision in the central region, the treated animals were statistically more myopic than controls with unrestricted vision. Moreover, the fovea is not essential for the recovery from induced refractive errors. Normally, if the lens creating this peripheral form deprivation is removed, the growth rate of the vitreous chamber decreases and the refractive error decreases to the emmetropic range. However, if the fovea of one eye is ablated by a laser at the time the form deprivation lenses are removed, both eyes (normal fovea and ablated fovea) track on the same path to normal focus.

All of these lines of evidence counter the assumption that the visual experience at the fovea dominates—or is even necessary for—normal emmetropization in the primate eye. Thus, human studies need to assess the visual experience across the entire visual field and may need to pay particular attention to the refractive error in the periphery.

Dr. Smith next discussed what is known about how this visual signal for focus or defocus is transformed into biochemical signals regulating axial growth of the vitreous chamber. Because FDM treatment produces a consistent, robust, effect on eye growth, experiments can use it to test whether a candidate element in the signal system is in fact involved. When that factor is removed or altered, is the myopic progression that would otherwise result from form deprivation reduced or altered? In other words, what components of the visual system are required for FDM to occur?

The surprising result of these experiments, Dr. Smith said, was how much could be removed from the visual system without interfering with the usual myopic result produced by form deprivation. The experiments have shown that the visual signal for axial growth does not have to leave the eye. Neither ablation of brain areas required for perceptual experience nor severing the optic nerve interferes with the expected progression of FDM. Neither does altering or blocking inputs to the eye from sympathetic or parasympathetic efferent nerves. By contrast, selectively depriving a portion of the eye restricts the axial elongation of FDM to just the portion of the sclera adjacent to the deprived areas **[13, 14]**. Thus, the mechanisms mediating the visual signal for eye growth appear to be local—they occur entirely within the eye. At present, the following characteristics of the signal system are consistent with the totality of experimental findings:

1. Ocular growth is regulated by retinal responses to the optical image at the retina. The visual stimulus is defocus.
2. The signals from the retina go through the retinal pigment epithelium and across the choroid. In the sclera, they cause active remodeling (structural degradation that modulates growth) of scleral tissue.
3. These structural changes in the sclera allow the eye to elongate.
4. The anterior chamber is relatively passive in this process. The cornea and lens are not involved in the signal pathway. Accommodation indirectly influences growth because it affects the location of the focal point relative to the retina. But the act of accommodation (e.g., feedback from the ciliary muscle) does not directly mediate the growth signal.

Dr. Smith also noted some of the specific biochemical receptor sites and signal molecules that appear to have a role in the signal cascade from the retina to the sclera. Although still sketchy, this emerging picture of the biochemical pathway already has shed light on some clinical results. For example, topically administered atropine is known to slow myopic progression in children. This treatment strategy originated from the hypothesis that the act of accommodation was directly involved in

the signal that stimulates axial growth. The recent work on receptor sites in the retina-to-sclera signal pathway indicates that the atropine interferes with one of the receptors in this signal cascade, rather than acting through atropine's cycloplegic effect on the ciliary muscle. Many details about the signal cascade, such as how it traverses the retinal pigment epithelium, are not yet known. With respect to what happens in the choroid, there is good evidence that choroidal retinoic acid is a signal molecule. Other data suggest that changes in choroid thickness move the adjacent portion of the retina toward the position of optical focus. Some evidence from a chick animal model suggests that particular growth factors are involved in the scleral response. Dr. Smith outlined how changes in synthesis and degradation rates for structural components of the sclera could cause loss of scleral tissue and structural remodeling, which allows the eye to grow.

Dr. Smith cautioned that other factors in addition to these local retinal mechanisms can affect refractive development and myopia in humans. For example, manipulation in one eye results in growth changes in the other eye, so interocular effects must be considered. Amblyopia and strabismus appear to interfere with the processes that maintain emmetropia, although the mechanisms of these effects are unknown. There are also other major unanswered questions. For instance, no hypotheses on how the eye determines the sign of optical defocus (hyperopic or myopic) have yet been experimentally confirmed. Nevertheless, the evolution in knowledge about myopia pathogenesis since 1970 is helping to shape potential intervention strategies. One such strategy would be to prescribe corrective lenses for peripheral refractive error, not just central refractive error. Because the optical surfaces of the primary components of the visual system—crystalline lens and retina—are aspheric, myopic eyes may be producing a significant defocus signal integrated across the visual field, regardless of the refractive state at the fovea.

After his presentation, Dr. Smith responded to questions on the age at which the eye normally stops growing and the implications for successful intervention to correct a myopic condition. In monkeys, after the initial period of relatively rapid newborn emmetropization, the process continues at a more gradual rate until 4–5 years of age, which corre-

sponds roughly with human adolescence. Based on his experience, Dr. Smith believes the magnitude of response to a change in the visual signal for eye growth declines with age, but primates appear to retain some sensitivity to FDM well into early adult life. Continued response to refractive status through early adult life has been demonstrated in other animals as well. In humans, the process apparently does not end in the early teens. One hypothesis is that these visual feedback mechanisms may continue to have a role in maintaining balance between the two eyes.

Clinical Management of Myopia: Present and into the Future

Dr. Tien Y. Wong

Dr. Wong discussed current treatment and clinical management options for progressive myopia, as well as the prospects for new strategies emerging from population-based and laboratory research. He concluded with an exploration of the public health rationale for attempting to halt or retard myopic progression. This last point is important, he emphasized, because the public health impact of myopia on a population of adults and children is not as well documented as are the consequences of diseases such as glaucoma, age-related macular degeneration, or diabetic retinopathy.

In 2002, Saw and colleagues reviewed the efficacy of current treatment options found in randomized clinical trials [15]. That review, and Dr. Wong's update through mid-2005 for this symposium, compared the mean difference from controls of the myopic progression rates for groups treated with bifocal or multifocal lenses, soft contact lenses, or pharmaceutical agents. Pharmaceutical agents that have been used in these trials include topically administered atropine, pirenzepine, adrenergic agents, and beta-blocking agents. The proposed mechanisms for treatments with corrective lenses are reduction of accommodative effort and improvement of image focus on the retina. The mechanism suggested for the adrenergic or beta-blocking drugs was reduction of intraocular pressure. For the muscarinic antagonists atropine and pirenzepine, the original hypothesis of reduced accommodative effort through the drugs'

cycloplegic effect has been supplanted by explanations favoring direct effects on scleral growth, as described by Dr. Smith. Systemic effects have also been hypothesized.

Of the five clinical trials of bifocal lenses for which results were published as of 2001, only one found a statistically significant difference in rate of myopic progression between the treatment group that wore bifocal lenses and the control group with single-value lenses. The 0.1 diopter of difference found in this study is not, in Dr. Wong's opinion, of clinical significance. The single clinical trial of soft contact lenses showed no advantage over single-value lenses. Five trials of progressive addition lenses versus single-value lenses, including two done after 2002, suggest a limited treatment effect in the range of 0.2 to 0.3 diopters. Although the reduction in myopic progression was statistically significant, the improvement was too small to justify recommending progressive lenses as a treatment for myopic progression **[15]**.

A study of undercorrection for central refractive error found that the rate of progression was enhanced, rather than inhibited, as had been proposed **[11]**. In another study, rigid, gas-permeable contact lenses were found to be no better than single-value conventional lenses for retarding myopic progression.

By contrast, three studies from 1989 through 2000 of topically applied atropine found a statistically significant and larger effect in slowing progression, compared with a normal saline placebo in the fellow eye. There was nearly a 1 diopter per year average reduction in myopic progression during the treatment period **[15]**. The recent Atropine in the Treatment of Myopia study has confirmed a substantial effect of atropine (1–1.5 diopters per year) in decreasing myopic progression, at least for the two treatment years **[16]**. Two studies since 2002 on pirenzepine drops—a muscarinic agent chosen to lessen the side effects from atropine treatment—found a statistically significant treatment effect **[17, 18]**. However, treated eyes averaged only about 0.3 diopters per year better than the control eyes.

Both the pathophysiological and clinical trial evidence, Dr. Wong said, confirms that atropine treatment retards myopia progression. However, when treatment is halted, a growth spurt occurs in axial length of

the previously treated eye, and the refractive error increases to nearly that of the untreated eye. The benefits are thus short term rather than persistent. Also, the side effects of long-term atropine administration are unknown and may include systemic effects. For current options other than atropine, the treatment effect is small at best. Furthermore, some of the treatment options are difficult to administer, and compliance issues are substantial [19].

Future treatment strategies, Dr. Wong suggested, should be evaluated from two clinical perspectives: their potential value for children at high risk of rapid progression myopia and their value for adults with late-onset progressive myopia. Studies of the risk factors for rapid progression, particularly in children, are needed to identify high-risk groups for treatment and to identify modifiable risk factors [20]. Dr. Wong added that, so far, the search for modifiable risk factors has been disappointing. All the risk factors reasonably well established at present only account for about 11 percent of the prevalence. To identify and learn how to manage environmental risk factors, he advocated the use of community-based randomized control trials. Community-based trials are valuable for studying intermediate factors (e.g., indoor environment, near-work activity) and even distal factors, rather than focusing on the proximate factors that are directly involved in the pathophysiology of myopic progression. Examples of possible distal factors include urbanization and a cultural emphasis on meritocracy, if it places a high priority on early scholastic performance [21]. Another important objective for such studies should be to learn about interactions among risk factors, such as children whose parents both have myopia and who are in cultural settings exposing them to substantial periods of near work at a young age.

With respect to randomized clinical trials that target childhood myopia, Dr. Wong recommended that such trials examine broader aspects of ocular structure and function than just refractive error and axial length. For example, is the treatment associated with visual field changes? Second, trials to date have not yet thoroughly studied the potential ocular morbidity, such as myopic macular degeneration and retinal detachment, associated with higher levels of myopia. Prevention of the irreversible visual impairment associated with these outcomes should be a guiding

objective for research and testing related to myopic progression. Third, attention in clinical trials to ethnic and other subgroup variations in treatment effects is important for differential treatment of subgroups with differing risk factors and for research insights to complement the findings from laboratory-based experiments. With respect to testing emerging strategies for mild to moderate myopia, Dr. Wong cited recent findings that perceptual learning techniques, which combine visual stimulation with facilitation of neural connections, may help individuals with low myopia (up to -1.5 diopters) improve their visual acuity and contrast sensitivity [22].

For treating progressive late-onset myopia in adults, Dr. Wong said that population-based studies are needed to determine how serious such myopia is as a public health problem and which population subgroups are at increased risk. In addition to seeking ways to retard progression in late-onset myopia, a better understanding is needed of adult morbidity consequent on high myopia, such as choroidal neovascularization (CNV), retinal detachment, and myopic maculopathy not related to CNV.

The last segment of Dr. Wong's presentation returned to the rationale for further research on ways to prevent or retard progressive childhood myopia. Already, fairly drastic treatments for young children, such as contact lenses or cholinergic inhibitors, have been attempted without adequate understanding of the pathophysiology of myopia. Should such treatments be attempted as a public health measure, given the controversies about whether prevalence and severity of myopia are increasing? Good evidence exists of increasing prevalence in East Asian children and adults [23], but there are not yet good data, for either children or adults, on Americans of East Asian ancestry.

The concern that myopia prevalence is increasing can best be addressed by studying a comparable population for several time periods using the same methods and definitions. Three lines of evidence that Dr. Wong views as meeting this criterion derive from the Beaver Dam Eye Study [24], from studies of Taiwanese schoolchildren [25], and from studies of schoolchildren and military enlistees in Singapore [26, 27]. For three successive five-year cohorts, the Beaver Dam Eye Study found

that refractive status at 55–59 years of age changed from +0.2 diopters in the oldest cohort to -0.13 and -0.5 diopters in the middle and youngest cohorts, respectively. With respect to ocular morbidity in association with myopia, the Blue Mountains Eye Study found that best corrected visual acuity decreased with severity of myopic refractive error, particularly for myopia higher than 3 diopters. Myopia was a predictor for visual impairment after five years (odds ratio = 1.26) and for blindness (odds ratio = 1.20). This study also found associations of severe myopia with myopic maculopathy [28], posterior subcapsular cataract [29], and primary open angle glaucoma [30].

As to whether a "myopia epidemic" is occurring and whether the consequences are a major public health concern, Dr. Wong said that the observed increases in prevalence of progressive myopia must be better understood. In particular, the potential impact on visual function of ocular morbidity associated with progressive myopia must be assessed. From a public health perspective of dealing with serious visual impairment and blindness, one should distinguish between low to moderate myopia (refractive error less than -6 diopters) and more severe myopia. However, even mild myopia has positive associations with cataract and glaucoma [31, 32]. Another question that population-based studies can address is whether the increasing prevalence and severity of myopia that have been observed in some East Asian groups are also occurring among Americans of East Asian ancestry or other identifiable high-risk groups within the U.S. population. Well-designed studies in this area could contribute to sorting out the relative contributions of genetic and environmental factors. Overall, Dr. Wong concluded, more-comprehensive approaches are needed, including long-term prospective studies and community-based trials to explore nonproximate environmental risk factors.

General Discussion on Myopia

The first topic raised during the session 2 general discussion was whether use of the term "myopia epidemic" was warranted. There was agreement on the need for research to follow the observed anomalies in prevalence

over time, in order to ascertain the rates of change in prevalence and severity over a relatively long period. Methods of studying the kinds of nonproximate factors Dr. Wong and Dr. Ellwein had suggested were raised and discussed, with general agreement on their usefulness.

In response to a question about variability in measuring refractive error in population-based trials, Dr. Smith said that retest differences are on the order of 0.37 diopters. Dr. Wong noted that variations of 0.5 diopters are common even in same-day measurements and appear to reflect the eye's accommodative status in response to just-prior visual experience, as much as measurement uncertainty. He considers a treatment effect of less than 0.5 diopters to be small. Dr. Smith added that some of the reported treatment differences are statistically significant for the large numbers analyzed, but they are not clinically significant with respect to preferring one treatment over another or over the control.

The participants discussed potential compliance effects in the studies cited. Dr. Wong described objective measures of compliance, based on pupil size, that were used in the Atropine in the Treatment of Myopia study. There was agreement that compliance issues will require further study.

A major topic of discussion was the point at which myopia becomes a functional impairment (or a major risk factor for future serious visual impairment). The consensus was that refractive error at or greater than -6 diopters is the major concern from this standpoint. Dr. Smith suggested that axial elongation, rather than the refractive error that is a more easily measured surrogate for elongation, may be the condition that correlates more strongly with serious ocular morbidity. Methods are now available for determining axial length accurately in a population screening context.

Dr. Smith was asked for his opinion on why the human subjects in the Asian studies of children do not show a recovery response with corrective lenses, which his experiments with monkeys show after FDM lenses are removed. The local retinal mechanisms determining the axial growth signal, he replied, may not be determined by refractive error at the fovea, which is what "correction" in human studies has typically meant. Corrected myopia may continue to progress because the signal to

slow down growth from the central area, which is in refractive focus, is overridden by the signal from the peripheral retina to increase growth. The eye may grow until there is balance in the integrated signal. Better approaches may be needed, such as annular progressive lenses, to achieve an optimal correction for the objective of controlling the growth signal.

The participants discussed the status of information on the genetic basis for myopia. Dr. Bateman mentioned that three or four gene loci have been identified for rare forms of high myopia (-20 to -30 diopters in some forms) with high familial association. For more common forms of myopia, the participants agreed that many components of the visual system might be subject to genetic variations that could alter susceptibility to particular environmental factors such as early near work. In response to a question on the evidence for genetic differences between groups of East Asian and European ancestry in myopia prevalence and progression rates, the discussion centered on the difficulty of separating the relative influences of genetic factors and environmental factors on the higher prevalences of myopia observed in children of Chinese ancestry. The participants agreed that this was a fertile area for further research in which groups carefully selected for ancestry and relevant environmental factors would need to be compared using standardized definitions and protocols.

In response to a question on negative effects of atropine treatment, Dr. Smith described results of studies on kittens in which apparently permanent changes in response to cholinergic blocking agents result from atropine treatment. However, species differences could be important here, and the participants agreed that there was insufficient work on long-term effects or on separation of the cycloplegic effects from effects on the retina-to-sclera signal cascade. Dr. Smith emphasized that the research on the signal cascade is still in its early stages, with much still to be done in identifying the pieces of the mechanism and understanding how the whole process works. In response to a question on pirenzepine, Dr. Smith said that results from ongoing clinical trials indicate that pirenzepine can slow the progression of myopia. The studies on atropine and pirenzepine at least establish the proof of principle that a topically applied agent can affect myopic progression. Whether these are agents one would decide to use clinically is another issue.

Session 3

Glaucoma

Epidemiology of Glaucoma

Dr. Barbara Eden Kobrin Klein

As an opening comment on the symposium's theme, Dr. Barbara Klein noted that ethnic diversity becomes a source of public health issues within countries, as well as among countries. Ethnic diversity has been an issue for immunizations in urban areas such as Miami, Florida, and for health care for migrant workers, who have a variety of ethnic backgrounds. Ethnic differences were also an issue for a study of cardiovascular disease risk factors in the Miami area. The questions being addressed at this symposium are thus significant for a much broader range of public health and health care delivery problems than just those related to major eye diseases.

Worldwide, glaucoma is thought to be the second leading cause of visual impairment. Among its many forms are primary open angle glaucoma (POAG), primary angle closure (acute and chronic) glaucomas, pigmentary glaucomas, normal tension glaucoma, pseudo-exfoliative glaucoma, congenital glaucomas, and secondary glaucomas.

POAG, the most common form, is estimated to be responsible for more than 10 percent of blindness worldwide. It is also the form for which we have the most data. The three characteristics that are typically used to identify POAG in epidemiologic studies are (1) damage to the optic disc (the location where the axons of the ganglion cells exit

the retina), which signifies defects in the retinal ganglion cells; (2) functional changes manifested by changes in the visual field; and (3) elevated intraocular pressure (IOP). Dr. Klein illustrated and commented on current clinical methods for evaluating the optic disc, particularly for the cupped appearance typical of POAG. As in myopia and age-related macular degeneration, difficulties in comparing population-based studies of glaucoma arise from the variations among studies in diagnostic criteria for abnormality of the optic disc. Similarly, the modalities for visual field testing vary. Interpretation of visual field abnormalities varies among testing centers and even from technician to technician within a center. Overall, Dr. Klein said, the diagnostic criteria for a visual field defect indicating glaucoma are "up for grabs." Although elevated IOP is not strictly appropriate as a definition of glaucoma, it has long been used in clinical diagnosis. It has also been used as a screening parameter in some epidemiologic studies because it is the strongest risk factor for damage to the optic nerve head and it is easy to measure.

