International Council of Ophthalmology

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A Research Agenda for Global Blindness Prevention

A Report of the International Council of Ophthalmology's Research Committee

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This report emerged from the Committee's meeting in Baltimore (October 27-29, 2002). It was subsequently circulated to all members of the Committee and refined as suggestions warranted.

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The report and related news are available online at:

http://www.icoph.org/research/agenda.html

Dissemination and Use:

While the Research Committee was impaneled by the ICO and reports to it, the Committee took as its charge recommendations broadly relevant to those interested in advancing blindness prevention, including IFOS and the NGO community.

It is the Committee's hope that this report will prove helpful to many individuals, organizations and institutions working toward our shared goal; and provide a useful starting point for those wishing to define the research agenda anew.

The Committee views its product as a "living document" that will change with future discoveries and input. To that end, the Committee recommends:

1) The Report be widely disseminated and placed on the ICO website
2) Be shared with other interested parties who may elect to place it on their websites as well, or hyperlink to its place on the ICO website
3) That a managed "chat room" be established on the ICO website that facilitates input, comments, and recommendations from interested individuals as a means of sharing information on ongoing projects that address key areas touched upon in this document in ways that encourage the continual growth and refinement of this report in an iterative process engaging the larger vision-research community.

This report is relevant to other ICO agendas, most specifically the International Clinical Guidelines ("operations research" provides evidence upon which guidelines are based). The Educational Committee may recommend those skills needed to conduct relevant research. This report also provides a basis for national, regional, and global support of vision research to support *Vision 20/20* and *Vision for the Future*, and the rationale for training vision scientists needed to carry out its agenda.

Locus of Investigation:

Many relevant research opportunities are "generic" or "transnational," such as the basis of cataractogenesis or relative cost-effectiveness, safety and benefits of alternative intraocular lenses. But the appropriate application of discoveries is local, and depends upon cultural, economic, and social conditions. This means that the results of "generic" research will often provide only a partial answer; the full, appropriate solution requiring further operational research at the local level (whether these are States within India or regions of Africa).

Caveats:

This report was not meant to address all important eye health and vision-related research opportunities and needs, and is not an exhaustive presentation of all important opportunities. Instead, it concentrates on those ocular diseases and conditions that cause the greatest vision disability in the largest number of individuals, particularly conditions being addressed in efforts to dramatically reduce unnecessary visual impairment and blindness among poor people, whether in the first or third world, urban or rural.

Terminology:

All issues identified in this report require urgent attention. However, the time it will take to complete these important research agendas differs greatly. The

following timeline realistically depicts the interval between formulating a research question, completing the investigation, and disseminating the results. This timeline is considerably longer than timelines used in framing programmatic goals.

Time	Duration
"Short"	1 to 10 years
"Medium"	11 to 20 years
"Long"	21 to 40 years

Appendix 1: An attempt was made to characterize those ocular and visually disabling conditions most relevant to the goals of *Vision 20/20* and *Vision for the Future* by their frequency (prevalence/incidence) in the population in 2002; the severity and frequency of the consequences of the condition and the degree to which current health systems have mitigated their impact; the degree to which existing technology is capable of preventing or remediating the problem if applied to the fullest extent possible; and the adequacy of local resources available for applying that technology. These characteristics are ranked separately for "wealthy" (OECD) and "poor" countries; however, one must remember that few countries are homogenous in their application of health care. Poor people in wealthy countries may lack adequate health services, while wealthy people in poor countries may have access to all the services they need. It should be recognized as well that populations living in remote, rural areas are generally the least well served, yet the urban poor may, in many countries, suffer equivalent neglect.

Appendix 2: A preliminary, generic description of major, complementary research avenues was presented to the ICO at its meeting in Sydney, Australia, April 2002. This provided a starting point for the Committee's deliberations.

