Looking Forward to 20/20: A Focus on the Epidemiology of Eye Diseases

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INTRODUCTION

The personal, social, and economic consequences of blindness and visual impairment continue to be important public health issues, especially in less developed countries. Based on 1990 population figures, there are an estimated 38 million blind persons, or 0.7 percent of the world's population, with best corrected visual acuity in the better eye of 3/60 or worse (1). This number is estimated to increase by 1–2 million persons each year. In addition, another 110 million persons, or 2 percent, have low vision, defined as best corrected visual acuity between 6/60 and 3/60 in the better eye (1). However, such statistics do not capture the fact that the burden of blindness falls disproportionately in the developing world, both because of the sheer numbers in their populations and because age-specific rates are severalfold higher compared with similar rates in North America or Europe. Moreover, the numbers do not convey the obscenity that probably two thirds of the blindness is due to causes that are either avoidable or remediable.

Projected demographic shifts globally suggest that visual loss will continue to be a public health problem into the future. Predictions for the population of the world foretell a "graying of the globe" as the proportion of those aged 65 years and older increases. With this aging will come a shift in the burden of diseases toward the chronic, age-related morbidities seen predominantly now in industrialized countries. While human immunodeficiency virus/acquired immunodeficiency syndrome will probably continue to take its devastating toll on the young adult populations in parts of Asia and Africa, for the most part, mortality from infectious diseases will be superseded by mortality from chronic diseases. This shift will have its parallel in a shift in the leading causes of blindness and visual loss, as infectious causes such as trachoma and onchocerciasis diminish in magnitude, and age-related causes such as cataract increase.

The last 30 years have brought an upsurge of interest in bringing public health approaches to understanding the distribution and causes of the major blinding eye diseases in the world. Knowledge of the epidemiology will guide both future research and programs targeted toward blindness prevention. Concerted efforts on both fronts are necessary, as the next century holds special significance for the eye care community: The year 2020, beyond the obvious characterization of excellent vision, is the target of the World Health Organization Global Initiative for the Elimination of Avoidable Blindness (2). The initiative, in partnership with governments, nongovernmental organizations, universities, and others, is a commitment to reduce blindness considered avoidable from diseases such as cataract, trachoma, onchocerciasis, and vitamin A deficiency (1). Control efforts are based, for the most part, on our understanding of the epidemiology of the disease.

In this short review, it is impossible to cover epidemiologic research in a field so heterogeneous as diseases of the eye. Rather, a synthesis of current knowledge for six of the main causes of visual loss will be presented, with a focus on the future of the epidemiology of eye diseases in the next century.

CATARACT

The major cause of blindness in the world is cataract or opacification of the ocular lens. An estimated 16–20 million persons are blind from cataract, although it is curable through cataract surgery with appropriate correction. In the United States, over 1.2 million cataract surgeries are performed per year, at a cost to Medicare of over 3.4 billion dollars (2). However, for most of the developing world, cataract surgery is inaccessible. From a public health perspective, then, research efforts in the prevention of blindness from cataract follow two major tracks. The first is health management research on how to provide effective, affordable, and safe cataract surgery. The second avenue is determining
risk factors for cataract, especially those that might result in interventions to delay either the onset or progression of the opacification process. It is in this arena that sound epidemiologic investigations are particularly contributory.

Progress in cataract epidemiology has been helped considerably by the recognition of three major types of cataract, each distinct anatomically and etiologically (3). Nuclear and cortical opacities are the most frequent types, with posterior subcapsular opacities more rare in the population. Nuclear and posterior subcapsular opacities are more frequent in surgical series because they tend to be more visually disabling. Of interest is the finding of variation in the prevalence of the different cataract types, comparing Caucasians versus African Americans (4, 5). Analyzed by type of cataract, Caucasians tend to have more nuclear and posterior subcapsular opacities compared with African Americans. These differences are not entirely explained by differences in exposures and suggest a fruitful avenue for further research into why the lens may have different susceptibilities within different ethnic groups. Of particular interest are populations, such as reported in India (6), where visual loss from cataract develops at earlier ages than in populations from more industrialized countries.

Risk factors, besides the well-known association with age, for each of the cataract types have been evaluated in numerous epidemiologic studies, and important strides have been made. Nuclear opacities have been linked to smoking, with evidence from a number of studies in different populations. The relation is biologically plausible, with a dose-response relation (3). Posterior subcapsular opacities may also be linked to smoking, although the evidence is less well established. Posterior subcapsular opacities have also been linked to steroid use and to alcohol use, particularly heavy drinking (3). Cortical cataracts have been associated with cumulative exposure to ultraviolet B radiation in sunlight (3). Recent research has demonstrated that even with the low levels typically seen in the general population, there is a demonstrable increased risk (7). For each of these factors, there are simple ways to modify exposure, or prevent exposure, in order to decrease the risk.