For her detailed comments on glaucoma epidemiology, Dr. Klein drew primarily on data from the Eye Diseases Prevalence Research Group,[1] as reported in *Vision Problems in the U.S.* **[6]**. Each of the eight studies that provided data for that report used standardized protocols and had similar distributions by age and by gender. Even so, the diagnostic criteria were not uniform across the eight studies. The results are further limited by inadequate representation, among the more than 37,000 participants, of persons of African or Asian ancestry and of Native Americans. The data on Hispanic Americans come from just one study and reflect primarily Americans of Mexican ancestry. The variations among the studies in diagnostic criteria for glaucoma illustrate the difficulty in comparing across studies, even when considerable effort has gone into coordination.

In her glaucoma prevalence estimates for people of African descent, Dr. Klein combined results from two of these eight studies—the Baltimore Eye Survey and the Barbados Eye Studies—plus a separate population study in Tanzania. The prevalence rates for people of European

[1]The participating studies and resource centers are listed at www.nei.nih.gov/eyedata/pbd_studygroup.asp.

ancestry come from five of the eight studies and include locations in North America, Europe, and Australia. Dr. Klein noted that, to the extent that geographic location (or factors related to it, such as cultural and environmental conditions) may influence prevalence, the pooled results may not be indicative of glaucoma prevalence for regional ethnic subgroups within the United States.

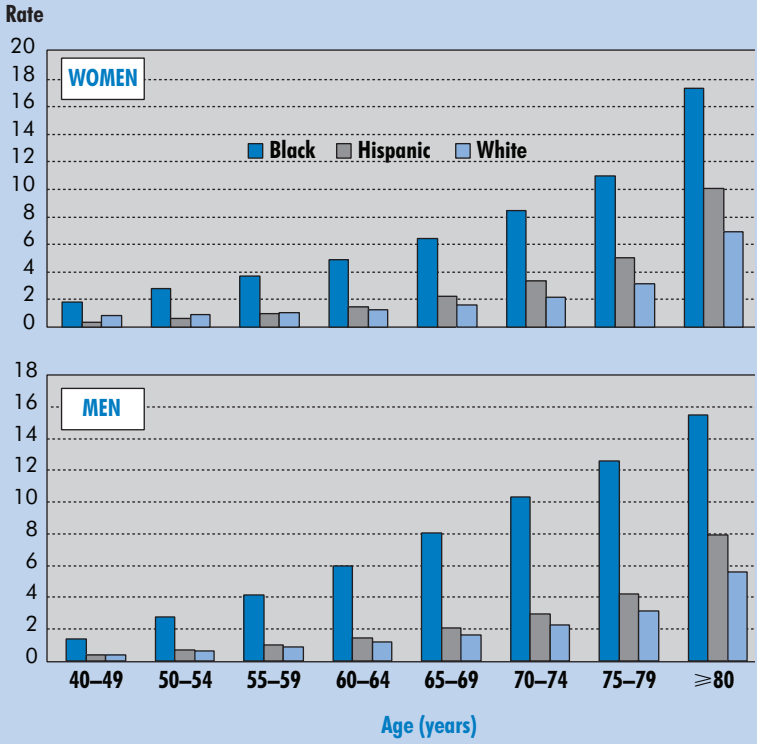
For both women and men, POAG prevalence increases with age. For each age group, the prevalence for those of African ancestry exceeds the prevalence for those of Hispanic or European ancestry (figure 4). For the Hispanic American group studied, there also appears to be higher risk for POAG, particularly in the older age groups. Earlier studies, which were of populations of predominantly European descent, found that prevalence increased with age and that gender differences were small or insignificant. While the prevalence was less than 1 percent for ages up to 60, POAG increased in these populations to 3–4 percent for ages above 75.

A separate study of a Hispanic American population, the Los Angeles Latino Eye Study, has found prevalence rates for POAG nearly twice those found by the Proyecto Ver, Arizona, study reported in *Vision Problems in the U.S.* Among the possible causes for this disparity, Dr. Klein said, were artifacts of study methodology and implementation, such as case definition and response bias, as well as real differences in environmental and genetic factors between these two Hispanic American groups.

In 2002, the 37.4 million Americans of Hispanic ancestry had the origins listed in table 3. Dr. Klein used the data shown in figure 1 (p. 13) to illustrate the gene pool diversity within the broad, culturally defined demographic category of "Hispanics." She also summarized the socioeconomic heterogeneity among Hispanic Americans.[2] The available glaucoma prevalence data for Hispanic Americans are derived from populations of primarily Mexican ancestry. Given that Americans of Mexican origin constitute only two-thirds of all Hispanic Americans, more data are needed on the 12.4 million who originated elsewhere and may be at even higher risk for glaucoma.

[2]Recent socioeconomic data on Hispanic Americans are available in U.S. Census Bureau publications such as **[33]**.

Figure 4. Prevalence of Open Angle Glaucoma by Sex, Age, and Race/Ethnicity



Source: **[6]**.

Of the recognized risk factors for open angle glaucoma other than ethnicity and age, Dr. Klein discussed diabetes mellitus, elevated blood pressure, and ocular characteristics other than elevated IOP. Persons with type 1 and type 2 diabetes have increased risk for glaucoma. One hypothesis is that diabetes may increase susceptibility of the optic nerve to damage initiated by elevated IOP. Another hypothesis is that diabetes contributes to elevated IOP, and there is evidence of an association of diabetes with increased IOP. Whatever the mechanism, the increased risk for diabetes for people of Native American ancestry may contribute

Table 4. Origins of Hispanic Americans, 2002

Origin	Percentage
Mexico	66.9
Central and South America	14.3
Puerto Rico	8.6
Cuba	3.7
Other	6.5

Source: [33].

to an increased risk for glaucoma for them and for those Hispanic Americans with substantial Native American ancestry. An association of open angle glaucoma with hypertension has been found in some studies but not all. Because hypertension correlates with increased IOP, IOP may again be the mechanism underlying this association. Other ocular factors associated with open angle glaucoma include central corneal thickness, refractive error, and high (severe) myopia. High hyperopia, by contrast, is a risk factor for angle closure glaucoma. For refractive status between these extremes (from +3 to -6 diopters), the data are mixed.

Among the evidence for genetic factors in glaucoma risk are data showing increased risk in particular families. There is evidence that some rarer forms of glaucoma may show Mendelian inheritance—and therefore may be largely determined by just a few genes or a single gene. However, from a population perspective, glaucoma must be viewed as a complex disease whose many forms are, like the many kinds of cancer, genetically heterogeneous. Even where there are family associations, the genes that segregate for increased glaucoma risk in one family may not be the same for another family. Susceptibility genes, gene-gene interactions, and the interactions between genome and environment come into play as well. An implication of this heterogeneity for potential pharmaceutical intervention is that different interventions may be advantageous for individuals of different glaucoma-prone genotypes. In the near term, however, Dr. Klein said that phenotypes based on ethnic characteristics

are likely to be as close to true disease genotypes as clinical diagnosis can come.

The epidemiologic data for forms of glaucoma other than POAG are much more limited. In the Singapore population, the prevalence rate for angle closure glaucoma—about 1 percent—for persons aged 40 years and older of Chinese ancestry was higher than for persons of Malay ancestry. In the population of Andhra Pradesh, India, the prevalence of angle closure glaucoma was about 1 percent for those aged 40 years or younger and 2 percent for those older than 40. Rates of angle closure glaucoma increase with age, and prevalences are higher for women than men. Among Mongolians, angle closure glaucoma appears to be more prevalent than open angle glaucoma. Elsewhere, even in Asia, open angle glaucoma is more common. A customary estimate is that angle closure glaucoma constitutes less than 10 percent of the glaucoma cases in persons of either African or European ancestry.[3]

The Blue Mountains Eye Study in New South Wales, Australia, found that the prevalence of pseudo-exfoliation glaucoma increases with age and is higher for women than for men. In that study, about 7 percent of the women aged 80 years and older had pseudo-exfoliation, which elevated the risk for glaucoma threefold.

In summary, Dr. Klein said that, in her opinion, the prevalence estimates for POAG, the most common form of glaucoma in the United States, are adequate for non-Hispanic European Americans, despite the differences in diagnostic criteria. The estimates of prevalence for other ethnic categories are less reliable, although the prevalences of POAG in African Americans and Hispanic Americans appear likely to be higher than for non-Hispanic European Americans of the same age. The prevalences for other forms of glaucoma in the United States are uncertain and need clarification.

During the question period, Dr. Barbara Klein explained how genetic panels of DNA samples are used to estimate gene pool contributions such as those in figure 1 [4]. The participants discussed popula-

[3]See comments by Dr. Friedman during his presentation on the likelihood of under-diagnosis of angle closure glaucoma unless gonioscopy is used in the screening process.

tion patterns within Central and South America and the genetic basis for skin color being a poor surrogate for gene pool characterization. In response to a question on linkage between hypertension and elevated IOP, Dr. Klein noted that blood pressure medications appear to decrease IOP. She agreed with a comment by Dr. West on the significant effect that variations in glaucoma definitions can have on prevalence estimates, and the symposium participants agreed that glaucoma is a strong example of a disease where standardization of criteria is needed. (See the discussion of conclusion 6.) Another study issue, Dr. Klein said, is low response rates when surveying traditionally underserved populations.

Dr. de Jong offered support for the position that elevated IOP should not be used as a defining characteristic for glaucoma. In the Rotterdam Eye Study, half of the glaucoma cases do not present an IOP elevated above the normal range. Dr. Klein agreed that half to a third of open angle glaucoma cases do not have abnormal IOP elevation, and the participants discussed the best way to represent IOP as a risk factor for glaucoma but not a defining characteristic. There was consensus on an existing description, cited by Dr. Kaufman, that glaucoma is a pressure-dependent disease at every level of pressure, not just with respect to risk but also with respect to clinical management. At any level, lowering IOP will slow glaucoma progression.

Pathogenesis of Glaucoma

Dr. David S. Friedman

Dr. Friedman reviewed the state of knowledge of glaucoma pathogenesis, including closing comments on issues specific to the pathogenesis of angle closure glaucoma. He began by discussing the optic disc excavation and nerve fiber layer defects that are defining pathophysiological features of advanced glaucoma. He then illustrated and described histologic and cellular changes that accompany these clinically distinctive structural features. A major weakness in current clinical definitions of glaucoma, he said, is that they fail to account for the effect of optic disc size when determining if the vertical cup-to-disc ratio is consistent with

glaucoma. Small optic discs can be consistent with glaucoma even when the vertical cup-to-disc ratio is in the "normal" range [34]. He also illustrated how varying amounts of nerve fiber loss, apart from the size of the excavated area, can influence functional loss.

There are ethnic differences related to disc size and disc rim area that could be a factor in the observed differences in the prevalence of glaucoma. For example, Americans of African ancestry tend to have larger optic discs than Americans of European ancestry, but their disc rim area tends to be smaller for the same disc diameter. Both differences create a biomechanical disadvantage in maintaining the supporting strength of the disc lamina as cell loss from glaucoma increases [35, 36].

Dr. Friedman next addressed the question of elevated IOP as a risk factor for glaucoma and whether "low tension" glaucoma exists. He agreed with the formulation, given by Dr. Kaufman at the close of Dr. Barbara Klein's presentation, that glaucoma is a pressure-dependent disease at every level of IOP. Nearly half of patients with open-angle glaucoma have statistically normal IOP on initial evaluation, Dr. Friedman said. With respect to the effects at the back of the eye and the response to IOP lowering, open angle glaucoma presents in the same ways whether the IOP is high or low relative to norms. Thus, in practice and in research, IOP should be treated as a continuous variable in its effect on disease progression. Although elevated IOP cannot be used to define who has glaucoma, it is the most consistent risk factor. It influences disease severity and progression rate, it can be used to induce glaucoma-like disease in animals, and it modifies other risk factors. Even when IOP is not above group norms, lowering IOP can slow disease progression.

One aspect of glaucoma pathogenesis, therefore, consists of conditions that can make IOP high or unstable. Poorer than normal outflow from the anterior chamber appears to be the cause of IOP elevation, and Dr. Friedman reviewed ways in which outflow blockage may occur. Sources of blockage are accelerated death of cells in the trabecular meshwork, accumulation of trabecular extracellular material, or accumulation of outflow-blocking material from elsewhere in the anterior chamber, as occurs in pigment dispersion syndrome or exfoliation-

induced glaucomas. One relatively rare way—occurring in just 1 percent of adults with open angle glaucoma—is blockage of the trabecular meshwork by excessive protein produced by the myocilin gene. However, IOP abnormalities may not be necessary, as there may be other factors that promote the death of retinal ganglion cells even at eye pressures that would normally be tolerated.

Loss of retinal ganglion cells is the defining characteristic for all forms of glaucoma. Loss of other retinal cells does not typically occur. The optic nerve head is a key site of glaucoma-related injury to retinal ganglion cells. The mechanism of cell loss is apoptosis—programmed cell death or "cell suicide" in response to an internal, genetically controlled mechanism—rather than necrosis of the cell caused by severe injury to a major anatomic or physiological component of the cell.

Many retinal ganglion cells die by apoptosis normally during embryonic development, as a consequence of axonal growth that does not result in connections to target cells in the brain. This apoptotic mechanism remains latent in mature ganglion cells. One hypothesis for glaucoma pathogenesis is that a signal for the apoptosis cascade is reactivated pathologically in mature retinal ganglion cells by conditions occurring in the optic nerve head. Disruption of axonal transport causes levels of neurotrophic factors at the cell body to decrease. This signal activates production of other factors that initiate the apoptosis sequence, which includes digestion of the cell's DNA and ultimately ends with cell death. Potential intervention strategies based on this hypothesis include preventing the initial injury to the ganglion cell axon, mitigating the decrease in trophic factor at the cell body, intervening in the initiation of apoptosis, or preventing secondary death of other retinal ganglion cells after one cell undergoes apoptosis.

For example, brain-derived neurotrophic factor (BDNF) is normally produced by the brain cells targeted by retinal ganglion cells. The retinal ganglion cells have specific receptors for BDNF coming from these target cells. The survival rate of cultured retinal ganglion cells increases if BDNF is added to the culture medium. Dr. Friedman reported that, in gene therapy experiments with a rat model of glaucoma, inducing BDNF expression decreased the expected loss of retinal ganglion cells by

38 percent [37]. Thus, increasing the level of neurotrophic factors such as BDNF, ciliary neurotrophic factor, or pigment epithelium-derived factor may reduce ganglion cell loss in humans.

Other animal experiments have shown that laser-induced glaucoma activates the MAP kinase pathway, which is an intracellular signaling pathway that occurs early in the cascade leading to apoptosis. Glutamate has been proposed as a factor in retinal ganglion cell apoptosis, but the data supporting this hypothesis are uncertain. Another factor posited to play a role in inducing ganglion cell apoptosis is nitric oxide, a free radical that can damage cells in various ways. Administration of aminoguanidine, a nitric oxide inhibitor, has reduced the loss of retinal ganglion cells in rat models of glaucoma [38, 39]. A number of free radical scavengers thus may act as endogenous neuroprotection agents in the retina, and inducing their production may reduce retinal ganglion cell loss.

The final topic of the presentation was on pathogenesis issues specific to angle closure glaucoma. Dr. Friedman thinks that angle closure may be more common than previously reported and may play a role in many cases diagnosed as open angle glaucoma. Several population-based reports of glaucoma prevalence have documented angle closure to be responsible for nearly 20 percent of all glaucoma in populations of European ancestry. In addition to being age-related and more prevalent in some ethnic groups, angle closure glaucoma has a three- to four-fold higher prevalence among women than among men. In populations of Asian women over age 60, 15 to 20 percent have a narrow angle, which Dr. Friedman defined operationally as the posterior trabecular meshwork not being visible for 270 degrees or more with gonioscopy. The risk for developing angle closure glaucoma for persons with narrow angles is considered moderate, but longitudinal study data to support specific risk estimates are limited. Dr. Friedman's working assumption in clinical practice is that elevated IOP in the presence of a narrow angle implies that angle closure is causing the increased pressure.

Defining angle closure glaucoma based on gonioscopy is becoming increasingly accepted. Smaller eyes and other features that interfere with outflow from the anterior chamber are risk factors for angle closure glaucoma. Dynamics of the response to light and dark appear to influence

angle closure, so examining patients in strong illumination may be an important cause of misdiagnosis.

To investigate mechanisms of chronic or intermittent angle closure glaucoma, Dr. Friedman has performed modeling simulations of the fluid dynamics for aqueous flow around the lens and the effect of anterior chamber pressure on posterior chamber pressure. If the flow is restricted, as occurs in some angle closure cases, the pressure differential between the anterior and posterior chamber can be as great as 6 mm Hg. Thus, an IOP of 20 mm Hg may, in some configurations found in angle closure, result in posterior pressures as high as 26 mm Hg. The optic nerve may be subject to higher pressures than are being measured at the cornea, and this may contribute to greater disease severity in angle closure glaucoma. Another dynamic factor in the mechanism of angle closure glaucoma may be vascular permeability of the choroid.

In response to questions, Dr. Friedman said that the chronic forms of angle closure glaucoma require longitudinal studies to assess whether their pathogenesis involves intermittent episodes of complete angle closure or gradual narrowing and closure of the angle (creeping angle closure glaucoma). On the topic of genetically linked differences that could account for disparities in prevalence rates for different ethnic groups, he and other participants noted that many structural features that are known to vary within a population—such as optic disc size and structure or lamina components—could alter susceptibility to functional loss. Biochemical and cytogenetic differences may also be aspects of glaucoma genotypes underlying differing susceptibilities to optic disc excavation, retinal ganglion cell response to axonal injury, or apoptotic cascade.

The participants and Dr. Friedman discussed at some length the epidemiologic data on prevalence of angle closure glaucoma relative to open angle glaucoma. Dr. Friedman noted that a number of studies that used gonioscopy to assess angle closure in predominantly non-Asian populations have reported rates in the range of 0.6 percent for angle closure glaucoma in adults aged 40 and older. By comparison, these studies found open angle glaucoma rates of around 2 percent. Thus, a three- to four-fold difference between the two conditions appears to be common in many non-Asian populations. Dr. Wong added that, among Singapore

Chinese, POAG is still twice as prevalent as angle closure glaucoma, so the ethnic disparity between open angle and angle closure glaucomas may be much less than is often assumed. In response to a question on the lack of optic disc excavation in acute angle closure glaucoma, Dr. Friedman said that he knew of no definitive explanation for this difference from chronic glaucomas. His results indicate that loss of elastin in the lamina of the optic disc is involved in the excavation typical of POAG, but there may be loss of other supportive tissue as well.

Glaucoma Clinical Management: Present and into the Future

Dr. Paul L. Kaufman

Although the disease outcome of glaucoma affects the optic nerve head and retinal ganglion cells at the back of the eye, all current clinical treatments for glaucoma in the United States focus on lowering IOP at the front of the eye. After reviewing these current medical and surgical therapies, Dr. Kaufman turned to trends for future treatment options. These include not only new ways to enhance anterior chamber outflow to lower pressure but also approaches for neuroprotection at the back of the eye.