GENERAL INTRODUCTION

The Committee broadly divided its research priorities into three general domains:

Operations Research:

Operations research responds largely to challenges posed by the fact that technology exists for preventing and treating/reversing visually impairing ocular disease and conditions, but for a variety of reasons, usually social, cultural, organizational or economic, large populations are not benefiting from this knowledge. A classic example is cataract, the single largest cause of blindness in the world. Operational research opportunities include ways in which to make surgical treatment less costly and more widely available. Operational research opportunities will generally yield useful, practical knowledge in the short- to medium-term. At present, there is little investment in operations research of visual problems, despite enormous opportunities for return on that investment. Operations research, particularly applied to delivery of cataract surgical services, is probably the single greatest research opportunity at present, and would yield enormous benefits to global blindness prevention programs in the near term.

Epidemiologic Risk Profile:

Epidemiologic studies include carefully designed, randomized trials (e.g., the relative ease, success, cost and benefit of aphakic vs. pseudophakic surgery; or phacoemulsification vs. extracapsular sutureless surgery). The benefits of such clinical studies can be expected in the short-term.

More innovative epidemiologic studies seek to identify underlying causal factors of human disease (e.g., why does blinding trachoma disappear "spontaneously" with seemingly small improvements in socioeconomic status?; or why do some, seemingly genetically similar populations suffer radically different rates of cataract?). Such classic epidemiologic studies (migrant studies, twin studies, etc.) are powerful tools for obtaining biologically important insights. A classic example was the recognition that the use of diethylstilbesterol in mothers was responsible for the subsequent epidemic of vaginal cancer in their offspring.

Epidemiologic studies seeking to identify causal environmental/behavioral agents are generally medium-term endeavors.

Basic Biologic Research:

Basic "mechanistic" research seeks to understand biologic mechanisms. Fundamental research discoveries are often serendipitous, but when they occur, may provide dramatic new modalities for understanding and preventing disease. Understanding lens physiology may one day provide insights that will permit prevention of cataractogenesis. Such research is generally of a long-term nature.

In general, the Committee considered basic, mechanistic, long-term research worth highlighting, but largely beyond its purview. The need for conducting such research is well established and will progress regardless of this Committee's attention.

The Committee spent more effort identifying opportunities in operational and epidemiologic research, which are neither well recognized nor well funded, and offer the most immediate opportunities for facilitating blindness prevention today and in the short- to medium-term.

Population Access and Appropriate Intervention:

The Committee's greatest concern was identifying research opportunities that would benefit underserved populations of poor countries. Some interventions, while not appropriate for mass application to the rural poor, are nonetheless applicable to wealthier segments of society with greater access to sophisticated eye care services. Those with such access should receive appropriate care, as defined in the International Clinical Guidelines. At this moment, research related to these issues are higher priorities for wealthier countries, though, for a variety of ethically and scientifically compelling reasons, it may be appropriate to conduct related research in poor populations.

CLINICAL CONDITIONS

1. Cataract

Among all ocular conditions, cataract takes "pride of place" as the single greatest cause of blindness in the world, primarily because poor people living in poor conditions do not have access to sight restoring cataract surgery. The primary challenge, from this perspective, is to reduce the cost and increase the efficiency of cataract surgery (with excellent sight restoring outcome), and find ways to provide these resources to poor living in remote rural areas or urban slums. These problems can respond to short- to medium-term operations research, including delineation of the level of education and training needed by eye health workers delivering cataract surgical services.

Cataract is also a major problem in wealthy countries, primarily because of the economic and human cost related to the large numbers of operations performed (increasingly at marginal levels of visual impairment that are nonetheless critical to maintaining employment and maximizing quality of life). Preventing cataractogenesis requires innovative epidemiologic studies seeking factors that increase the risk of disease (short- to medium-term) and mechanistic studies of lens biology (medium- to long-term).

Research Opportunities

Short-term (largely analytical):

- Estimate the "burden of disease" posed by cataract, adjusted for differing levels of visual demands and visual deficit.

- Compare the cost-benefit of cataract surgery performed at different levels of visual acuity (adjusted for visual demands)

- Identify those factors responsible for regional and global variations in "per surgeon" cataract surgical rates (financing, facilities, expectations, culture, training, patient demand) adjusted for the age distribution of the population, the visual criteria justifying surgery, etc.