Theoretically, lens opacification can also result from inadequate defense mechanisms to protect the proteins and membranes from oxidative stress, as might occur with chronic exposure to ultraviolet B. Thus, several investigations have focused on the role of diet and supplement use in providing antioxidant protection against cataract. However, the results often have been conflicting and do not suggest that any one micronutrient or supplement is protective. Ongoing clinical trials may provide data on any protective effect from the use of specific supplements; at present, the promotion of vitamins or minerals to prevent cataract is unjustified.

As cataract epidemiologists look forward into the next century, where are the fruitful avenues for research? As the global population ages, visual loss from cataract will continue to cause a significant burden of visual loss. One important avenue of research is clearly outcomes research. The determination of the effectiveness of programs to reduce cataractous blindness, in terms of both surgical coverage and visual rehabilitation, is of paramount concern. Recent data from India and China raise concerns about the long-term successes of programs in these areas and should lead to remedial action (8, 9). Genetic epidemiology holds promise for elucidation of the etiology of cataract. Several studies are currently underway to identify candidate genes for lens opacification. The genetic components of posterior subcapsular opacities, nuclear and cortical cataract, have not been studied in detail, although one set of studies suggests a strong genetic component for the latter two types (10, 11). Studies in twin populations have great potential to add to research in this area.

At present, no genes that may be involved in the opacification process, such as those which regulate the lens crystallins or gap junction proteins, have been linked strongly to age-related cataract. Once likely candidate genes are discovered, epidemiologic studies on the importance of the genes within populations will be crucial. Studies that also focus on gene-environment interactions will probably yield the most new information. However, until there are laboratory breakthroughs in the genetics of cataract or new markers linked to cataractogenesis, it is unlikely that any further cross-sectional studies or even longitudinal studies will yield significant information on major new risk factors for cataract; rather they will elucidate the risks associated with known factors.

There is considerable medical and financial interest in identifying an antcataract agent, so it is likely that work by basic scientists will proceed on potential new drugs. Ultimately, clinical trials will be needed to assess the efficacy of any new agent, which will raise the questions of when to begin treatment and for how long. Much thought must be given to appropriate human models for testing drugs against age-related cataract, which generally takes a long time to develop from insults that may be lifelong.

Other epidemiologic studies consider cataract or lens opacities as independent predictors of disability and death. Several investigators have found that nuclear cataract or mixed nuclear cataract is an independent predictor of mortality, even adjusting for sev-
eral other strong predictors (12). Such findings may provide a window for biologists in the field of aging to locate a common pathway describing both lens opacification and other premortal events at the cellular and subcellular levels. The field of cataractogenesis illustrates well the feedback loop necessary between laboratory science and epidemiology in order to advance etiologic research.

**TRACHOMA**

The second leading cause of blindness worldwide is an infectious eye disease caused by *Chlamydia trachomatis*. Trachoma, once endemic in most countries of the world, has largely disappeared from industrialized countries and, thus, has largely been forgotten as a cause of blindness. However, this ocular infection continues to affect an estimated 590 million people, of whom 5.9 million are irreversibly blind, and remains hyperendemic in many areas of Africa, Asia, and the Middle East (13). The highest rates of trachoma are found in the most resource-poor communities and among the most vulnerable members—women and children.

In the last 10 years, considerable progress has been made in the understanding of trachoma immunology, epidemiology, and approaches to control (13). Yet, many links are still not well understood along the pathway from initial ocular infection, to repeated reinfec-
tion that is the hallmark of trachoma, to scarring of the conjunctiva, and finally to trichiasis (in-turning of the eyelashes until one or more touch the cornea) and corneal opacification. The long time course from active disease in children to sequelae in middle age or later has prevented detailed longitudinal studies. The acquisition of repeated infections or persistent infection suggests the absence of any long-lasting protective immunity. In fact, the immune response may be the key factor for the serious clinical manifestations of trachoma and is a significant issue for research into a candidate vaccine. There appears to be a subset of persons in these hyperendemic communities who are unable to clear infection and who respond with severe, inflammatory trachoma that persists over time. Such children are at greater risk of developing scarring and probably represent the subgroup at risk for blinding sequelae.