The hierarchy of current treatment options for open angle glaucomas starts with attempting to open up the natural drainage channels for aqueous outflow and progresses to creating a new drain. The final resort is "turning off the faucet" (decreasing aqueous production), even though aqueous inflow is not abnormal in glaucoma.

Among the medical treatment options, six classes of drugs have been or are currently used. Cholinergic agonists contract the ciliary muscle, distorting the trabecular meshwork to enhance outflow. β_2-adrenergic agonists may directly or indirectly affect the trabecular meshwork or enhance the secondary uveoscleral outflow route. However, they are now seldom used because of side effects. The most often used agents at present are the prostaglandin $F_{2\alpha}$ analogues, which act primarily or exclusively on uveoscleral outflow by enabling fluid to flow more easily through the strands of ciliary muscle and out via the sclera.

Three classes of secretary suppressants—β_2-adrenergic antagonists, α_2-adrenergic agonists, and carbonic anhydrase inhibitors—all suppress aqueous humor formation. Half of the classes of medications now being used, Dr. Kaufman noted, attempt to reduce secretion of aqueous humor, rather than increasing outflow, which is directly related to the underlying disease condition.

The current treatment options also include a range of surgical therapies. In laser trabeculoplasty, a laser is used to make a series of burns around the trabecular meshwork. The effectiveness of this treatment in increasing outflow is now believed to result from biological changes to the cells of the trabecular meshwork. The magnitude of typical IOP lowering produced by laser trabeculoplasty is about 30 percent, which is similar to typical outcomes with medical treatment. Surgical trabeculectomy performed appropriately may generate a greater IOP reduction and in some cases may be required. If these approaches do not lower IOP sufficiently, the next step in the treatment hierarchy is often incisional filtration surgery: either a trabeculectomy to create a channel bypassing the obstructed trabecular meshwork or a variant of non-penetrating surgery. Antimetabolites are often administered following these surgical procedures to prevent wound-healing that would block the new outflow pathway. Non-penetrating surgery does not lower pressure as much as trabeculectomy, but it has fewer complications. One such technique, viscocanalostomy, results in permanent changes in Schlemm's canal that enhance drainage. Dr. Kaufman described it as difficult surgery with a steep learning curve. Drainage implants, the next step in the treatment hierarchy, provide an artificial replacement for the natural drainage channels.

When all the options for increasing outflow have been exhausted and the visual potential of the eye is already limited, the final treatment option for the front of the eye is cyclodestruction, which destroys the ciliary body to shut down the inflow of aqueous humor. Cryotherapy, diathermy, and, more recently, laser photocoagulation are techniques that have been used for cyclodestruction.

For treatment of angle closure glaucoma, laser iridotomy (incising the iris) is now used instead of surgical iridotomy. Other laser techniques

can be used to attempt to reshape and open the angle. When these approaches are insufficient, the same treatment hierarchy used in open angle glaucoma is employed.

Potential new approaches for outflow enhancement include increasing the porosity of the trabecular meshwork pathway and enhancing outflow via the secondary, uveoscleral pathway. A new class of medical treatments under development, the cytoskeletal agents, aims to increase porosity of the trabecular meshwork by relaxing the lattice-like structure that provides the principal resistance to outflow. This lattice consists of collagen beams surrounded by a layer of epithelial cells. The epithelial cells are connected to each other and to the extracellular matrix by junctional complexes consisting of many different structural and signal transduction proteins. Biochemical signals can alter cell shape by acting on cytoskeletal components within the cell such as actin. In monkeys, administration of chemicals that disrupt the actin cytoskeleton or relax the actin-myosin system, such as intracameral cytochalasin B, can cause a transient but substantial increase in outflow through the trabecular meshwork. The effect on IOP, Dr. Kaufman said, is "like a pharmacological trabeculotomy." The mechanism is of interest because there are no current pharmacologic approaches that directly target the trabecular meshwork without the side effects of the cholinergic and adrenergic agonists.

A class of compounds called latrunculins (because they were first isolated from a sea sponge formerly called *Latrunculia magnifica*) interfere with the self-assembly of the actin cytoskeleton. Deterioration of the actin microfilament bundles loosens the cell-cell junctions, resulting in cell separation and increased porosity of the lattice structure in the trabecular meshwork and the outer meshwork beyond the lattice, which constitute the area of major flow resistance. When administered to monkey eyes, latrunculins produce substantial IOP lowering and can double or triple the outflow facility through the trabecular meshwork. The effect can be sustained for at least several weeks, and the treatment is well tolerated, with no observed negative effects on the cornea or other tissues where cells' actin framework might be adversely affected. Dr. Kaufman described other agents, besides the latrunculins, that are being investigated for similar effects in altering the actin-myosin system

and the cellular junctions that appear to control porosity through the trabecular meshwork.

Among treatments under investigation to increase uveoscleral outflow, Dr. Kaufman described studies of prostaglandin $F_{2\alpha}$ derivatives. These agents up-regulate production of matrix metalloproteinases by the ciliary muscle and down-regulate collagen production. The consequence is increased porosity and outflow via this secondary natural route. The prostaglandin derivatives mimic a natural cascade in response to an eye injury. A broad implication of this result is that many other factors in the injury response cascade could be targeted for intervention, either with small molecule (drug) therapy or with gene therapy. It may thus become possible to target the ciliary muscle only, avoiding side effects. A gene therapy technique for effecting such an intervention would bypass problems with maintaining strict patient compliance with a daily regimen of topical administration.

Knowledge of the mechanisms of neuronal death and their prevention, delay, or reversal is now sufficient to envision glaucoma therapies directed at the retinal ganglion cells and axons. Dr. Kaufman organized the potential neuroprotection approaches that are actively being investigated under four headings:

- Protection of healthy but at-risk retinal ganglion cells and axons,
- Rescue of marginally damaged retinal ganglion cells and axons,
- Regeneration of axons when the cell body is still alive, and
- Replacement of retinal ganglion cells (e.g., using stem cells).

An example of the first approach is the use of a synthetic peptide copolymer called Cop-1 to decrease the loss of retinal ganglion cells in rodent models of glaucoma [40]. Clinical trials in the near future are likely for several agents, such as Cop-1, that are already in use for other purposes. Future stem cell therapies for glaucoma could target the retinal ganglion cells directly, the supporting cell structures or functions in the optic nerve head, or the trabecular meshwork.

In considering any of the neuroprotection approaches for treating glaucomatous conditions that already are present at the back of the eye, Dr. Kaufman warned that changes in the central nervous system on the

brain side of the optic nerve must also be considered. Before attempting a neural rescue or regeneration approach for retinal ganglion cells, one should consider whether brain cells have already been lost. He illustrated this point with micrographs of the lateral geniculate nucleus in a normal primate brain compared with the brain of an animal with experimentally induced glaucoma. There are far fewer cells in the latter because this area of the brain has been deprived of input from retinal ganglion cells. Similarly, experimentally induced glaucoma produces characteristic changes in the visual cortex.

Gene therapy approaches are applicable to either IOP lowering or protecting retinal ganglion cells at the rear of the eye. These approaches, Dr. Kaufman emphasized, refer not to replacing a defective gene but to reprogramming target cells by transferring genetic material into them so that they produce more or less of a factor that influences physiological functioning. The factor that is up-regulated or down-regulated may influence glaucoma pathophysiology directly, or the change in the factor may have a beneficial effect in a glaucoma situation. Dr. Kaufman described results from use of modified adenovirus to transfer the gene for production of caldesmon, a protein component of the actomysin filaments in the cytoskeleton, into the anterior segment of primate eyes. After perfusion with the adenovirus construct, outflow facility doubled, compared with controls perfused with adenovirus not containing the caldesmon gene. This increased outflow indicates that the trabecular meshwork lattice had been relaxed. Other laboratory studies with viral vectors have investigated transfer of the gene for BDNF to retinal ganglion cells to protect them from induced glaucoma **[37]** and the transfer of the gene for human p21 protein to prevent wound-healing in a rabbit model for glaucoma filtration surgery (sclerostomy) **[41]**. Dr. Kaufman described the p21 protein transfection technique as ready for clinical trial, if a pharmaceutical firm were willing to undertake such a trial for a gene therapy treatment.

For targeted delivery of small-molecule therapeutic agents to the back of the eye, promising new approaches include trans-scleral administration, intraocular administration via the anterior segment, and intraocular administration via a biological or mechanical device implanted

in the posterior segment. One technique using the latter approach is encapsulated cell technology, in which living cells that have been bioengineered to produce a therapeutic agent are encapsulated within a semipermeable polymer membrane. The device is attached to the inside of the sclera and resides within the patient's peripheral vitreous. The therapeutic agent diffuses through the capsule pores and across the vitreous to the retina [42]. A clinical trial is in progress for treatment of the retinal photoreceptor degenerative disease retinitis pigmentosa using cells transfected with a gene that produces ciliary neurotrophic factor, a growth factor effective in many neurodegenerative conditions. The encapsulated cell technology device and implantation technique used in this trial are directly applicable to other retinal diseases including glaucoma.

New monitoring techniques are also under study. There is credible evidence that IOP fluctuation may be a risk factor for glaucoma, independent of the average pressure. For example, the relative risk of glaucoma progression within 5 years for patients with a diurnal IOP range of 5.4 mm Hg is more than five times the risk for patients with a diurnal range of 3.1 mm Hg [43]. Continuous monitoring of IOP could be an effective part of the preventive regimen for patients with fluctuating IOP. A pressure sensor can be mounted in a contact lens or implanted in the anterior segment. The sensor would produce a telemetry signal acquired by a receiver in the patient's pocket.

Research on both the anterior segment and the back of the eye is being aided by new functional testing and structural imaging techniques. In vivo visualization of cellular ultrastructure has been applied to both the trabecular meshwork and retinal ganglion cells. Dr. Kaufman described how one line of research on detecting apoptosis in retinal ganglion cells [44] might be used clinically to track the progression of glaucoma damage at the optic nerve head and the effectiveness of a course of treatment.

During the next decade or so, Dr. Kaufman foresees major new advances for glaucoma treatment and management in the following areas:

- Development of new small-molecule drug therapies based on more detailed understanding of glaucoma pathophysiology,
- Gene therapy, and
- Diagnostics.

General Discussion on Glaucoma

Dr. Ronald Klein asked whether clinical trials of glaucoma treatments or other clinical experience have found ethnic differences in response to treatment. Dr. Kaufman said that, except for differences related to wound-healing and ocular pigmentation, he knew of no fundamental differences in how ethnic groups respond to the IOP-lowering drugs now in use. He also saw no basis for anticipating there would be qualitative differences in reaction to any of the approaches based solely on *ethnic* characteristics. However, there probably are pharmacogenetic differences that could be usefully applied to differential treatment of disease-relevant or treatment-relevant genotypes in any population, if only we could recognize the relevant genotypes.

This point led to a question on the reliability of steroid responsiveness as a predictor for glaucoma susceptibility and whether there were ethnic differences in steroid responsiveness. Dr. Kaufman replied that steroid response may not be a predictor for "normal tension" glaucoma, although high-pressure POAG patients do appear to be steroid-responsive. Dr. Wong added that his group had not seen an ethnic difference within Asian populations in steroid responsiveness. As to a mechanism to explain the association of steroid responsiveness with glaucoma, Dr. Kaufman suggested that steroids may cause condensation of the cytoskeleton in trabecular meshwork cells, decreasing their capacity to expand and open up the lattice. In general, he said, whatever the biochemical mechanism involved, a pressure increase due to reduced outflow requires a structural change that increases resistance to aqueous flow through the trabecular meshwork.

Dr. Barbara Klein asked if the frequent need for several medications to lower IOP in Americans of African descent was an indication of differential response to treatment. Dr. Kaufman agreed that this was one possible explanation. But another possibility is that there are group differences in the severity of the underlying conditions, requiring more than one therapeutic approach to overcome them.

Dr. Kaufman agreed with a comment that glaucoma could be called a disease of the retina (specifically of the nerve fiber layer of the inner

retina), as well as an optic neuropathy. The key distinction is that it does not involve the photoreceptors, retinal pigment epithelium, or other specialized cells of the outer retina. He also agreed that standardization of the methods for measuring IOP is needed if continuous IOP monitoring and treatments based on the diurnal range of IOP are to be used effectively in clinical management.

Dr. Bird asked whether the genetic factors in glaucoma susceptibility were likely to act at one location (e.g., the trabecular meshwork or the optic nerve head) or at a variety of locations in different people (different disease-relevant genotypes). Dr. Kaufman replied that he expected that genes relevant to glaucoma susceptibility might express in different locations including the front and the back of the eye. There was general agreement with Dr. Bird's comment that, before one knows the genes involved in a complex disease such as glaucoma, one is unlikely to recognize the phenotypical characteristics that distinguish distinct genotypes of the disease. These points led to general discussion of whether treatment strategy should ultimately be specific to the genotype or whether a mechanism for general amelioration of pathogenic conditions would be more effective. Dr. Kaufman noted that the general form of this question is also reflected in the current treatment approaches to outflow facility, in which the most-used methods do not address the condition causing the outflow restriction. Dr. Bateman added that a further complication could be that structural conditions in the trabecular meshwork result in part from genetic differences that express only during embryogenesis or early development, not at the time of glaucoma onset as typically defined. Dr. Friedman suggested that the disparities in glaucoma prevalence underscore the need to develop cohorts of ethnic groups that can be followed to study potential genetic bases for pathophysiology and pharmacogenetics. Dr. Chader remarked that variations in some very general genes (genes expressed in many cell types) may be a factor in glaucoma susceptibility and genotype differences. This occurs in retinitis pigmentosa, where about half of the genes that have been implicated in one or another form of the disease have very general roles in many cell types but have polymorphisms that affect the photoreceptor cells in ways that lead to or enable the disease condition.

Session 4

Diabetic Retinopathy

Epidemiology of Diabetic Retinopathy

Dr. Ronald Klein

Dr. Ronald Klein framed his presentation as an answer to the question: "What is the burden of diabetic retinopathy in different racial/ethnic groups?" After an introductory description of the ocular consequences of diabetes mellitus, he reviewed the existing data on prevalence and incidence of diabetic retinopathy within racial/ethnic groups, including the relative importance of known risk factors. A critical implication of these data is that prevention and amelioration of progressive visual impairment and blindness from diabetes depends on overcoming barriers to delivery of health care and health information to groups at increased risk of diabetes and its consequences, including diabetic retinopathy. Dr. Klein ended the presentation with his perceptions of future needs and the directions that should be pursued to meet them.

The earliest clinically observable signs of diabetic retinopathy are retinal microaneurysms (stage 1). These are not specific to diabetes; they can result, for example, from hypertension and are found in 7 percent of the nondiabetic population. More severe stages are manifested by hemorrhages and lipid exudates, cotton wool spots (signs of microinfarcts in the retinal nerve layer), and macular edema. Swelling from macular edema is one of the principal causes of visual impairment from diabetes. In the advanced stage of diabetic retinopathy called proliferative diabetic

retinopathy (PDR), new blood vessels develop from venules on the optic disc and elsewhere. Untreated, these new vessels proliferate and tend to bleed, leading to scarring. The stages prior to PDR are collectively referred to as nonproliferative diabetic retinopathy (NPDR). Although these signs of diabetic retinopathy have been known and studied for more than a century, not until the 1970s and 1980s was a severity scale based on a standard classification scheme used nearly universally in epidemiologic studies and clinical trials.

The high risk of visual function loss and blindness that diabetes poses is illustrated by data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) **[45, 46]**. This longitudinal study is following a cohort of patients in 11 Wisconsin counties who were diagnosed in 1980–82 with type 1 diabetes (defined by onset at 30 years of age or younger) or type 2 diabetes (onset at 30 years of age or older). Table 5 includes prevalence rates at baseline, plus incidence and progression rates for 10 years of following the ocular health of the study cohort. Particularly important from a public health perspective is that, despite being in treatment for diabetes throughout the study period, most of the cohort experienced a clinically meaningful progression of two steps or more along the diabetic retinopathy scale.

The risk of diabetic retinopathy increases with the number of years that a patient has diabetes. It also increases with poorer glycemic control (higher than normal blood sugar levels), higher blood pressure, presence of diabetes-associated kidney disease (diabetic nephropathy), and higher serum lipid levels. In the WESDR, the risk of retinopathy progression by two or more steps on the severity scale increased with the level of glycosylated hemoglobin—an indicator of elevated blood sugar. As figure 5 shows, above the first quartile in level of glycemic control, the rate of progression was far more dependent on the level of glycemic control than on the type of diabetes. At every level of glycosylated hemoglobin above normal, there was a benefit, in terms of reduced risk of progression, from lower glycosylated hemoglobin level at baseline. Beyond just the increased risk of diabetic retinopathy progression, even a small increase in glycosylated hemoglobin level over the 10-year period was associated with statistically significant increases in risk of progression to

Table 5. Prevalence, Incidence, and Progression of Diabetic Retinopathy

Disease Characteristic[a]	Diabetes Onset Younger Than 30 Years (Type 1 Diabetes)	Diabetes Onset 30 Years or Older (Type 2 Diabetes)
Any retinopathy, prevalence at baseline	71%	50%
PDR, prevalence at baseline	23%	5%
Clinically significant macular edema, prevalence at baseline	6%	5%
Incidence in 10 years (from no signs to any stage)	89%	71%
Progression, two steps or more in 10 years	76%	60%
PDR, incidence in 10 years	30%	16%
Clinically significant macular edema, incidence in 10 years	14%	13%

Note: Results from WESDR, 1980–92. Study population was primarily Americans of European ancestry.

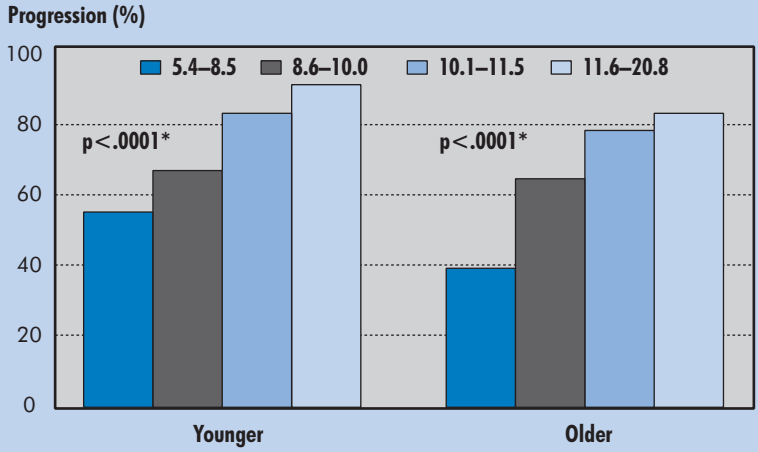
[a]Incidence rates are the percentage of patients who began with no signs of a disease characteristic but developed signs within 10 years.

Sources: **[45, 46, 47, 48, 49]**.

PDR, visual loss, and serious systemic consequences of diabetes (proteinuria, lower limb amputation, and death from ischemic heart disease). In another study, the Diabetes Control and Complications Trial (DCCT), intensive glycemic control produced a 75 percent reduction in progression of retinopathy in type 1 diabetes. Similarly, the United Kingdom Prospective Diabetes Study (UKPDS) found a 25 percent reduction in progression of retinopathy with tight glycemic control in persons with newly diagnosed type 2 diabetes.

Turning to the main theme of the symposium, Dr. Klein reviewed the evidence for differences in prevalence of diabetic retinopathy among racial/ethnic groups. At the start of the WESDR in 1980, there were

Figure 5. Ten-Year Progression of Retinopathy by Quartile of Glycosylated Hemoglobin



*Mantel-Haenszel test of trend.

Sources: [45, 46].

anecdotal clinical observations that the rates of severe diabetic retinopathy were higher among African Americans and Hispanic Americans than among non-Hispanic European Americans. There were few data, even clinical anecdotal evidence, on retinopathy in diabetic Asian Americans. In 1995, Dr. Ronald Klein and Dr. Barbara Klein wrote in the second edition of *Diabetes in America*, "At present, published data are not available on the prevalence of retinopathy and macular edema in black populations living in the United States."

Dr. Ronald Klein next presented a table showing population-based studies to date that provide data on prevalence of any diabetic retinopathy and of PDR, based only on crude prevalence rates without controlling for comparability on risk factors such as duration of diabetes, glycemia, or blood pressure. For type 1 diabetes, the rates for any diabetic retinopathy and for PDR were fairly comparable in the WESDR (predominantly Americans of European ancestry) and the New Jersey 725 study of African Americans, conducted from 1993 to 1997 [50, 51].

The prevalence rate of 71 percent for any retinopathy in the WESDR compares with 64 percent in the New Jersey 725 study; a PDR rate of 23 percent in the WESDR compares with 19 percent in the New Jersey 725 study. For type 2 diabetes, however, data from three studies in which the examination for diabetic retinopathy was an add-on to a broader investigation of morbidity and health differences reported higher crude rates among African Americans than for Americans of European ancestry for any diabetic retinopathy and for PDR. These three studies were the Third National Health and Nutrition Examination Survey (NHANES III), the Atherosclerosis Risk in Community Study, and the Cardiovascular Health Study.

Dr. Klein discussed five methodological differences that make it difficult to draw comparisons across these studies, the WESDR, and other population studies:

- **Ascertainment of the study sample.** Example: the screening criteria used to determine the base population of diabetes patients to be studied were more restrictive for the WESDR.
- **Historical period of the study.** Example: WESDR initial prevalences reflect treatment conditions in 1980–82, before current blood pressure–lowering drugs were available. Glycosylated hemoglobin levels were higher then than now.
- **Sample characteristics.** Example: The studies are likely to differ in distribution in subject age and duration of diabetes.
- **Definition of disease.** Example: the definition of diabetes in 1979 was a fasting blood sugar level of 140 mg/dL or greater; the current definition is a fasting blood sugar level of 126 mg/dL or greater.
- **Fundus photography.** The add-on studies use just one 45-degree nonstereoscopic color field in one eye, rather than several 30-degree color stereoscopic fields from each eye, as were used in the WESDR and the Beaver Dam Eye Study.

Despite these limitations, Dr. Klein said that NHANES III provides a good starting point for examining differences among ethnic groups. It used a stratified multistage sample design and oversampled for non-Hispanic Americans of African ancestry and Mexican Americans. In

the sample of 9,737 people who were 40 years of age or older, 1,205 had a diagnosis of diabetes, of which 1,180 were considered to have type 2 diabetes. The crude prevalences among African Americans for three categories of diabetic retinopathy were about double the prevalences for non-Hispanic European Americans. However, when the rates were controlled for the known risk factors of poor glycemic control, high systolic blood pressure, duration of diabetes, and severity of diabetes (measured by need for insulin therapy), there was no significant difference between non-Hispanic African Americans and non-Hispanic Americans of European ancestry in prevalence of retinopathy. Furthermore, the effect of these known risk factors appeared to be similar in the two groups. The NHANES III investigators concluded that the higher prevalence of retinopathy in African Americans with type 2 diabetes appears due, in part, to poorer control of blood sugar level and blood pressure. These are both factors that can be influenced by treatment and patient involvement.

To introduce his summary data on the prevalence of diabetic retinopathy in Hispanic Americans compared with non-Hispanic European Americans, Dr. Klein again discussed the differences in sample criteria and study design among the studies. He noted comments from the literature that the higher prevalence of diabetic retinopathy found in a regional population of Mexican Americans, when compared with non-Hispanic European Americans in the same region, appears more likely to reflect subpopulation differences associated with medical care or perhaps sample design, rather than a general genetic predisposition to more severe complications of diabetes [52]. In the NHANES III results, Mexican Americans diagnosed with type 2 diabetes were three times more likely than non-Hispanic European Americans with type 2 diabetes to have any retinopathy and to have either moderate/severe NPDR or PDR. Although the Mexican Americans were more likely to have poor glycemic control and high systolic blood pressure than non-Hispanic European Americans, these differences were not sufficient to account for all of the increased prevalence of retinopathy in Mexican Americans. The odds ratio for Mexican Americans, after controlling for other factors, was 2.15, with 95 percent confidence limits of 1.95–4.04. A similar twofold increase in risk for Mexican Americans has been reported from

an analysis of pooled data from the Proyecto Ver study, the Los Angeles Eye Study, and the Beaver Dam Eye Study [53]. Dr. Klein suggested that incidence data from longitudinal studies of Hispanic American populations are needed to sort out the roles of the various factors that could be contributing to the increased risk of more severe retinopathy in Mexican Americans compared to non-Hispanic European Americans.

For Native Americans, Dr. Klein summarized the limited data available from long-term studies of Pima Indians and Oklahoma Indians, but he cautioned that these and other studies did not collect similar data in non-Hispanic European Americans. As a result, the prevalences of retinopathy cannot be compared with non-Hispanic European Americans. One population-based study of Japanese Americans found lower rates of diabetic retinopathy than were reported for European Americans in the Beaver Dam population. Similar limitations as described above limit comparisons from this work. There are no other population-based data on Asian American groups.

Dr. Klein next turned to the implications of these data for preventing visual loss as a consequence of diabetes. Taken together, the epidemiological and clinical trial data show that blindness and visual loss from diabetic retinopathy can be reduced by (1) intensive control of blood sugar and blood pressure, and (2) early detection and treatment of vision-threatening diabetic retinopathy through dilated eye examinations. In the WESDR, only 67 percent of persons with known high-risk characteristics for severe visual loss or clinically significant macular edema had been seen by an ophthalmologist within two years of their WESDR examination. Insurance coverage for an eye examination was highly correlated with having had an examination in the past year. A range of reasons were given for not having an eye examination, but the most frequent reason was that the subject experienced no problem with his/her eyes.

These same barriers, found 25 years ago in the WESDR, are still operable in high-risk ethnic groups today. Despite the results of the DCCT and UKPDS highlighting the value of strict glycemic control, the percentage of WESDR subjects within 2 standard deviations of the mean glycosylated hemoglobin for nondiabetics barely changed over the period

from the 1980–82 baseline through the 1994–95 follow-up. Data from NHANES also show little change in glycosylated hemoglobin levels over a 10-year period since dissemination of the DCCT and UKPDS findings. A major issue, therefore, is how to reduce the high rates of noncompliance with recommendations that are known to ameliorate the risk of vision loss. A related issue is how to deliver adequate medical care to those with diabetes but without medical insurance.

From his review of the literature, Dr. Ronald Klein concluded that the new data coming from population-based studies such as NHANES and recent meta-analyses by the Eye Diseases Prevalence Research Group suggest that there are differences in diabetic retinopathy prevalence among some racial/ethnic groups. For some groups, such as African Americans, the difference in prevalence and severity can best be explained in terms of modifiable factors, such as glycemic control and blood pressure. For other groups, including Mexican Americans, longitudinal data are needed to sort out the contribution from potential risk factors. Dr. Klein affirmed a recent statement from the Eye Diseases Prevalence Research Group that "further research using a nationally representative sample would be useful to clarify whether the risk of vision threatening retinopathy among persons with diabetes mellitus varies by race or ethnicity" [54]. Current estimates of the population burden of retinopathy, by severity, are needed to track the efficacy of new screening programs and of changes in diabetes management. To illustrate the difference that more effective diabetes management and risk factor control can make, Dr. Klein presented five-year cohort data on type 1 diabetes patients at the Steno Diabetes Center, Denmark [55].

For future directions in treating diabetic retinopathy, Dr. Klein recommended:

- Developing new means to overcome the barriers to normalizing blood glucose, blood pressure, and serum lipid levels;
- Improving the understanding of how genetic-environmental interactions are involved in the differential incidence and progression of retinopathy among diverse population subgroups; and
- Developing new approaches to make dilated fundus examinations more acceptable to patients.

During the post-presentation discussion, Dr. Klein was asked about information on how dietary changes from one generation to the next within an ethnic group affect prevalence and severity of diabetes. He replied that diabetes prevalence has increased due to higher prevalence of obesity, which is associated with diets high in calories and with lower physical activity levels. Stated simply, if the calories consumed can be reduced or worked off, and obesity thereby avoided, then the incidence of diabetes can be decreased. To a question on the effect of mortality from diabetes on estimates of retinopathy in long-term longitudinal studies such as the WESDR, Dr. Klein agreed that the impact is profound, as severe retinopathy is an indicator of systemic disease (e.g., diabetic nephropathy) associated with increased mortality. Thus, persons who develop severe retinopathy before their follow-up examination are more likely to die before being seen, resulting in underestimation of the incidence of this complication. One approach is to use best and worst case scenarios in deriving progression statistics. For the worst case scenario, all patients who died are assumed to have severe retinopathy present. The best case scenario assumes that none who died have this condition. Dr. West described a new statistical technique, which adjusts for death as a competing risk, to estimate the risk of an outcome that is not death.

A question on whether the prevalences of diabetic retinopathy in general and of PDR are decreasing in the United States led to a discussion of problems in drawing inferences from data that are not comparable in study population characteristics, experimental design, and other factors. With respect to the underlying question, Dr. Klein emphasized the need for well-designed incidence studies to assess whether expensive interventions—like some of those suggested for age-related macular degeneration (AMD)—actually improve outcomes for patients.

Dr. Frank recommended that a principal message from this presentation for the symposium report should be that we have sufficient knowledge of the mechanisms to prevent and treat diabetic retinopathy. The major obstacles are providing access to health care and motivating those at risk to maintain the preventive regimens that have been proven to make a difference. Dr. Klein added that studies such as NHANES are finding that, regardless of ethnic category, Americans are suffering the

consequences of poorer health care delivery than is available in many other developed countries.

Pathophysiology of Diabetic Retinopathy

Dr. Robert N. Frank

The mechanisms that produce diabetic retinopathy are not yet known. Dr. Frank reviewed the data on pathogenesis to highlight potential mechanisms and consider how best to determine which of these are involved and what roles they play. He began with an overview of five known risk factors for diabetic retinopathy and their relationship to the disease's pathophysiology:

- Duration of diabetes,
- Hyperglycemia (blood glucose control),
- Hypertension (demonstrated in controlled trials only for type 2 diabetes),
- Heredity (familial clustering in the DCCT), and
- Patient age (retinopathy is rare before puberty, regardless of diabetes duration).

With respect to duration, studies such as the WESDR have show that progression to the more severe stages of diabetic retinopathy correlates with the number of years that a patient has been diabetic. This implies a pathogenic mechanism that develops over a period measured in years.

Hyperglycemia is a necessary condition for development of diabetic retinopathy. The DCCT showed that tighter control of blood glucose begins to decrease the risk of progression after 2.5 years of control and continues to decrease the risk relative to laxer control of blood glucose. The UKPDS found that even a mean difference of 1 percent in blood glucose control made a significant difference in risk of retinopathy progression for type 2 diabetics. Both the clinical trials in humans and studies of animal models of diabetes have shown that the effect of hyperglycemia on retinopathy develops slowly, but disease progression

also continues after glycemic control is tightened. Except for the very late stages of PDR, there is no point at which deleterious effects cannot be at least slowed by controlling hyperglycemia, although the effects cannot be reversed. (For about 10 percent of type 1 diabetes patients who already have signs of retinopathy when glycemic control is tightened, the retinopathy worsened. Several mechanisms have been proposed for this phenomenon.) Follow-up of DCCT subjects after the initial study period found that, although the DCCT tight control group eventually reverted to about the same mean level of glycosylated hemoglobin as the conventionally controlled group, the conventionally controlled group continued to experience increased risk of retinopathy progression.

For type 2 diabetes, the UKPDS found that hypertension control also slowed retinopathy progression. Blood pressure control by any means appears to be effective in slowing retinopathy, at least for type 2 diabetes and, by analogy (although this has not yet been actually demonstrated), for type 1.

The DCCT found statistically significant familial clustering of severe diabetic retinopathy. Among first-degree relatives, the correlation for parent-child pairings was statistically significant, but the correlation for sibling pairings was not [56]. With respect to age as a risk factor, several studies have found that retinopathy does not develop in type 1 diabetes until puberty, even if the onset of diabetes is in infancy. With respect to a possible mechanism for this phenomenon, Dr. Frank suggested that the growth spurt typical of puberty is associated with increased secretion of various hormones and growth factors, such as the insulin-like growth factors. These latter growth factors have been associated with retinopathy-like changes in human diabetic subjects. Work by Dr. Lois Smith indicates that insulin-like growth factors may be permissive factors, allowing angiogenic factors such as vascular endothelial growth factor (VEGF) to exert an effect [57].

Dr. Frank discussed what is known about diabetic retinopathy at the cellular level from studies of diabetes in humans and in animal models. Basement membrane thickening, for example, is a major consequence of human diabetes. Molecular components of that thickening may include extracellular matrix molecules that influence the behavior of other cells

involved in promoting retinopathy. Blood flow retardation through loss of autoregulation of blood flow is another phenomenon of diabetes that has been studied for a potential role in retinopathy. Reduction of blood flow and autoregulation has been reported repeatedly in chronic diabetes. These conditions could cause acute relative hypoxia and consequent adverse effects.

Inflammation and inflammatory changes appear not only in diabetic retinopathy but also in AMD and other eye diseases. Changes in adhesion molecules and cytokines such as the interleukins may affect the adhesion of leucocytes to blood vessel walls, capillary permeability, and other changes that modulate retinopathy outcomes. Breakdown of the blood-retina barrier has long been associated with diabetic retinopathy and macular edema. It may be related to inflammatory changes. VEGF may be involved in this breakdown—a possibility that needs further study.

The selective loss of capillary pericytes in diabetic retinopathy has been recognized since the 1960s, but the mechanism of this loss and how it might influence further disease development are still unclear. Programmed cell death (apoptosis) is involved in this loss. Pericytes often function like smooth muscle in retinal capillaries, and they may have a role in maintaining the blood-retina barrier. However, attempts to show contractility in retinal capillaries have been unsuccessful. Removing pericytes may stimulate proliferation of some endothelial cells, even though other endothelial cells die. Endothelial cell loss appears to occur after pericyte loss or perhaps simultaneously with it. If pericytes are lost, microaneurysms and proliferation of acellular capillaries may result from the removal of a factor (not yet determined) that inhibits endothelial proliferation.

Another important feature of diabetic retinopathy is hypoxia, whether resulting from retarded blood flow or from loss of capillary cellularity and function through proliferation of acellular capillaries. Hypoxia is certainly a strong stimulus for later severe changes such as neovascularization. Dr. Frank illustrated this point with fluorescein angiograms showing that new vessels apparently develop at the border of capillary-free zones.

Dr. Frank next reviewed the principal lines of evidence supporting a variety of pathogenic mechanisms proposed to account for these aspects of retinopathy and its progression to more severe forms. Involvement of the sorbitol pathway mechanism, which involves the enzyme aldose reductase, was proposed as far back as the late 1950s. The hypothesis is that accumulation of sorbitol within cells damages them. However, several controlled clinical trials of aldose reductase inhibitors have failed to show a protective effect. Although the sorbitol hypothesis is out of favor at present, extenuating reasons have been suggested for the failure of the inhibitor trials.

A second proposed mechanism, the protein kinase C pathway, led to thus far unsuccessful clinical trials of a protein kinase C_β inhibitor for control of diabetic macular edema or for control of neovascularization. However, more recent studies of this drug show more promise. A third proposed mechanism implicates advanced glycation end products (AGE) and their cellular receptor sites as components in the slow onset and gradual progression of diabetic retinopathy. The hypothesis for this mechanism holds that simple glycation products of proteins and other biomolecules increase with blood glucose concentration. These initial products aggregate to form macromolecules: the AGE, which can be very long-lived and could damage cells and tissues. There have been some positive animal studies supporting this mechanism, but no well-designed human trials. A trial of an AGE inhibitor, aminoguanidine, was stopped by its sponsor without explanation. Dr. Frank believes a human trial of some appropriate AGE inhibitor would be worthwhile because the proposed mechanism is certainly plausible.

With respect to the hypothesis of an inflammatory mechanism for diabetic retinopathy, Dr. Frank suggested that the next step should be a clinical trial to determine whether stronger anti-inflammatory drugs than aspirin would have a positive effect. Aspirin, which was tested in the Early Treatment Diabetic Retinopathy Study (ETDRS), was found to be ineffective for reducing the risk of disease progression **[58]**.

Oxidative stress has been suggested as a mechanism for diabetic retinopathy, as it has been for several other pathologies. Nonetheless, a use-

fully authoritative clinical trial of antioxidants does not appear likely any time soon, in Dr. Frank's opinion.

The evidence of familial clustering of diabetic retinopathy supports hypotheses of a genetic disposition for this complication of diabetes. One hypothesis is that high blood glucose somehow affects particular genes directly. Techniques of genetic analysis are being applied through the Familial Investigation of the Nephropathy of Diabetes study, sponsored by the National Institutes of Health, to further develop and test this hypothesis for the pathogenesis of diabetic nephropathy and diabetic retinopathy.

Dr. Frank emphasized that these mechanisms are not mutually exclusive. Several may be involved in the onset or progression of diabetic retinopathy. Although the aldose reductase inhibitors and a protein kinase C_β inhibitor have had negative results in human clinical trials, alternative explanations consistent with the hypotheses have been suggested to account for the negative trial results. The other mechanisms have not been rigorously tested on cases of human diabetic retinopathy.