A major, multisectorial campaign to eliminate blinding trachoma as part of the World Health Organization’s global initiatives has just been launched. The strategy relies on provision of surgery to repair existing trichiasis, antibiotics to communities to reduce the pool of chlamydia infection, and improved water and hygiene to interrupt transmission. Projects on trachoma control have been launched in five countries, with several others in the planning stage. For the future, important epidemiologic research on trachoma can take place in the context of this new initiative. For example, the role, if any, of persistent infection remains to be elucidated, along with the immunologic characteristics of persons susceptible to persistent infection and disease. In particular, the significance of the relatively high rate of laboratory evidence of infection in the absence of disease, particularly in adults, is not understood. Newer laboratory techniques for detection of chlamydial DNA have revolutionized our understanding of the relation between trachoma and chlamydial infection, and even greater understanding of infection will emerge with the use of quantitative techniques. The use of genovar typing has the potential to elucidate the source of new infections in communities after mass treatment, and new mapping technology used longitudinally can chart the spread of disease over time. As a result of past active trachoma in persons in hyperendemic communities, trichiasis will continue to be a major problem for at least 20 years into the future. If epidemiologic studies can determine risk factors for the progression of disease from conjunctival scarring to trichiasis, then interventions may be designed and tested that will interrupt the progression. With concerted effort by epidemiologists, program managers, and all the partners in the initiative, trachoma may well decline as a cause of blindness worldwide.

**ONCHOERCIASIS**

Onchocerciasis or “river blindness” remains an important public health problem in the 30 African countries with endemic foci. At present, an estimated 300,000 persons are blind from the disease (1). A nematode worm is the cause of onchocerciasis. Ocular lesions and other systemic manifestations are caused by the microfilariae or first stage larvae of the adult worm. Microfilariae can be found in all the ocular tissues except the lens. In the cornea, manifestations can lead to sclerosing keratitis, a common cause of blindness in the savannah regions. Microfilariae in the posterior eye tissues can lead to optic neuritis, optic atrophy, and choroidalretinal lesions. The microfilarial load in an infected person can reach 150 million, and infected persons are the source of infection for the blackfly vector. Heavy transmission is associated with ocular complications of onchocerciasis, with data showing that the highest prevalence rates of ocular complications are found in the villages with the highest transmission rates (14). The different strains of *Onchocerca volvulus* are also associated with differences in the risk of blinding complications. Onchocerciasis is transmitted by blackflies that breed
in rivers and streams (hence the alternative name for the disease). As many as 10–15 percent of the population are blind in the communities hardest hit by onchocerciasis (14). Villages lose their male work force to blindness, and eventually the villages are deserted with subsequent loss of arable land.

A large body of work has characterized the epidemiology of onchocerciasis that reflects the complex interactions among the populations at risk, the vectors, and the parasite itself (14). Since 1987, the prevalence of onchocerciasis and its blinding complications has been decreasing, largely because of the distribution programs for ivermectin, a safe and effective microfilaricide. National onchocerciasis control programs planned or functional in 36 countries are aiming for zero incidence of blindness from the disease by 2020 (1). Already, 11 countries in west Africa have eliminated onchocerciasis as a public health problem with an estimated 600,000 cases of blindness prevented (1). Clearly, the hope for achieving the goal for the future lies with adequate coverage of communities with mass chemotherapy using ivermectin.

Future epidemiologic research on onchocerciasis can contribute to improving the control programs. For example, research is needed on the development and evaluation of methodologies for monitoring the outcomes of mass distribution on parasite density and ocular and dermal complications of diseases. The effect of mass treatment on reducing transmission and the added benefit of vector control need further investigation. Finally, because the adult worms can live up to 20 years, ivermectin distribution programs must be maintained for several years until the macrofilariae have died out. Therefore, there is need of a safe and effective macrofilaricidal agent that can be used in mass campaigns. The safety and efficacy of such agents will need testing in appropriate clinical trials.

**VITAMIN A DEFICIENCY**

The strides made in prevention of blindness from onchocerciasis are matched by the global effort to reduce childhood vitamin A deficiency and the ocular complication of xerophthalmia. Vitamin A is necessary for the maintenance of myriad physiologic functions, including rod and cone function and normal epithelial cell differentiation. With vitamin A deficiency, dysfunction of the rods (night blindness), corneal xerosis, ulceration, and necrosis (keratomalacia) can occur. Sommer (15) has demonstrated correlation between the severity of xerophthalmia and the mean level of serum retinol and carried out seminal work showing the rapid reversal of clinical manifestations with vitamin A therapy. The link between low levels of vitamin A and childhood morbidity and mortality, however, propelled the issue of vitamin A deficiency into a major public health problem. With the endorsement of the reduction of vitamin A deficiency worldwide as part of the policy of several national and international organizations, major programs on supplementation and fortification are underway. Although it is currently estimated that xerophthalmia blinds about one-half million children every year, as a result of current efforts, vitamin A deficiency is not expected to be a major cause of blindness in the next millennium (1).

Epidemiology continues to have an important role within this initiative. As Sommer (15) points out, there is an urgent need for a robust field technique that can definitively test individual vitamin A status. Such potential tests will need standard evaluations of validity, reliability, and predictive value prior to implementation.

**AGE-RELATED EYE DISEASES**

National and international control efforts to reduce blindness from infectious causes and large-scale efforts to reduce childhood blindness from xerophthalmia will result in a greater proportion of global blindness attributable to eye diseases of aging. In addition, reduced mortality in many developing countries, together with a dropping birth rate, virtually ensures a greater burden of visual loss from these causes in the future. The primary, age-related eye diseases are cataract (which has already been discussed), glaucoma, and macular degeneration.

**Glaucoma**

Glaucoma is a slowly progressive loss of retinal ganglion cells, resulting in atrophy of the optic nerve and loss of peripheral visual function. About 10 percent of those affected lose the ability to read and become legally blind. However, glaucoma is still in the early stages of being characterized epidemiologically. Several types of glaucoma are now recognized, chiefly, angle closure and open angle types, each with different risk factors (16).

Open angle glaucoma was formerly defined as a condition of "elevated" intraocular pressure, arbitrarily set at >21 mmHg, 2 standard deviations above the mean (16). Population-based surveys have since demonstrated that more than half of those with glaucomatous field loss have intraocular pressure <21 mmHg (17). As a result, the clinical paradigm has shifted so that glaucoma is based on structural optic nerve damage and functional loss of peripheral field. There are investigators who subdivide open angle glaucoma into "low tension" glaucoma versus classical glaucoma accompanied by elevated intraocular pressure, but this classification is not universally accepted (17).
Several population-based studies of glaucoma have been carried out, providing new data on prevalence, incidence, risk factors, and genetic contributions. However, comparison among them is difficult because of differences in characterizing glaucoma. Thus, one area that requires further work is standardization of diagnostic methods, including intraocular pressure, cup-disc ratio, visual field testing, and inclusion of gonioscopy (the latter examination vital to identifying angle closure glaucoma).

From the studies carried out thus far, a few key risk factors have emerged. The primary risk factor for open angle glaucoma is elevated intraocular pressure. While it is clear that using intraocular pressure alone as a diagnostic criterion or screening tool should be discouraged, the prevalence and severity of glaucoma increase with increasing intraocular pressure, and high intraocular pressure is a risk factor for development of glaucoma.

Ethnic differences in the prevalence of the various types of glaucoma are marked. African Americans are at four times higher risk for open angle glaucoma compared with Caucasians, with the highest rates being reported in Caribbean Blacks (16, 17). On the other hand, angle closure glaucoma appears to be more common among Asian populations, particularly Chinese persons (16). Smaller ocular dimensions, particularly a shallower anterior chamber, are more common in persons with angle closure glaucoma. Females are also at greater risk for this type of glaucoma, although the reasons for the gender predilection are unclear.

A family history of glaucoma confers greater risk of open angle glaucoma, and twin studies show a moderate heritability index (19). Several genetic loci and one sequenced gene for glaucoma have been reported and are currently being investigated.

Glaucoma represents a ripe field for epidemiologic investigation in the next century. The development and testing of new screening modalities are a high priority with a new field test showing great promise at present. Further work on the different rates of open angle glaucoma among Caribbean, African, and African-American Blacks should lead to the identification of new, possibly environmental risk factors. Exciting strides in the genetics of glaucoma should lead to epidemiologic studies in different population groups. The long-term value of treatment for angle closure glaucoma requires further testing. Reduction of intraocular pressure has been shown to be effective for halting progression of field loss, but decisions on the optimal use of drugs, surgery, or laser treatments (particularly in less developed countries) await further trials.

**Age-related macular degeneration**

Age-related macular degeneration (AMD) is the leading cause of visual loss in older Caucasians in the United States. In the most severe forms of AMD, either the retinal pigment epithelium may atrophy completely (geographic atrophy or "dry AMD"), or growth of new vessels and leakage can occur (exudative or "wet" AMD), with possible detachment of the retinal pigment epithelium and retina as well. There is currently no effective treatment that will prevent AMD or restore vision once it has been lost. Treatment to delay the progression of vision loss is effective only for a relatively small subset of those with exudative AMD. Thus, research into the pathogenesis and treatment of this disease should have a high priority.