With respect to the role of growth factors in neovascularization, Dr. Frank thought that current trials of anti-VEGF agents for AMD could prove relevant to treatment of diabetic retinopathy. A caveat is that anti-VEGF agents tested on animal models of retinal neovascularization only reduced the neovascularization by about 40 percent. Although VEGF is important, there may be other growth factors involved. A treatment approach that targets a number of these factors may be more effective. The presence of VEGF in many types of nonvascular retinal cells indicates that diabetic retinopathy probably is a disease of retinal metabolism more generally, even though its clinical manifestations are observed in retinal blood vessels. In other words, the effects on blood vessels may be secondary to effects on other retinal cells, including Müller cells and other glial elements. In both animal and human studies, up-regulation of VEGF occurs very early in the onset of diabetes. There is a disconnect, then, between the rapid appearance of VEGF in diabetes and the delayed onset and gradual progression of diabetic retinopathy over a course of years.

Phenomena such as the delay of onset of retinopathy until puberty suggest that other factors may have essential roles, with or without VEGF up-regulation. Among the other growth factors for which some suggestive evidence of involvement can be cited are platelet-derived growth factors, angiopoietins, and pigment epithelium-derived factor (PEDF). PEDF appears to inhibit neovascularization, and its concentration decreases in some circumstances where VEGF increases and neovascularization occurs. A gene therapy approach to up-regulate PEDF is being tested in a clinical trial as a therapeutic approach to inhibit choroidal neovascularization in wet AMD.

Dr. Frank concluded his presentation with a list of established pathophysiological aspects of diabetic retinopathy that a fully satisfactory mechanism must explain:

1. Diabetic retinopathy is clearly a response to chronic hyperglycemia, with a definite dose-response relationship.
2. The onset of retinopathy in response to hyperglycemia is slow, and reversal after correction of hyperglycemia is also slow.
3. There is probably a genetic disposition to retinopathy (as well as a genetic disposition to diabetes).
4. Regardless of prior duration of diabetes, onset of puberty appears necessary for onset of retinopathy.
5. Retinal microvessels are affected, but the anatomically similar cerebral microvessels are not affected either in humans or in animal models.
6. What is the role of basement membrane thickening?
7. What is the role of pericytes, and of their selective dropout early in progression of the disease?
8. What is the role of retarded blood flow and autoregulation?
9. What role do inflammatory mechanisms play in onset and progression of diabetic retinopathy?
10. VEGF is clearly important, but why is it up-regulated early, whereas observable effects occur much later and progress gradually? What other growth factors are involved, and how are they involved?

Clinical Management of Diabetic Retinopathy: Present and into the Future

Dr. Stephen J. Ryan

Dr. Ryan described current practices in both systemic and local clinical management of diabetic retinopathy in light of the epidemiology and pathophysiology of the disease, as reviewed in the previous two presentations. He then discussed the likely directions for future treatment and management of the disease.

Current treatment emphasizes monitoring for the onset of the disease, then timely intervention when treatable disease appears. The current intervention approaches include both systemic therapy and local therapy that does not target a specific disease mechanism (nonspecific local therapy). Studies such as the WESDR, DCCT, and Diabetes Retinopathy Study have provided insights and recommendations, which the American Academy of Ophthalmology has incorporated into its preferred practice pattern for patients with diabetes mellitus. For example, the recommended follow-up interval for monitoring patients decreases according to the severity scale described by Dr. Ronald Klein and the risk of progression to PDR at each severity level (table 6).

With respect to treatment, as Dr. Klein and Dr. Frank emphasized, glycemic control is without question the single most effective treatment for diabetic retinopathy. Local treatment undertaken by ophthalmologists is always a downstream therapeutic effort, secondary to systemic control of blood sugar as long as the risk for vision loss is not immediate. However, as the previous presentations also emphasized, achieving a tight level of blood sugar control over an extended time has been an elusive public health goal.

Other modifiable risk factors are known or under investigation. Control of blood pressure has been established as another systemic goal for managing diabetic retinopathy. Trials are under way to examine the relationship between control of diabetic nephropathy and progression of retinopathy. The WESDR and ETDRS found correlations of serum lipids (cholesterol and triglycerides) with retinal hard exudates and moderate

Table 6. Recommended Follow-up Intervals for Levels of NPDR

Level of NPDR	Proportion with PDR within 1 year	Proportion with High Risk PDR within 1 year	Follow-up Interval
Mild	5%	1%	9–12 months
Moderate	27%	5%	6–8 months
Severe	52%	14%	3–4 months
Very severe	75%	45%	2–3 months

Source: American Academy of Ophthalmology, Diabetic Retinopathy Preferred Practice Pattern.

vision loss, but whether reducing serum lipid levels can affect progression of retinopathy has yet to be tested.

For local management of PDR, the therapies proven effective are scatter panretinal photocoagulation and focal laser photocoagulation. Side effects of the former include reduced peripheral, night, and color vision, so the preferred practice is to defer its use in patients whose PDR does not carry a high risk of vision loss. Focal laser photocoagulation of leaking lesions can reduce risk of moderate vision loss in patients with clinically significant macular edema, but it may produce scotoma (blank spots) in the visual field. Foveal burns may reduce visual acuity, and there may be an increased risk of choroidal neovascularization. In general, the mechanism by which photocoagulation therapies ameliorate progression is not well understood, but they have been proven effective.

For patients with a non-clearing vitreous hemorrhage or advanced PDR, vitectomy has been proven to reduce severe vision loss. However, the procedure risks include infection, retinal detachment, and recurrent hemorrhage. Vitrectomy to treat refractory macular edema is supported by anecdotal case studies but has not been proven in clinical trials.

Steroid injections are common in current clinical practice, although they have not yet been proven in controlled clinical trials. Anecdotal case studies suggest a short-term benefit, and several randomized clinical trials for long-term safety and efficacy are now in progress.

Dr. Ryan summed up the limitations in current management of diabetic retinopathy. Most important, screening rates are extremely low in populations that epidemiology studies show are at increased risk, even though it is well known that timely detection and treatment can prevent or slow the progression of diabetic blindness. For example, the screening rate in some communities in Los Angeles is less than 2 percent of diabetes patients. Progress on the monitoring front appears stymied by three mutually reinforcing factors: barriers to health care access in some communities, the lack of awareness and public education about the risks to vision from diabetes, and the fact that the disease is frequently asymptomatic until it is at an advanced level physiologically. Intensive systemic control of blood sugar and blood pressure is effective, but overcontrol can cause complications from hypoglycemia or hypotension. Finally, the clinically proven local therapies are nonspecific and destructive of normal structure and function. These local treatments do not target the underlying pathogenesis, and they do not address some mechanisms of visual loss such as macular ischemia.

Future management approaches must address each of these limitations. Effective early screening and public education are essential to prevent or delay onset of the ophthalmic consequences of unmanaged diabetes. The treatment goal must be to control blood sugar early and routinely, rather than relying on late-stage vitrectomy to limit or retard severe vision loss and blindness. Knowing more about the early predictors of disease progression will aid in identifying the patients at highest risk. A major challenge will be to establish and sustain targeted education programs that are effective in modifying lifestyle, increasing the awareness of diabetes complications, and communicating the importance of screening. From this standpoint, Dr. Ryan said, an implication of the rapid increase in obesity in both men and women in the United States is that entire behavior patterns need to be modified, beginning at the primary school level.

Non-mydriatic cameras (cameras that do not cause pupil dilation) can aid in standardized remote screening of fundus photographs, as has been done with the Joslin Vision Network and the Inoveon Diabetic Retinopathy System. Automated retinal diagnostics, digitized retinal

photography, and automated computer-based evaluation could be incorporated in an effective nationwide screening network.

New systemic therapies to achieve tighter physiologic control of blood sugar include pancreas transplants to restore normal insulin homeostasis. Devices that combine constant insulin monitoring with insulin pumps are another option. New classes of pharmacologic agents and insulin analogues will change the rate of insulin absorption from subcutaneous tissues to mimic more closely the normal secretion of insulin from the pancreas.

Novel local treatments being investigated include mild macular grid photocoagulation and the use of a micropulse laser to deliver short pulses of laser energy. In addition to these advances on current nonspecific approaches, local specific approaches are emerging. A specific therapy targets one or more of the fundamental pathophysiological mechanisms described by Dr. Frank. The objective in seeking effective specific local treatment approaches is to improve the risk-benefit profile, including less toxicity and fewer side effects, compared with current nonspecific treatments. Dr. Ryan discussed several classes of anti-VEGF agents that are in clinical trial for safety and efficacy in treating diabetic retinopathy: protein kinase C inhibitors, VEGF aptamer, anti-VEGF antibody, and corticosteroids.

Among other growth factors under study are insulin-like growth factor, PEDF, and AGE inhibitors. Clinical studies are also in progress for antioxidants and neuroprotection factors. A new, more potent aldose reductase inhibitor, Fidarestat, has been tested in an animal model but is awaiting clinical evaluation [59]. Adult stem cells derived from bone marrow (endothelial progenitor cells) have been programmed to either promote or inhibit retinal neovascularization [60]. Combination treatments such as focal laser photocoagulation combined with steroid administration are being assessed [61].

Thus, numerous novel therapies, targeting a specific aspect of the underlying pathogenesis of diabetic retinopathy, are on the horizon. The sheer number and diversity of candidates raises two issues for Dr. Ryan: (1) How can all these potential therapies be most efficiently evaluated? (2) How can clinical trials for the most promising candidates be rapidly

organized and efficiently conducted? A potentially major contributor to practical answers to both questions is the Diabetic Retinopathy Clinical Research Network (DRCR.net). This collaborative network is dedicated to facilitating multicenter clinical research on diabetic retinopathy, diabetic macular edema, and associated conditions. With 100 sites and 200 physicians currently participating, DRCR.net supports identification, design, and implementation of multicenter clinical research initiatives. Important to its efficiency are streamlined processes for research agreements and Institutional Review Board approvals.

Dr. Ryan concluded his presentation with the following summary observations:

- Systemic management of diabetes to prevent retinopathy will remain the most effective and important approach for reducing diabetic blindness in the future.
- Future systemic approaches will aim to achieve a normal physiological glucose/insulin homeostasis.
- Improvements in diagnostic technologies, combined with focused educational programs, will be critical for successful screening, early detection of disease, and prevention of disease progression.
- Local therapies for diabetic retinopathy management will target fundamental disease mechanisms. They will probably be synergistically combined for greater effectiveness.
- As specific therapies with fewer toxicities are developed, preventive strategies will be an important aspect of future management.
- Because diabetes is a chronic disease, sustained delivery platforms providing long-term dosing with therapeutic agents are likely to become an important facet of future treatments.

General Discussion on Diabetic Retinopathy

Dr. Bateman asked if there were estimates of the potential savings from effective screening for diabetic retinopathy. Dr. Ronald Klein replied that one estimate, based on the DCCT results, was that 1 million person-years of legal blindness could be avoided if tight glycemic control

could be sustained for the population with type 1 diabetes. A similar estimation has been applied to type 2 diabetes results from the UKPDS. Because the requisite screening and control programs are not cost-free and typically require a substantial up-front investment to realize the overall social benefit, detailed cost-benefit analyses were only performed in the 1990s, after the DCCT, ETDRS, and UKPDS.

Dr. Klein described anecdotally the difficulties in establishing even a basic program at the community level. These difficulties, he said, illustrate fundamental weaknesses in the U.S. health care delivery system. Dr. Klein and Dr. Ryan discussed some of the findings from the Los Angeles Latino Eye Study, which further illustrate how few of those at risk of diabetic blindness are even aware of their developing retinopathy [62].

The participants discussed current work in the area of telemedicine approaches to screening and patient monitoring. Dr. Ronald Klein, Dr. Yee, and others described some of the issues that have arisen, such as the extent of centralized analysis and interpretation of screening photographs, compared with capabilities, distributed among multiple sites, to deliver care and monitor patients in a local setting. Technology options, such as improved non-mydriatic cameras for fundus photography, are advancing. Administrative procedures that combine local screening of patients with centralized analysis and evaluation of the photographs have worked well. Dr. Straatsma commented that widefield non-mydriatic cameras are capturing retinopathy in the peripheral retina that would be missed with fewer or narrower fields. He noted that the burden on public health resources will only increase over time, if screening programs for conditions such as diabetic retinopathy are unavailable to undocumented aliens, more than half of whom are of Mexican ancestry.

The next area of discussion was the role of nonvascular retinal tissue and cell types in diabetic macular edema and retinopathy. In response to a question on the role of the retinal pigment epithelium (RPE) in failure of the blood-retina barrier, Dr. Campochiaro said that he has found the primary breakdown to be at the inner blood-retinal barrier. In severe cases, breakdown of the outer blood-retina barrier also occurs. The participants discussed clinical signs of RPE breakdown versus inner bar-

rier breakdown, such as the use of optical coherence tomography and functional testing to indicate RPE involvement. Dr. Frank noted that the RPE is a source of VEGF, which it normally secretes on its basal side (side toward the choroid). PEDF is secreted on the apical side (toward the photoreceptor cells and inner retina). This may explain, he said, why there normally are no blood vessels in the outer retina. Perhaps these growth factor secretion patterns are altered or even reversed in macular edema. As evidence that the pathogenesis of diabetic macular edema lies within the retina, Dr. Campochiaro described studies by his group of the effect of supplemental inspired oxygen on patients with diabetic macular edema. The results indicate that hypoxia plays a significant role in diabetic macular edema, and it is known that hypoxia leads to VEGF up-regulation. Administration of a VEGF antagonist also substantially reduced diabetic macular edema. So there is good evidence, Dr. Campochiaro concluded, that the primary pathology in diabetic macular edema is hypoxia, that VEGF plays a substantial role, and that VEGF antagonists can have a significant effect in reducing the edema.

With regard to maintaining blood glucose control, Dr. Bateman asked whether insulin pumps have helped to decrease incidence and progression of diabetic retinopathy. Dr. Frank described the results from the DCCT, in which one group of subjects was placed on insulin pumps and another had multiple daily injections. After the study period, during which administration was closely supervised, the group on insulin pumps regressed to about the same level of glycosylated hemoglobin as the group that had received injections, suggesting that patient compliance is essential even with the pump technology. Dr. Ronald Klein added that a problem with insulin administration for type 1 diabetes is avoiding severe hypoglycemia. The ability to administer insulin to tightly control hyperglycemia without inducing episodic severe hypoglycemia is the real dilemma in the whole treatment strategy. Dr. Frank agreed, noting that there was a fourfold increase in severe hypoglycemia in the DCCT tight control group, compared with conventional control of blood sugar.

Dr. Ronald Klein said that this issue of improved glycemic control extends further into the central themes of this symposium. Is health care that enables and supports tight glycemic control being extended

to minority groups? The only study currently tracking this over time, he said, is NHANES. However, a difficulty for national surveys such as NHANES is that there are very few persons with type 1 diabetes in the national sample studied. The WESDR and more recent NHANES data show that glycemic control is not improving much in the type 2 diabetic population in the United States. Only about 35 percent maintain the blood sugar levels recommended by the American Diabetes Association.

Dr. Wong and Dr. Ronald Klein discussed the differences in involvement of identified modifiable risk factors between African Americans and Hispanic Americans. Dr. Wong asked how strongly the results indicate that the elevated risk for African Americans is due to differences in health care access. Dr. Klein said there may be a number of factors involved, but that a similar degree of glycemic control would probably produce a similar effect on diabetic retinopathy across the ethnic groups. The relevant question, then, is what it takes to achieve that level of control for a particular group. Many factors could be involved in group differences on that question. Dr. Frank added that some cultural factors, such as degree of trust in one's doctor, might be more difficult to change than the term "modifiable factor" suggests.

In relation to neurotrophic agents—PEDF and others—that might be applicable to diabetic retinopathy and macular edema, Dr. Chader asked if there is evidence to suggest a specific neuronal cell type or class of cells that should be targeted for study. Dr. Frank replied that little is known yet about which specific cells in the retina are affected in diabetic retinopathy, even though, in terms of underlying pathogenesis, it is truly a disease of the retina. In this respect, the state of knowledge about diabetic retinopathy differs from that in AMD, retinitis pigmentosa, or glaucoma, where more is known about the neural cells involved in onset and progression.

Session 5

Degenerative Diseases of the Macula

Aging Macular Disease Worldwide

Dr. Paulus T.V.M. de Jong

The macula lutea of the retina was first described by Francesco Buzzi in 1782. A century later in 1885, the first formal report was published of macular degeneration associated with old age, then called "senile macular degeneration." Over the next 120 years, the name used for the disease has varied, with "age-related macular disease," "aging macular disease," and "senior macular disease" being recent contenders with the slightly older variants "age-related macular degeneration" and "age-related maculopathy." Fortunately, many of these variants share a common acronym: AMD.

A more difficult problem for epidemiology than the disease's name has been the variability in criteria for identifying AMD and its stages or variants. As a result, Dr. de Jong said, the diagnosis of AMD has typically been by exclusion of other similar-appearing disorders. Population-based studies are limited in the extent of verification criteria that can feasibly be implemented. Standardization of definitions and screening criteria for AMD incidence and severity (progression or disease pathway variant) have been problems, as they have been for glaucoma and diabetic retinopathy. The current international classification system

for AMD has several dozen signs and criteria to consider in identifying AMD and grading its severity. In a longitudinal study, how can incidence and progression be defined, in a way that enables meaningful cross-study comparisons, when so many distinct factors must be applied and weighed? Another problem for cross-study comparison and meta-analysis is the variation in reporting of prevalence and incidence statistics. For example, some studies report age-stratified prevalence or incidence with nonstandard age ranges, while providing no overall statistics by which readers can compare the results with other studies. Against this background of definitional and classification issues, Dr. de Jong described the five-stage classification system for incident AMD used by the Rotterdam Eye Study.

The reasons for pursuing the epidemiology of AMD include determining the magnitude of the public health problem, determining priorities in providing ophthalmic care to individual patients, and making decisions on allocation of research funds. For Dr. de Jong as a practicing ophthalmologist, the strongest reasons are to obtain insights into factors that might prevent, delay, or reduce irreversible losses of visual function in patients with AMD, to obtain clues about AMD etiology, and to generate new paradigms and hypotheses for AMD pathophysiology.

Studying AMD in diverse populations is a way to sort out the contributions of genetic and environmental risk factors, with nutrition and socioeconomic factors included in the latter category. Dr. de Jong reviewed the reasoning from current knowledge of the human genome for concluding that the traditional view of differing human "races" lacks a scientific basis and is of little interest for the epidemiology of AMD. On the other hand, a concept of ethnicity can be useful if it comprehends the environmental contribution from factors such as shared culture, nutrition, and language, plus secondary factors such as co-adaptation with parasitic or commensal species.[1] Also, the full range of objectively identifiable genetic factors must be considered, such as cytochrome P-450 diversity, pharmacogenetic differences, and others. To

[1]A "commensal" signifies a symbiotic relationship between organisms in which only one of the symbiants benefits.

illustrate potentially interesting *ethnic* differences in AMD prevalence, Dr. de Jong presented data from the EUREYE 2005 study for seven cities in seven different European countries. Late-stage AMD prevalences were in a band from 3 percent to 4 percent for five of the cities: Bergen, Norway; Tallin, Estonia; Belfast, United Kingdom; Paris, France; and Verona, Italy. Alicante, Spain, was exceptionally low at about 1.3 percent, and Thessaloniki, Greece, was high at 4.7 percent.