Progress has been made in the development of standardized systems for classification of AMD, using stereoscopic fundus photographs (20). The ocular lesions thought to be early signs of AMD are also part of the standardized system but are undergoing scrutiny. For example, one early sign (drusen, >63 μ or soft drusen) appears to be common with increasing age, is relatively unstable over time, and is equally common in racial groups at low risk for severe AMD (21-23). It is probable that the degenerative changes in the retina are the result of multiple pathophysiologic processes, many of which are not visible in fundus photographs and, thus, do not lend themselves to ready definition of early disease for epidemiologic purposes. Further work on imaging systems, particularly those that might characterize alterations in an important retinal component (Bruch's membrane), would be invaluable in identifying early stages of disease.

Risk factors for AMD have been investigated in a number of epidemiologic studies. Interest in a possible association between AMD and cardiovascular disease, as well as in the potential for common risk factors, has driven much research. However, the results have been inconclusive. The relation with blood pressure or hypertension is inconsistent. Most studies have not found any relation between serum cholesterol and AMD. A direct link between AMD and cardiovascular disease has also been inconsistent, although a possible link with evidence of carotid artery disease is intriguing (24). The most consistent finding is the association with cigarette smoking. A dose-response relation has been found between cigarette smoking and neovascular AMD in case-control, cross-sectional, and prospective studies (25). A cross-sectional, population-based study found no significant association with signs of early AMD, although a prospective study in the same population linked smoking to the risk of developing very large (≥250 μ) drusen (26, 27). Such data again point to the lack of concordance between risk factors.
Four cross-sectional surveys provide data to suggest that Caucasians have higher prevalences of severe AMD, compared with either Mexican Hispanics or African Americans (or Barbadians). Few differences were observed in the prevalences of early AMD (22, 23) although some signs showed variation by ethnic group. Studies currently underway in diverse populations offer fruitful opportunities for research into the genetics of AMD. In fact, several lines of research demonstrate the important role of genetics in the development of AMD. Much work remains in this area, however, as the phenotypic heterogeneity and genetic heterogeneity of AMD point to a very complex disorder. Work with the ABCR gene and its variants was initially promising, but it now appears less likely to be a major genetic risk factor.

The role of light damage in the risk of AMD is unsettled, although the theory has biologic plausibility. The difficulties of characterizing retinal exposure to either visible or near-ultraviolet radiation have resulted in significant measurement error in studies attempting to evaluate the association. Moreover, the retina has numerous defense mechanisms against oxidative stress. Thus, the association between chronic exposure to light and increased risk of AMD, if one exists, is probably very complex and may reflect heightened susceptibility to light damage coupled with a particular pattern of exposure that evades adaptation mechanisms.

In the next century, research on AMD will become an even higher priority. The goals will focus on unlocking the molecular and biochemical bases for both geographic atrophy and exudative AMD, leading to the development of new treatments to prevent their onset. Epidemiologic research could contribute by developing improvements in characterizing early AMD, working along with investigators interested in enhanced imaging. Further work on the interaction of genetic and environmental factors in diverse populations is likely to provide important new insights.

SUMMARY

The encouraging scenario of international efforts to eliminate preventable and avoidable blindness is the legacy of public health ophthalmology in the 20th century. With active programs currently in place or beginning for the major cause of blindness in childhood and two of the leading infectious causes of blindness, it is natural that research in eye disease will shift even more heavily toward the leading causes of blindness in the older ages. The age-related eye diseases will rapidly become the most common causes of blindness and visual loss and, with the exception of cataract, are the more difficult to identify, diagnose, and treat. The human misery and social cost of blindness, especially in the countries that can ill afford it, are profound. To combat this problem, epidemiologic research in ophthalmology should look toward the following major areas:

1. the identification and testing of better screening modalities to determine early changes possibly amenable to preventive strategies. This includes detection of vitamin A deficiency as well.
2. the creation of uniform definitions for diseases, particularly glaucoma and early AMD, which have relevance for epidemiologic research into risk factors.
3. increased multidisciplinary research, working with investigators skilled in molecular genetics, biologic markers for age-related diseases, and those interested in new imaging and vision-testing techniques.
4. ongoing work in clinical trials of new approaches to prevent or delay the onset of vision loss from eye disease, including future vaccines for chlamydia and onchocerciasis.

The major public health issue of blindness prevention will not disappear in the next century but only shift emphasis to different causes if the current programs achieve the success that is hoped. Future epidemiologic research will continue to require a concerted, sustained, and multidisciplinary effort in order to contribute to the vision research agenda in the next century.

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