To prepare for the symposium, Dr. de Jong performed an extensive literature survey, comparing prevalence data for early-stage or any AMD from 60 published studies worldwide. He also compared prevalence data for late-stage AMD from 46 studies. Incidence data for early- and late-stage AMD were available from 11 studies, with study times ranging from 4 years in the Barbados Eye Studies to 14 years for data from Copenhagen. Dr. de Jong stressed, and the other participants agreed, that variations in study design and methodology of the various studies made it difficult to draw meaningful comparisons across them.

Based on his review of the epidemiologic literature on AMD, Dr. de Jong concluded that there was not yet decisive evidence of large differences in prevalence or incidence of early- or late-stage AMD among specific ethnic populations. The differences that have been found could be due to environmental or cultural influences. The inability to use demographic categories of ethnicity as indicators of genetic differences may be a major reason why clearer trends have not been confirmed in multiple studies. Dr. de Jong expects that the rapidly expanding knowledge about the molecular biology of ocular function and of ocular pathophysiology will help to clarify the roles of genetic and environmental factors in AMD and other eye diseases. For example, in the early 1970s, there were only about 25 publications annually on AMD and 5 on glaucoma. Recently there have been about a thousand articles annually on each of these diseases. His primary recommendations for the symposium to consider were to: (1) adopt an improved uniform classification system applicable to the constraints of population-based studies and (2) provide guidelines for minimum reporting of incidence and prevalence results in population studies, to allow for interstudy comparisons.

During the post-presentation questions, the participants discussed the reliability of data showing a lower prevalence for AMD in populations of African ancestry than in populations of European ancestry. A related topic was whether these differences, if real, are likely to involve genetic as well as environmental factors. Apparent ethnic differences in the ratio of geographic atrophy to choroidal neovascularization (CNV) in late-stage AMD were also discussed. There was general agreement that the reported results are constrained by the relatively small numbers of AMD cases in a general population sample and by the vagaries of classification described by Dr. de Jong. Some participants considered the lower prevalence of early- and late-stage AMD among African Americans, relative to the general population, to be reliably established; others questioned whether there might be additional environmental confounders that affected the reported results. There was general agreement that the results to date do not establish whether the differences observed are due to genetic factors, environmental factors, or a combination.

In response to a question about AMD prevalence among Asians and the types and severity of macular degenerative disease observed, Drs. Tano and Wong described recent study results comparing Asians and other ethnic groups. Dr. Tano said that macular disease in the Japanese population appears to have a different distribution of characteristics, such as lesion size and higher prevalence in males than in females, than has been reported for populations of primarily European ancestry. Dr. de Jong noted that this result contrasts with a recent study of residents of Hawaii, in which Hawaiians of Japanese or other Asian ancestry had the same prevalence of AMD as Hawaiians of European ancestry. Dr. Wong emphasized the point that recent population-based studies of Asians have not found as great a difference from European populations as has often been assumed. He described recent studies in which prevalences of cataract, glaucoma, and macular degenerative disease for Asian populations were the same as those reported for Americans of European ancestry in the Beaver Dam Eye Study and other studies. Until appropriate studies are done with a standard classification and grading system, he said, it will not be possible to state conclusively whether Asians differ in AMD prevalence from Europeans. The participants discussed the dif-

ficulty in controlling for ubiquitous environmental factors and how one might select study samples to control for such confounders, when testing for differences in genetic disposition to AMD incidence or progression. They agreed on the importance of identifying and confirming the principal risk factors for this disease.

The Pathogenesis of AMD

Dr. Peter A. Campochiaro

Several years ago, the debate about the role of genetic factors in AMD was similar to the current debate about myopia in being inconclusive. Now, however, there is general acceptance that AMD is a multifactorial disease in which genotype at least confers susceptibility to environmental risk factors, if not leading directly to pathology. Although the AMD phenotype is not fully established (as Dr. de Jong noted), Dr. Campochiaro presented a list of characteristic signs on which there is widespread agreement:

- Presence of drusen,
- Hyperpigmentation (indicating areas of proliferation of retinal pigment epithelium [RPE]) or hypopigmentation (areas of RPE dropout),
- Geographic atrophy (areas of atrophy of RPE, photoreceptors, and choriocapillaris; some variants of geographic atrophy may represent a distinct AMD phenotype) in late-stage AMD,
- CNV as a late-stage alternative pathway to geographic atrophy, and
- Detachments of the RPE.

A point of continuing debate is whether CNV occurs as part of a continuum from early-stage AMD or should be viewed as a distinctive complication of late-stage AMD. As Dr. de Jong noted, it is not uncommon for the same patient to have geographic atrophy in one eye and CNV in the other. Although these signs constitute the clinical phenotype called AMD, Dr. Campochiaro believes it is likely that several

different diseases, in terms of the underlying pathogenesis, share these clinically observable features. As the genetic components of these distinct diseases are identified and their physiologically distinct expressions are recognized, distinguishable phenotypes will be defined. This iterative process of refining and distinguishing phenotypes based on genotype discovery is occurring now for retinitis pigmentosa, which in the past was viewed as a single disease, rather than as a family of allied diseases, as it is now known to be.

The unequivocal risk factors for AMD are age, family history, and smoking. Possible risk factors, found in some studies but not in others, include the risk factors for cardiovascular disease, such as hypertension and a high-fat diet.

Some features of AMD pathology are well established. The rod photoreceptors seem more susceptible than cones, in that the rods die before the cones do. The biggest risk factor for CNV is diffuse thickening of Bruch's membrane. There are occasional giant cells (macrophages), but these are not a prominent feature of AMD. In CNV, Bruch's membrane is penetrated at multiple sites by new vessels originating from the choroid. Although the new vessels can be ablated by laser treatments, neovascularization typically recurs, indicating a continuing stimulus for this sequela. Vascular endothelial growth factor (VEGF) is certainly an important component of this stimulus.

The theories of AMD pathogenesis that Dr. Campochiaro discussed involve one or more of the following major mechanisms: inflammation, abnormalities of the extracellular matrix in Bruch's membrane, and oxidative damage. Attention is currently focused on the inflammation hypothesis because of the recent demonstration that a polymorphism in the gene for complement factor H occurs more frequently in AMD patients than in age-matched controls **[63, 64, 65]**. Although the meaning of this association for AMD pathogenesis is not yet clear, it is likely related to the role of factor H as a negative modulator of the complement cascade. The polymorphism may decrease the binding of complement factor H to complement-reactive protein or to heparin. The result would be to increase the participation of complement in damaging Bruch's membrane, thereby enabling new vessel prolifera-

tion through it from the choriocapillaris. However, functional studies to test this hypothesis are yet to be reported. A related line of evidence is that patients with a particular kidney inflammation called dense deposit disease (membranoproliferative glomerulonephritis II) also present an AMD-like phenotype. This disease, which can be caused by a deficiency in complement factor H, also produces deposition in Bruch's membrane of electron-dense drusen-like deposits, which include complement components. The protein constituents of typical AMD drusen include complement proteins, as well as others that appear more closely associated with an oxidative damage mechanism **[66, 67]**. Some epidemiologic studies of AMD have found elevation of complement-reactive protein in serum.

All these lines of evidence suggest that inflammation plays a role in at least some cases of AMD. However, questions about this mechanism remain to be answered. What are the functional consequences of the polymorphism for complement factor H? A cautionary note comes from the recent experience in presuming that proteases and protease inhibitors were central to AMD pathogenesis because a mutation in the gene for a protease inhibitor was identified as the cause of Sorsby disease, a macular dystrophy with early onset progressing to CNV. However, subsequent work demonstrated that mutant forms of the gene in patients with Sorsby disease do not affect the protease inhibitory activity of the protein. A second question is whether this polymorphism is associated with increased risk of AMD for other ethnic groups. Third, animal studies can be done with an existing mouse model that lacks the gene for complement factor H, but confirmation with a mouse model having this polymorphism would also be helpful. A fourth question is whether patients with dense deposit disease show evidence of inflammation of the choroid, Bruch's membrane, or the RPE even before they develop the AMD-like phenotype with CNV. Finally, do patients with inflammatory eye disease have a higher incidence of AMD?

The second major mechanism proposed for AMD involves abnormalities in the extracellular matrix in Bruch's membrane. One line of support for this hypothesis is that diffuse thickening of Bruch's membrane—not the presence of drusen—is the biggest risk factor for devel-

opment of CNV. A second line of support is that mutations in two fibulins, which are a family of proteins found in the extracellular matrix, cause AMD-like phenotypes [68, 69]. Although neither of these mutations is present in typical AMD patients, further work on the entire fibulin family found that 7 of 402 AMD patients had sequence variations in another fibulin: fibulin 5. None of these sequence variations occurred in 429 age-matched controls [70]. The sequence changes are in a section of the gene for fibulin 5 where a base change significantly alters the expressed protein. This work also found variants of other fibulins that occurred only in AMD patients and not in controls. It thus appears that fibulin variants cause AMD-like phenotypes, and at least some typical AMD cases—currently estimated at 3 to 4 percent—involve fibulin variants. Additional work has been done that elucidates how variations in the fibulins lead to abnormalities in the extracellular matrix. In particular, the fibulin-5 variants may interfere with formation of elastin, a connective component of Bruch's membrane. All the AMD patients with these variants had some RPE detachment. If this association is confirmed, it may be the first clinically recognizable phenotype of a distinctive AMD genotype.

A third line of evidence supporting the extracellular matrix mechanism is the discovery that mutant forms of a tissue inhibitor of metalloproteinases (TIMP3) cause thickening of Bruch's membrane and an AMD-like phenotype. TIMP3 differs from the other three known TIMPs in being insoluble and binding tightly to the extracellular matrix. It is normally found in high concentration in Bruch's membrane. In addition to being a metalloproteinase inhibitor, TIMP3 inhibits angiogenesis. The mutations of interest all involve a change at one end of the protein, a change that enables protein aggregation. Fibulin-3 is a strong binding partner with TIMP3, and the two proteins are colocalized in Bruch's membrane in disease states including AMD.

A fourth line of evidence relates to a single base pair mutation in a cysteine protease inhibitor, cystatin C. Although cystatin C is expressed throughout the body, it is particularly abundant in RPE cells, which secrete it from their basal surface into the extracellular matrix of Bruch's membrane. When the variant cystatin C is expressed, it accumulates in

the cell's mitochondria preferentially to being secreted. This variant was associated with an increased risk of AMD in 167 German patients, compared with 517 controls (odds ratio = 2.97) [71].

Another AMD-like phenotype, with thickening of Bruch's membrane, drusen-like deposits, and perhaps CNV, occurs in a mouse model deficient in a chemokine, Ccl2, or the Ccl2 receptor. The chemokine is involved in macrophage function, and the deficient mice have fewer macrophages in Bruch's membrane [72]. This linkage suggests that macrophages may play an essential role in removing some of the normal buildup of material in Bruch's membrane. A human study of sequence variations in another chemokine receptor, CX3CR1, supports the hypothesis that macrophages are needed to remove normal deposits and may reduce the risk of AMD [73]. Still another AMD-like phenotype, including CNV, occurs in a late-onset retinal degeneration caused by a mutation in the short-chain collagen CTRP5. The mutation results in buildup of extracellular matrix in Bruch's membrane [74].

All this evidence suggests that abnormalities in the extracellular matrix in Bruch's membrane can lead to AMD-like phenotypes. Some patients with AMD have protein variants linked to AMD or AMD-like phenotypes, and there are mechanistic explanations why these variants should increase the risk of AMD. There are, of course, many unanswered questions about the linkage of such abnormalities with AMD. The mechanism by which the fibulin mutations cause AMD or an AMD-like phenotype is still not definitively known. Is it excessive extracellular matrix or some other pathway? Are there variants in other components of Bruch's membrane that also increase AMD risk (and may represent distinct disease genotypes)? Of central importance to this symposium is whether there are ethnic variations in prevalence of these AMD-linked genetic variants. To Dr. Campochiaro's knowledge, these variants have not been studied in populations of African or Asian ancestry. As an extension of the mechanism, are there mutations that increase the risk of AMD in other genes related to controlling the turnover of extracellular matrix in Bruch's membrane?

The third major mechanism proposed for AMD pathogenesis is oxidative stress. The Age-Related Eye Disease Study showed that anti-

oxidants and zinc reduce the incidence of neovascular AMD in patients already at high risk for CNV (e.g., a patient who already has CNV in the fellow eye) [75]. Dr. Campochiaro was surprised that a positive effect of antioxidants taken as a dietary supplement could be demonstrated, and the positive effect with zinc was a further surprise. Those favoring a role for complement factor H in the inflammation mechanism have argued that zinc is needed for normal functioning of factor H. Zinc is also a cofactor for numerous enzymes, including metalloproteinases and superoxide dismutase.

A second line of support for the oxidative stress mechanism are proteomic analyses of drusen, which found a large number of oxidized proteins, as well as the complement-related proteins noted above for the inflammation mechanism [76]. The analyzed drusen also contained crystallins, which are proteins that protect against oxidative damage.

A third line of evidence involves lipofuscin, which is postulated to cause oxidative damage and accumulates in the RPE of patients with Stargardt's disease and to a lesser extent in AMD patients. In the presence of light or other oxidative conditions studied in vitro, the major constituent of lipofuscin, A2E, acts as a generator of free radicals, which damage cells. Although the specific mechanism responsible for recessive Stargardt's disease (and the large amount of lipofuscin produced by it) does not play a substantial role, if any, in AMD, the lipofuscin that is present in AMD may play a role in oxidative damage of RPE cells. A transgenic mouse model with a mutant form of ELOVL, a family of enzymes involved in elongation of very long chain fatty acids, also accumulates lipofuscin (containing A2E) in the RPE. In humans, this ELOVL mutant is responsible for autosomal dominant Stargardt's disease. The mouse model develops retinal degeneration that is greater in the central retina than in the periphery [77].

A fourth line of evidence is that iron-induced oxidative damage may result in an AMD-like phenotype. In a mouse model deficient in two metal-processing proteins, ceruloplasmin and hephaestin, iron accumulates in the retina and RPE. The subsequent retinal degeneration is hypothesized to result from oxidative damage [78]. Human patients deficient in ceruloplasmin also have an overload of iron and develop an

AMD-like phenotype. Furthermore, postmortem examination of eyes from AMD patients has found increased levels of iron in the RPE [79].

A fifth line of evidence ties directly to the issue of population differences in AMD susceptibility. Some polymorphisms in the gene for paraoxinase, a protein that prevents oxidation of low-density lipoproteins, have been associated with increased risk of AMD in a Japanese cohort [80, 81]. There was no association found in persons with Anglo-Celtic ancestry. Thus, there may be polymorphisms that increase risk of AMD in one ethnic group but are either not present or do not produce the risk (because of other factors) in another ethnic population. The larger lesson from this work is that a difference in a single nucleotide pair within a gene can make a substantial difference in disease risk and in the disease phenotypes in different populations.

In summary, Dr. Campochiaro said that susceptibility to AMD is a complex trait. Several genetic variants are known to, or are likely to, increase susceptibility to environmental factors; several are known to, or are likely to, decrease susceptibility. It is very likely that genetic differences among different racial groups include differences in these AMD susceptibility genes. Thus, one can anticipate that there will be different AMD disease subtypes and different responses to therapies, depending on the AMD-relevant genotype of the patient. These differences can be used to learn more about AMD pathogenesis. They may also require differential therapeutic approaches to provide the most effective care.

Questions for Dr. Campochiaro were included in the general AMD discussion after the presentations by Drs. Bird and Tano.

Clinical Management of AMD: Present and into the Future

Dr. Alan C. Bird

In populations of European ancestry, CNV is by far the most common form of late-stage AMD. In treating CNV, the objective is to destroy the new vessel complex while preserving the RPE and photoreceptor cells. The disappointing results of current laser-based CNV treatments may in part come from the nature of the close physical proximity of the cell sys-

tems to be preserved and the vascularization to be removed, combined with the amount of heat energy delivered to the area by the treatment techniques. Another possibility is that the RPE is already discontinuous prior to treatment and photoreceptors overlying the discontinuities are already lost. Dr. Bird described the evidence favoring the first possibility for classic cases of AMD-related CNV.

When Dr. Bird began examining CNV patients using fundus autofluorescence of lipofuscin prior to treating their CNV, he expected to find evidence of RPE discontinuities. If the distribution of the lipofuscin fluorescence signal in the central retinal region is uniform, he reasoned, then the RPE is intact, the photoreceptor population is normal, and photoreceptor outer segments are being recycled normally.[2] Brighter than normal areas indicate a higher metabolic load on the RPE cells, resulting in increased lipofuscin accumulation. Dark regions within the otherwise fluorescing central region are a sign of RPE cell loss, photoreceptor cell loss, or both. As expected, cases of retinal tear and retinal scarring show dark areas on the autofluorescence. image corresponding to the loss of RPE. However, many patients who had substantial loss of visual acuity and fundus photographs showing classic areas of CNV but no lesions retained continuous, uniform autofluorescence. This pattern indicates continuous RPE throughout the area of neovascularization. In these cases, the new vessel complex must therefore still be external to the RPE layer. Even after lesions occurred from the area of CNV, the autofluorescence remained normal and continuous. This implied that the RPE layer was physically continuous and had not been disrupted by the new vessel complex. In general, Dr. Bird and his colleagues found no clear correlation of abnormal autofluorescence with either loss of visual acuity or with duration of CNV. The implication is that one cannot assume that a patient who presents with CNV has irretrievably lost either RPE or photoreceptors in the area of neovascularization.

If RPE and photoreceptors are retrievable in many patients presenting with CNV, do the current treatments damage the functional systems

[2]Phagocytosis of photoreceptor outer segment discs and recycling of their components was described in the third Eye Disease Symposium report: [3], p. 9.

that one wants to preserve? Dr. Bird reviewed the theory underlying photodynamic therapy (PDT), in which a dye (verteporfin) absorbing at the wavelength of a low-energy laser is preferentially associated with endothelial cells of the new vessel complex. When laser light irradiates the dye, the resulting photosensitization of the endothelial cells should kill them selectively, destroying the complex but leaving nearby RPE and photoreceptor cells largely undamaged. However, the dye in fact diffuses beyond the endothelial cells of the new vessels, so the cellular damage from photosensitization is not sufficiently localized to the new vessel complex [82].

An alternative to physical treatments, which are not sufficiently selective at the histologic level, is to use a biological agent that targets the new vessel complex more specifically. In the clinical trial of Macugen (pegaptanib sodium), a VEGF-inhibiting aptamer, the Macugen treatment performed better than PDT [83, 84]. Nevertheless, in Dr. Bird's view there was a disappointing loss of visual acuity within 6 weeks (2 letters), continuing to a loss of 8 letters after 2 years. An ideal treatment for CNV should produce a gain in visual acuity, at least initially, if the RPE and photoreceptors are not yet irretrievably lost. Macugen did not stop new vessel growth and did not halt leakage. However, other biological agents, or mixtures of several, may work better.[3] Dr. Bird believes that, before patients are admitted to new trials of CNV treatments, they should first have autofluorescence examinations to determine whether their RPE and photoreceptors are present. Moreover, autofluorescence monitoring during treatment should be used to follow the survival of photoreceptors and RPE.

Next, Dr. Bird turned to the relationship between pathogenesis and treatment approaches for geographic atrophy, the second most frequent late-stage outcome of AMD. Geographic atrophy is preceded by an increase in central retina autofluorescence, followed by a loss of photo-

[3]Since Dr. Bird's presentation in June 2005, much more promising results for inhibiting CNV have been reported from the clinical trial of another aptamer, ranibizumab (Lucentis) [85]. Dr. Bird describes these results as proof of the principle that, with a good biological agent for inhibiting CNV, vision improvement can be expected.

receptor cells. The current understanding of the recycling of photoreceptor outer segment discs is that the shed discs form a phagosome, which is engulfed and degraded by the RPE cell. Recycling of most phagosome components to the outer segment is crucial, as the supply of new constituents from plasma is insufficient to sustain the normal rate of outer segment disc formation and replacement. If phagosome degradation is experimentally blocked, the outer segments become shorter and eventually the photoreceptor cells die. Rod photoreceptors are more susceptible than cones. Lipofuscin increases the pH within the phagosome, which halts degradation and the recycling of outer segment component materials. One hypothesis for reducing geographic atrophy is to reduce the accumulation of lipofuscin by reducing the vitamin A supplied to the retina.

A third late-stage outcome of AMD associated with visual loss is RPE detachment. Dr. Bird and his colleagues have developed the hypothesis that detachment occurs because Bruch's membrane becomes hydrophobic and fluid derived from the RPE cannot escape freely through it to the choriocapillaris [86]. In this case, prevention of the accumulation of lipids in Bruch's membrane, or mobilization of lipids already present, might be a reasonable prophylaxis or treatment for RPE detachment.

A frequently reported effect of laser coagulation is that it causes drusen to disappear. Several trials of this approach to treat large drusen are in progress, but the biology underlying the effect is unclear. One hypothesis is that the laser treatment increases macrophage activity. After a laser spot destroys a small area of RPE, surrounding RPE cells migrate into that area. Laser coagulation has been used to decrease the risk of visual loss in the fellow eye when a retinal tear has already occurred in one eye. Dr. Bird suggested that further investigation of these phenomena are needed to understand what is happening and to assess whether laser coagulation as a treatment for some late-stage conditions might be improved.

Concerning the Age-Related Eye Disease Study trial of dietary supplements, Dr. Bird was surprised that the group of patients with large drusen (category 3) and those with geographic atrophy in the fellow eye did not benefit, at a statistically significant level, from a supplement of

antioxidants and zinc. The only group that unequivocally benefited was patients with CNV in the fellow eye. He noted that, despite the size of the study sample, the entire positive effect was that 12 patients did not have visual loss who would have been expected to have loss if untreated.

In his summary, Dr. Bird recommended that future treatment of CNV should aim to disable the new vessel complex but spare the RPE. More knowledge of the properties of the RPE and of the pathogenesis of CNV will enable better treatments with biological agents than those currently being tested. Again, the objective should be to kill new endothelial cells in the blood vessels without affecting the RPE cells. Patients selected for CNV trials should be characterized first with respect to RPE loss, and autofluorescence or other techniques such as optical coherence tomography (OCT) should be used to monitor RPE status during and after trial treatments. Better delivery systems are needed, particularly for controlled delivery of optimal agent concentrations over an extended time. Genetic discoveries are likely to provide new forms of treatment, better ways to identify those at elevated risk, and better animal models for studying pathogenesis and proposed therapeutic approaches. To compensate for the lack of a fovea and short life spans in the most likely species for transgenic models, additional degrees of stress on the central retina may be appropriate to produce effects similar to those of aging in the human macula. The genetic and environmental factors that contribute to initiation and early to intermediate progression of macular disease need to be investigated further. There is insufficient understanding of the intermediate mechanisms leading up to the late-stage outcomes, when visual loss is difficult to avoid. In particular, other animal models that reproduce any portion of an established AMD pathway will provide valuable tools for further learning.

During the question period, Dr. Bird said that he and his colleagues have not investigated ethnic differences in autofluorescence. Dr. Bird described his interest in using autofluorescence to compare the population of Iceland, where geographic atrophy is the dominant late-stage endpoint, with other populations where CNV is the dominant AMD endpoint. In answer to a question on potentially important differences among drusen, such as the older interest in hydrophilic versus hydro-

phobic drusen, Dr. Bird agreed that differences in drusen may be worth studying, as some soft drusen autofluoresce and others do not. The amount of neutral lipid in drusen varies, and it correlates well with fluorescein binding to the druse.

Clinical Management of Polypoidal Choroidal Vasculopathy: Present and into the Future

Dr. Yasuo Tano

Dr. Tano began by describing the emergence, over the past 15 years, of recognition that polypoidal choroidal vasculopathy (PCV) is a disease distinct from other macular degenerative disease [87, 88, 89]. Prior to that time, PCV, AMD, and retinal angiomatous proliferation were typically diagnosed as the same disorder. Dr. Tano estimates that more than 30 percent of cases formerly diagnosed as AMD in Asian patients are in fact PCV. It appears to be more prevalent in populations of Asian or African ancestry than in populations of European ancestry (table 7).

A cautionary note is that, in 2002 when PCV was first being recognized in China and the diagnostic method for it was still primitive, the prevalence among presumed AMD cases was just 9.3 percent. Two years

Table 7. Prevalence of PCV in Patients Initially Diagnosed with AMD

Population	Prevalence (%)
American	6
Caucasian	4
Italian	9.8
Greek	8.2
Japanese	23
Chinese (2002)	9.3
Chinese (2004)	22.3

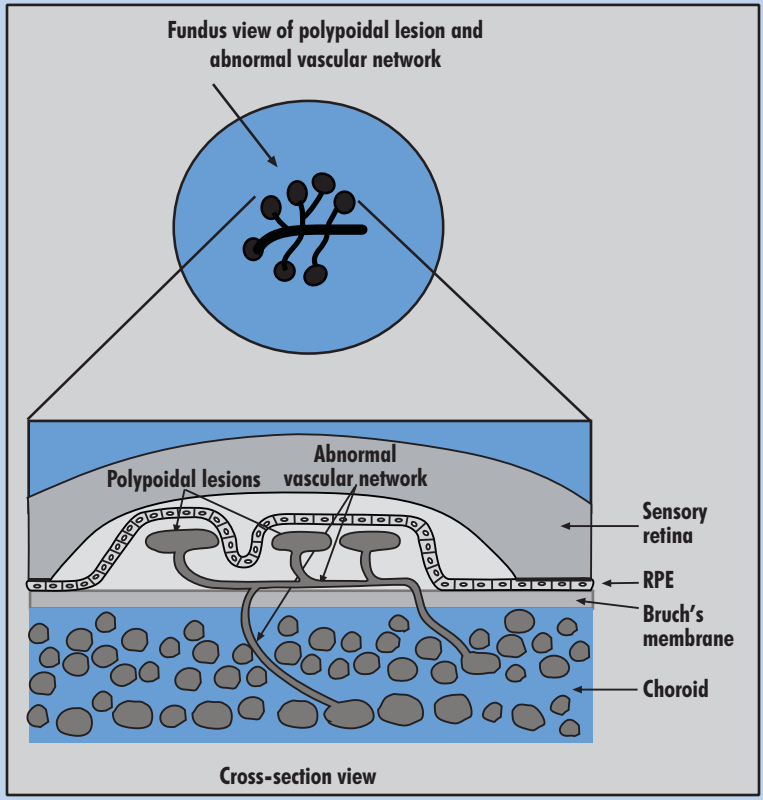
later, a prevalence of 22.3 percent was reported from a study of Hong Kong Chinese. Anecdotally, one Chinese ophthalmologist has said that his cases are up to 40 percent PCV. Thus, the low percentages reported in some populations may reflect diagnostic capability rather than an objective difference in the ratio of AMD to PCV among choroidal neovascularization patients.

Early-stage PCV is characterized by multiple recurrent serosanguinous RPE detachments, progressing to massive retinal hemorrhage and posterior uveal bleeding syndrome. In PCV the new vessel network typically displays pulsating bulb-like nodular lesions at the termini of the new vessels. These polypoidal lesions are located between the RPE and Bruch's membrane (figure 6). The new vessels are highly dilated, often occur in clusters, and have very thin walls.

Among the significant clinical characteristics of PCV, the relative risk for developing PCV is 4.2 times higher for persons of Asian or African ancestry compared with those of European ancestry. The mean age at onset is 60–68 years. Males represent 65 to 68 percent of PCV patients in Asian populations but only about 15 percent in populations of European ancestry.

Although a diagnosis of PCV can be made using funduscopy or fluorescein angiography, indocyanine green (ICG) angiography is the preferred technique for visualizing PCV dilatation and the abnormal vascular network surrounded by polypoidal lesions. More recently, OCT has been used as a substitute for ICG angiography. Protruding orange-red lesions in the funduscopic field, in either the macular or papillary region of the retina, are a necessary condition for a diagnosis of PCV. When fresh, the legions are red to orange-red; with age they become whitish yellow to whitish gray, as fibrin accumulates. Regions of RPE atrophy are often associated with older areas of neovascularization. Other features occur that resemble typical AMD phenomena, making an ICG angiograph essential for correct diagnosis in some cases. Dr. Tano and his colleagues have characterized two subtypes of PCV lesion: exudative and hemorrhagic. The hemorrhagic type more closely resembles AMD. In fluorescein angiographs, areas of nodular hyperfluorescence associated with the polypoidal legion "hot spots" are typically surrounded by granu-

Figure 6. Polypoidal Choroidal Vasculopathy



Source: Adapted from Uyama, M. et al. *Text and Atlas of Macular Diseases.* Tokyo: Igaku-Shoin. 2000, p. 115.

lar hyperfluorescence. Characteristic features of PCV in OCT imagery include steep, dome-like elevations of the RPE where polypoidal lesions raise the RPE off Bruch's membrane. The abnormal vascular network appears as irregular thickening of the RPE line with a double-layer signature. Thus, careful examination with the proper tools can definitively distinguish PCV from AMD.

PCV can cause significant visual loss through three sequelae: (1) persistent exudation from subfoveal polypoidal lesions, (2) submacular dense hemorrhage, and (3) development of subfoveal neovascular

lesions or subfoveal classic CNV. Fairly often, individual polypoidal lesions regress spontaneously, over a period of months to several years, leaving an enlarged network of blood vessels visible by ICG angiography.

Current treatments for PCV include conventional laser photocoagulation, feeder-vessel treatment, transpupillary thermotherapy, PDT, and full macular translocation. Laser photocoagulation is successful if no post-operative subretinal hemorrhaging occurs. The grapelike polypoidal lesions can often be fully ablated. However, potential complications from laser photocoagulation include, besides subretinal hematoma, a classic CNV disciform response to photocoagulation treatment, RPE atrophy at the fovea, and recurrent exudative change.

If a lesion is under the fovea and a feeder vessel into the subfoveal network can be located, then feeder-vessel photocoagulation may be an appropriate treatment. Dr. Tano described successful use of this technique in which the lesion subsequently disappeared and visual acuity was restored to 20/20. If the feeder vessel is found, the treatment success is about 80 percent. However, in only about 20 percent of cases can the feeder vessel be identified. Transpupillary thermotherapy is seldom used now, but it can work well in some cases.

PDT is at present the more common treatment for subfoveal PCV. Improvement in visual acuity has been reported in 45 to 67 percent of cases, with stabilization of vision in 87 to 95 percent **[90, 91, 92, 93]**. Although these results compare favorably with the use of PDT for CNV in late-stage AMD, there is substantial risk of subretinal hemorrhage after PDT treatment of PCV lesions. Subretinal hemorrhage occurred in 11 of 45 eyes treated for PCV (25 percent), compared with just 2 of 125 eyes treated for AMD (1.6 percent). These hemorrhages typically occur between 1 and 3 months after the PDT treatment, not immediately after it.

Dr. Tano described the treatment of subretinal hemorrhage using a pneumatic displacement technique to move the hemorrhage away from the macula. PDT may follow if necessary. In some cases, visual acuity after displacement can be as high as 0.9 or 1.0, but CNV or subsequent hemorrhage at the macula often occurs. Treatment success is very low if the displacement treatment occurs more than 2 weeks after the hemor-

rhage begins. In treatment of 42 eyes by pneumatic displacement of a submacular hemorrhage, 19 percent had improved acuity at follow-up, 33 percent were stabilized, and 43 percent had decreased visual acuity after treatment. The mean time to follow-up examination after treatment was 23.5 months and ranged from 6 to 95 months.

Dr. Tano summarized current clinical management for PCV as follows: If vision is good and no exudates or lesions are observed, no treatment is performed. If vision is decreased and there are any exudates or lesions present, then extrafoveal lesions can be treated with thermal laser photocoagulation. Subfoveal lesions can be treated with PDT. Subfoveal lesions with an identified extrafoveal feeder vessel can be treated by photocoagulation of the feeder vessel. If there is vision loss and subretinal hemorrhage, pneumatic displacement can be used for a minimal to moderate hemorrhage. Massive subretinal hemorrhage requires surgical drainage. For macular or peripapillary PCV, thermal laser or feeder-vessel photocoagulation can be employed, but not PDT because of damage to the optic nerve fibers. Because the knowledge of PCV and experience with its treatment are relatively recent, Dr. Tano thought it premature to suggest what the trends might be for future clinical management. If post-operative hemorrhage can be avoided, PCV appears relatively straightforward to treat.

During the post-presentation questions, Dr. Ronald Klein asked about the reliability of using fundus photography to diagnose PCV, given that population studies typically cannot undertake ICG angiography or OCT as a screening procedure. Dr. Tano replied that the reliability of funduscopy is probably sufficient for screening populations of European ancestry. However, the darker the eye pigmentation, the more difficult clear differentiation of PCV will be. ICG angiography is the key to making a final diagnosis. In response to Dr. Klein's second question on the prevalence of PCV lesions in the general population in Japan, Dr. Tano said that such a study has not been done, but he suspects that at least 20 to 30 percent of AMD cases in populations of East Asian ancestry are PCV.

In response to a question on the percentage of grapelike PCV lesions that progress to the RPE atrophic stage, Dr. Tano said that it depends on

the subtype of the lesions. The exudative variety can persist for a long time. If the subretinal network persists, a whitish spot indicating RPE atrophy will develop. But there may also be spontaneous regression of the lesions and the new vessel network, with return of good vision. In answer to another question, Dr. Tano said that most ophthalmologists working on PCV believe the appearance of the subretinal neovascular network represents dilation of the vessels rather than the new vessels that occur in CNV. This represents an important difference between PCV and wet AMD. In response to a question about the prevalence of geographic atrophy in the Japanese population, Dr. Tano said that, according to the Hisayama study, the prevalence was about 0.2 percent [94]. This is lower than in populations of European ancestry. The only familial connection for PCV appears to be the indirect factor of hypertension. Hypertension increases the risk of hemorrhage, and hypertension has a familial association.

Dr. Bird asked if macular disease appears to be increasing in prevalence in Japan, as others have suggested. Dr. Tano agreed, noting that when he started residency training, he saw no cases of AMD or PCV. He did not begin to see AMD-like lesions until 15 to 20 years ago. With respect to whether AMD presents differently in the Japanese population than it does in populations of European ancestry, Dr. Tano said that the typical AMD case in Japan has much fewer drusen and much less geographic atrophy. Both hard and soft drusen occur, although segregated soft drusen may be more frequent. Although the CNV complex in wet AMD may typically be smaller, it is otherwise similar to CNV in persons of European ancestry. Asked about the hypotheses informally suggested for this apparent emergence of macular disease in the Japanese population over the past several decades, Dr. Tano said that this increase coincides with the cultural change from a traditional Japanese diet to one increasingly similar to that of the United States and Western Europe. The coastal areas of China are now experiencing an increase in both AMD and proliferative diabetic retinopathy, but not areas further inland, where traditional diets and lifestyles still dominate. He added that the increase in PCV may be related to the increase in hypertension in Japan.

General Discussion on Degenerative Diseases of the Macula

Dr. Campochiaro replied to a question on the total percentage of AMD cases that would be covered by the AMD-like phenotypes of specific genetic variations he had described during his presentation. The March 2005 publications on the complement factor H polymorphism reported that 50 percent of AMD patients in the sample studied had this gene variant. However, Dr. Campochiaro added, having the variant does not in itself give the individual AMD; it increases susceptibility in some way. For the fibulin variants that have been associated with AMD-like phenotypes, the total percentage is perhaps 4 to 5 percent of AMD cases. He further cautioned that the reports of other genetic variants with AMD-like phenotypes are still isolated reports and association studies. These preliminary results require further documentation and confirming studies in different patient populations.

Dr. de Jong confirmed that the 50 percent number is about what has been found for the complement factor H polymorphism in the Rotterdam Eye Study AMD population. There is also a dose-dependence effect, as patients who are homozygous for the polymorphism have an even higher odds ratio than heterozygotes. When presence of the polymorphism is combined with presence of complement-reactive protein, the odds ratio for risk of AMD rises to 20.

Dr. Chader affirmed Dr. Campochiaro's point that a number of these early, indicative reports require follow-up and replication to confirm their hypotheses. He cited the example of the ABCA4 gene in Stargardt's disease, which initially was viewed as a major factor in AMD pathogenesis. A key point, he noted, is that polymorphisms or mutations in specific genes probably increase susceptibility or create a disposition, which can be triggered or increased by environmental factors such as smoking, or perhaps diet, as well as by additional genetic factors. The discussion continued, with general agreement that the research results are showing that AMD is multifactorial, with a range of both genetic and nongenetic conditions underlying events in the extended and branching pathways from initiating events or conditions to disease endpoints that cause visual loss or blindness. However, the participants also agreed

that the tools for unraveling this complexity—such as DNA samples from all participants in the major population studies, the human genome mapping from the Human Genome Project, and the new diagnostic and imaging technologies—are far more powerful than those available just five years ago.

The participants also agreed that continuing skepticism is warranted about the more sensational interpretations of some early results. The good news is that associations between genetic factors, such as the gene variants described by Dr. Campochiaro, and conditions resembling stages of complex ocular diseases are being found. The caveat is that these results often turn out to be more limited than initial optimistic interpretations suggest. In particular, the lay media tend to overemphasize these optimistic extremes, leading the general public to believe that persons who will get a disease like AMD later in life already can be identified by genetic screening. Extrapolations from results in a small study population to a larger population—either an entire ethnic group or the general population—are often disconfirmed when further studies are performed. The participants discussed some of the study design limitations and sample biases that can skew results, as well as the prospects for employing global population diversity as a tool for carefully controlled and designed studies.

Dr. West said that Dr. Campochiaro's presentation had impressed on her the "family of diseases" character of diseases like AMD, when the prevailing clinical diagnostic criteria are applied. "We are putting into one bag [one ocular disease] a lot of very different disease pathways and endpoints," she said. She asked the group to consider what efforts can be made, and at what level they should be pursued, to characterize genetically relevant phenotypes more closely. Dr. Bird agreed with her point and described the way in which his group is developing a computer-searchable database of AMD case characteristics. This database can identify AMD cases that have the same or similar qualitative as well as quantitative characteristics. DNA samples have been collected for all 1,600 cases in the database. Qualitatively defined phenotypes of AMD will be needed, he said, not just prevalence data for AMD generically. Dr. Wong described the International CNV Study, in which a

number of research centers in the Asian-Pacific region are cooperating in investigating the proportion of CNV cases that are related to AMD, PCV, severe progressive myopia, or other pathologies. The data from this study will also be available for phenotype studies within a disease family such as AMD. Dr. Ronald Klein noted that analyses of the genetic data for AMD have been limited in the past by uncertainties in how to define disease onset and the stages in progression prior to late-stage endpoints. His comments brought out the importance of an iterative process between genotyping analyses of genetic information and phenotype studies that incorporate known or suspected genetic associations.

Following up on Dr. Wong's comment about the International CNV Study, Dr. Campochiaro asked Dr. Tano about the percentages of CNV he sees that can be attributed to pathologic myopia, as opposed to AMD or PCV. Dr. Tano replied that his clinic in particular has a high rate of referrals for CNV from progressive myopic degeneration of the retina, but less than the number of cases of AMD-related CNV.

Dr. Chader summarized some of the differences in disease characteristics among populations of Asian, European, and African ancestry that had been described during all of the symposium presentations. For the final day of the symposium, he asked the participants to consider the implications of these differences for understanding the pathophysiology of these ocular diseases and ultimately for improved treatments. At the least, he said, this wealth of information on disease differences should be mined, and the potential advantages for research presented by population diversity should be pursued systematically. The other participants responded with examples of issues and study efforts that could be undertaken to address them, if international cooperation were a priority.

Business Perspectives on Transitioning New Treatments into Practice

Along with inviting participants who could provide insights on the causes and treatments of complex ocular diseases in diverse populations, the meeting organizers sought to stimulate discussion on how to improve the transition from research results to practical delivery of benefits to patients. Given that new medical treatments become generally available only after commercialization by companies in the private sector, two entrepreneurs with extensive track records in successful commercialization were invited to address the symposium. Dr. Eugene de Juan, one of the most successful entrepreneurial academic ophthalmologists, spoke to the participants on Tuesday morning. Mr. Alfred Mann, who has had a distinguished career in bringing innovative medical devices to market, spoke at the symposium dinner on Monday evening. Both speakers were asked for their ideas on how best to foster partnerships with the private sector to move promising research through clinical trials and into practical treatments for ocular diseases.

Paths to Treating Diverse Eye Diseases in the Future

Dr. Eugene de Juan

Dr. de Juan introduced his presentation as a reflection on his personal experience in developing more than 100 products for commercial medical use. Knowledge alone is not enough, he insisted; we must apply the knowledge. Being willing to apply it is not enough; we must do it. He

distilled the lessons from his own experiences into three axioms for transitioning new treatments from the laboratory bench to the clinic.

Axiom I

The economic value of a new (and better) proprietary treatment is directly proportional to its clinical value. Thus, a highly effective treatment for a serious, previously untreatable disease like age-related macular degeneration or diabetic retinopathy will have—and will deserve—a high economic value. A corollary to this axiom is that a new treatment will fail if it cannot be sustained economically—that is, if someone cannot make a living selling it.

Axiom II

Economic value integrates many other values. More than just dollars, economic value includes social costs and benefits. The costs to society of functional impairments are huge. If the health care that we know about were to be delivered fully to the population at risk, the social value would be immense: far beyond the value of continuing research while delivering only the current level of care.

Dr. de Juan applied these two axioms to the question of when to decide to pursue a therapy. The problem addressed by the therapy must be well defined; the medical need must be understood. His personal preference is to think about problems that have a discernible solution, so that the path forward is clear. In addition, to have economic value, the treatment developer must be able to get the new treatment to patients within a reasonable time. There must also be evidence of safety and efficacy in humans.

A second question that can be answered from these axioms is "Who should develop new therapies?" Physicians who understand both the science and the patients' disease should be the proponents of new therapies. Unfortunately, the research doctors who meet this criterion are "frogs": they are like amphibians who live half their lives in the research laboratory and half in clinical practice. Because of difficulties these frogs face in surviving with their time split between clinical practice and research, Dr. de Juan sees a growing crisis for therapy development and transition. The salary that a researcher funded by the National Institutes

of Health can make is half what a doctor makes in a medical teaching center, and that is half what the physician can make in private practice. Research physicians, therefore, are an endangered species of "frog," and society needs to find ways to save the species from extinction.

If one assumes that the medical value of a new treatment equals its economic value, then seven factors jointly determine this value:

- The number of patients;
- The severity of the disease;
- The stage of life when the patient is affected;
- The societal costs of patients affected with the disease;
- The difference in quality of life for patients with the disease, compared with that for successful treatment;
- Societal perception of the need for treatment (example: the fear factor in AIDS or avian flu); and
- The effectiveness of the treatment.

These factors can be applied to evaluating the medical value of treatment for any disease. When a new company—or a new program within an existing venture—is being started to market a treatment for any disease, the first step is to evaluate these seven factors. That is always the first thing done in a business environment, but it is never the first consideration in evaluating research grant applications or research papers submitted for publication. If the desired outcome is getting the treatment to patients, economic value should be the driver. In evaluating these factors to determine medical/economic value, consideration of population diversity is intrinsic because it influences many of the basic seven factors: the number of patients, the stage of life, societal costs, etc. Dr. de Juan therefore sees no need to argue for ethnicity or related group distinctions as a separate consideration when assessing the medical value of a new treatment.

Axiom III

The cost of development of a new treatment has to be less than the time-adjusted risk of the untreated disease. In short: you cannot always lose money.

In discussing this axiom, Dr. de Juan presented some economic fundamentals of new treatments for a disease. Fifty percent of medical profits come from the U.S. market. So treatments have to be approved in the United States if an investor wants access to half of the potential profit. One way to evaluate the value to the affected individual of a treatment is to ascertain the value to the individual of avoiding the dysfunctional consequences of living without treatment. How much would one pay to be able to hear, to see, etc.? To avoid prejudices about the cost of medical treatment in dollars, Dr. de Juan likes to express such values in units of consumption items, such as "BMW units." How many BMWs would one forego for functional health? When expressed in these units of comparative value, he said, the cost of current treatments, such as $2,000 for cataract surgery, is not high.

The avoidable societal cost if patients receive more effective treatment is another economic variable that requires more serious evaluation. What is the cost to society if the treatment is not available or, even if available, is not followed by the patient? Dr. de Juan illustrated this point with the practice in Iceland of enforcing treatment to prevent diabetic retinopathy in diabetes patients. The basic argument is essentially the same as the argument for requiring occupants of a car to wear seatbelts or to use car seats for small children.

On the topic of how to drive new treatments toward acceptance in medical practice, Dr. de Juan offered the following suggestions. First, determine who is paying and why they are paying for it. Second, make an argument for the economic value of treatment based on the cost of treatment relative to the total costs, to the individual and to society, of not treating the patient. Target the needs of government entities, health insurers and society, as well as the needs of the patient. Do not ignore the economic interests of the physicians (do they get paid to give the treatment, or do they lose income if the treatment is effective?), the economic interests of the companies, or even the economic and career interests of academic researchers.

To illustrate his three axioms, Dr. de Juan discussed why surgical techniques and surgically implanted devices are successful. They are primarily developed by physicians for clear medical problems that have

a foreseeable solution. Clinical testing typically comes much sooner in the development process than occurs in therapeutic drug development. In his opinion, the animal models used in developing drug-based therapies are not always reliable predictors of the clinical response to pharmacological treatment of the human form of a disease. For example, no animal model for diabetes develops diabetic retinopathy, and there is no adequate animal model for age-related macular degeneration.

On the role of academic medicine, Dr. de Juan said that art and science are products of affluent societies, which can afford to support individuals in activities that do not produce revenue. Academic goals, such as grant-based research and personal education, are not the same as societal medical treatment goals. Because they are not intrinsically focused on achieving final ends, academic structures lack strong incentives to achieve practical results. By contrast, for-profit companies have to reach practical ends to stay in existence. Therapeutic medical research, Dr. de Juan concluded, should start with showing that it is possible to reach the end goal. It should follow a more business-oriented approach, with a clear, documented plan that shows how the proposed treatment approach will be economically cost-effective, barring unforeseeable events. Most eye treatments do not come about through a fully rational path. There are many false starts. What happens in tissue cultures or an animal model is not the determining factor in eventual success or failure of the treatment; human response to the treatment is by far the major factor. In general, successful eye treatment therapies were not developed from knowledge about disease pathogenesis but from attempts to treat the pathological consequences of the disease.

Major obstacles that need to be overcome to produce more rapid and effective therapies, according to Dr. de Juan, include:

- Lack of academic incentives for development, rather than just invention. Most of the medical/economic value is in the development.
- Lack of academic recognition for the value of being in a supporting role. Academic rewards to entire research teams are needed.
- The work is too complicated for an individual to make substantial progress alone. New organizational structures are needed that support and foster effective teaming and provide rewards for it.

- Academic communities need a clearer understanding of conflict of interest issues. Academic institutions need to develop practical, functional policies on conflict of interest.
- Issues concerning the equity stake for researchers on federal grants must be resolved.
- The academic reward system needs revision to value true humanitarian accomplishment (societal benefit) rather than just traditional academic measures.
- A feasible yardstick is needed to measure progress toward desirable outcomes, with tangible rewards based on that progress.

Dr. de Juan concluded with some suggested lessons for improving the government role in implementing new treatments.

- Fund treatment development efforts.
- Support development of new means for rapid, inexpensive testing.
- Fund people as much as ideas.
- Support translational efforts. Involve more physicians who are involved in treating patients.
- Support mentoring programs. Research physicians lack the time for effective mentoring, but this is a highly productive interaction, which produces long-term societal benefits.

An Entrepreneurial Perspective on Transitioning Research into Delivered Health Care Products

Mr. Alfred E. Mann

After the dinner for symposium participants and guests on Monday, June 13, Dr. Robert White of the Washington Advisory Group introduced a guest speaker, Alfred E. Mann. Mr. Mann is noted for his work in developing and bringing to market a range of medical devices including heart pacemakers, drug delivery technologies for treatment of diabetes, cochlear implants, and neurostimulation systems to compensate for a range of neural deficits. He currently serves as chairman of the board and chief executive officer of MannKind Corporation, a diversified bio-

pharmaceutical company focused on developing novel therapeutics and drug delivery systems. Mr. Mann was elected to the National Academy of Engineering in 2000.

In his remarks, Mr. Mann focused on an example of the partnership between academic scientists and companies in developing a retinal implant. He began by recalling the beginnings of his association with Dr. Mark Humayun and Dr. de Juan on extending the use of implanted electrode devices for restoration of hearing to restoration of vision.[1] The development process began by using a set of specially built goggles to determine the minimum number of pixels needed for useful vision. The team estimated that about 600 pixels were necessary. To study what could be learned from a simple retinal stimulation device, they began with a simple 16-pixel implant that could be transformed from a cochlear implant. To produce useful visual percepts from an electrode device implanted on the surface of the retina, the plan was to work up to 64 pixels, then 256, and perhaps ultimately to 1,000 pixels.

The first patient to receive the 16-pixel implant was a 74-year-old man who had been blind for 50 years. In the first test after the device was implanted, a large "L" was projected on the wall in front of the patient. When he was asked if he could see anything, the patient answered, "Not really." As disappointment settled into the team, he added, "Just a couple of lines. One goes like this (indicating a horizontal line with his hand); the other goes up and down." At a later date, this patient was taken outside. He just kept looking up at the sky, saying, "Isn't that beautiful, isn't that beautiful!" Thus, surprisingly good results were obtained, even with this 16-electrode prototype implant.

The retinal device has now been implanted in six patients. The third was a woman who was able to recognize individual items of tableware placed in front of her with just the 16-channel implant. The team, currently comprising about 60 people, represents a good working partnership between academic scientists such as Dr. Humayun and the engineering expertise of a for-profit company. The team is now finishing test-

[1]Dr. de Juan described the biomimetic epiretinal implant system in his presentation at the third Eye Disease Symposium. See **[3]**, pp. 52–55. This retinal prosthesis has been reported in technical detail by Dr. Humuyan and colleagues **[95, 96]**.

ing and integration on a 60-channel device, which will be implanted in patients in 2006. During the next year, improved software for this system will hopefully provide a virtual equivalent of 500 to 1,000 pixels. The device may not restore sight in the fullest sense, Mr. Mann said, but such a system may enable blind people to have useful visual perception. It may allow a blind person to recognize friends sitting around a table or to read the large-print version of the *Reader's Digest*.

Mr. Mann concluded with comments on other drug delivery systems and advanced bionics on which MannKind Corporation and other of his companies are currently engaged. In pursuing a program for a spinal cord stimulation system to relieve chronic pain, Mr. Mann identified a parallel need for a pump for delivering drugs. Mr. Mann told the engineers that ultimately a pump is needed that can be mounted on the head, to deliver drugs to the brain, eye, or ear. A device that could deliver new classes of drugs directly to these sites could help in multiple specialties. It must be refillable as well as programmable, with an accurate delivery system, and the development effort will require several more years. Noting the symposium's interest in diabetic retinopathy, he described recent discussions of an insulin delivery system for type 2 diabetes, capable of maintaining normal glycemic function without the risk of hypoglycemia or hyperglycemia.

A recurring theme throughout Mr. Mann's remarks was the necessity for an entrepreneurial spirit, coupled with the value of close liaison between the academic research community and private companies, in bringing new medical technology into the market.

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Appendix A

Symposium Participants and Observers

Co-Chairs

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Other Attendees

Robert Drabkin, *Symposium Organizer*
Los Angeles, California

John Hetherington, M.D., *Symposium Organizer*
University of California Medical Center
Belvedere, California

Alfred E. Mann, *Special Guest Speaker*
MannKind Corporation

Elaine Robinson, *Program Administrator*
Washington Advisory Group, an LECG Company

Robert M. White, Ph.D. *Program Director*
Washington Advisory Group, an LECG Company

Robert J. Katt, Ph.D., *Rapporteur and Consulting Technical Writer*
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Appendix B

Symposium Agenda

Sunday, 12 June 2005

8:30–9:30 a.m.	Informal meetings of the four presentation teams 1. Myopia 2. Glaucoma 3. Diabetic Retinopathy 4. AMD and PCV
9:30–10:00 a.m.	Welcoming remarks and logistics – *Dr. Robert White*

Session 1: Introduction: Ethnic Differences in Eye Diseases

10:00–10:40 a.m.	Ophthalmic Epidemiology: Lessons for Treatment of Ocular Diseases in Divergent Populations – *Dr. Sheila West*
10:40–11:20 a.m.	Clinical Considerations: Lessons from China and Far East – *Dr. Robert Yee*
11:20–12:00 a.m.	Worldwide Education and Training in the Detection and Treatment of Eye Diseases – *Dr. Bradley Straatsma*
12:00–12:30 p.m.	General Discussion: striking differences, trends in the future, impact on American ethnic groups, etc.
12:30–1:30 p.m.	Lunch

Session 2: Myopia

1:30–2:10 p.m.	Epidemiology – *Dr. Leon Ellwein*
2:10–2:50 p.m.	Pathophysiology – *Dr. Earl Smith III*
2:50–3:30 p.m.	Clinical Management: Present and into the Future – *Dr. Tien Yin Wong*
3:30–4:00 p.m.	Break
4:00–5:00 p.m.	General Discussion on Myopia

Monday, 13 June 2005

Session 3: Glaucoma

8:00–8:40 a.m.	Epidemiology – *Dr. Barbara Klein*
8:40–9:20 a.m.	Pathophysiology – *Dr. David Freidman*
9:20–10:00 a.m.	Clinical Management: Present and into the Future – *Dr. Paul Kaufman*
10:00–10:30 a.m.	General Discussion on Glaucoma
10:30–10:45 a.m.	Break

Session 4: Diabetic Retinopathy

10:45–11:25 a.m.	Epidemiology – *Dr. Ronald Klein*
11:25 a.m. –12:05 p.m.	Pathophysiology – *Dr. Robert Frank*
12:05–1:00 p.m.	Lunch
1:00–1:40 p.m.	Clinical Management: Present and into the Future – *Dr. Stephen Ryan*
1:40–2:10 p.m.	General Discussion on Diabetic Retinopathy

Session 5: Macular Degeneration Diseases and Neovascularization

2:10–2:50 p.m.	Epidemiology – *Dr. Paulus de Jong*
2:50–3:15 p.m.	Break
3:15–3:55 p.m.	Pathophysiology – *Dr. Peter Campochiaro*
3:55–4:35 p.m.	AMD Clinical Management: Present and into the Future – *Dr. Alan Bird*
4:35–5:15 p.m.	PCV Clinical Management: Present and into the Future – *Dr. Yasuo Tano*
5:15–5:45 p.m.	General Discussion

Tuesday, 14 June 2005

Session 6: General Recommendation and Final Report

8:30–9:00 a.m.	The Path to Treating Diverse Eye Diseases in the Future – *Dr. Eugene de Juan*
9:00–11:00 a.m.	Reports and Draft Recommendations from the Sessions 15 minutes for recommendations (bullet points) 15 minutes for discussion
9:00–9:30 a.m.	1. Ethnic Differences in Eye Diseases – *Dr. Sheila West*
9:30–10:00 a.m.	2. Myopia – *Dr. T. Y. Wong*
10:00–10:30 a.m.	Break
10:30–11:00 a.m.	3. Glaucoma – *Dr. Paul Kaufman*
11:00–11:30 a.m.	4. Diabetic Retinopathy – *Dr. Stephen Ryan*
11:30 a.m.–12:00 p.m.	5. Macular Degenerative Disease – *Dr. Alan Bird*
12:00–1:00 p.m.	General Discussion: New Ideas and Final Report
1:00 p.m.	Adjourn