- Assess factors that determine local indications for cataract surgery, and their appropriateness

- Identify constraints to cataract surgical manpower (number of physicians/ophthalmologists trained; proportion adequately trained in modern pseudophakic surgery)

- Identify resources and incentives required to motivate/train existing cataract surgical manpower to better meet quality standards and higher surgical volumes, and to provide services to the less accessible poor

- Develop simple methods for monitoring and evaluating surgical outcomes and benchmarking these against quality standards

- Mathematically model alternative approaches to best meet today's demand/needs, and those of the future (given changing demographics, visual demands, geographic distributions of patients and providers, reimbursement schemes and technology)

- Compile and assess data on the severity and extent of cataract visual impairment and blindness attributable to different types of cataract (may require additional, sophisticated – if relatively small – population surveys)

Short- to Medium-Term (largely operational research directed at increasing the amount of effective, high-quality cataract surgery provided to those presently underserved, primarily by identifying ways in which to reduce the marginal costs of cataract surgery and increase geographical and financial access to effective surgical services):

- Devise and evaluate alternative approaches to increasing access of underserved populations to trained cataract surgeons:
    - Incentives for/requirements of ophthalmologists (mandatory service in underserved areas at completion of training; regular rotations to underserved areas)
    - role of non-physicians/non-ophthalmologists in delivering care to populations suffering a chronic paucity of trained ophthalmic surgeons (alternative formulation: "What is the minimal education, training and experience required to perform different roles in the delivery of safe and effective cataract surgery, including the surgery itself?")
    - role and impact of certification and credentialing, CME, and clinical guidelines on performance standards and outcome

- Identify ways to minimize costs associated with each component of cataract surgery (preoperative workup; facilities; equipment; supplies and consumables [sutures, visco-elastics, IOLs]; personnel, etc.), including alternative and emerging surgical techniques/ technology

- Determine longer-term (3 to 10 years) post-operative outcomes following alternative surgical approaches

- Develop and test ways to optimize case-finding and generate patient demand (compliance)

- Identify the attributes that distinguish those systems for delivering services that are effective and efficient

- Compare cost-benefit trade-offs between techniques that reduce the need for follow up (primary posterior capsulotomy; preoperative/interoperative antibiotics; greater precision in determining IOL power; multi-focal lenses)

- Evaluate alternative cost recovery mechanisms and their ability to contribute to long-term sustainability of local cataract surgical services

- Compare the cost-effectiveness of alternative organizational schemes for maximizing "through-put" of the operative process (one vs. multiple operating tables; maximal delegation of responsibility) suitable to local conditions

- Design and test pricing and marketing strategies that result in sustainable cataract surgical programs (cross-subsidization between higher and lower fee facilities), adjusted for the elasticity of pricing/disposable income distribution of the local population (e.g., general ability/willingness to pay 1-3 months wages for cataract surgery)

Medium- to Long-term (progress in understanding lens biology and developing interventions that reduce the incidence/progression of cataract):

- Search for epidemiologic insights into environmental causality (e.g., compare environmentally disparate, genetically similar populations with different age-specific incidences of clinically significant cataract)

- Conduct basic ("mechanistic") lens research to identify the biologic basis of different forms of cataract.

2. Trachoma

Trachoma is the second leading cause of avoidable blindness and visual impairment. Recent analyses suggest the burden on quality of life attributable to the discomfort of trichiasis may be as great as that traditionally attributed to the reduction in visual acuity.

Active (and blinding) trachoma occurs in a highly focal pattern among poor populations. While it is reasonably well established that recurrent reinfection with Chlamydia trachomatis results in chronic inflammation, scarring, trichiasis, and corneal opacification, the exact relationships between these entities is unclear. What is particularly vexing, but serves as grounds for optimism and research-based enlightenment, is the way in which trachoma has spontaneously disappeared from many areas of the world: not just Appalachia (US) or Finland (in the 1940s), but more recently Indonesia, Mali, and much of India and Pakistan. Saudi Arabia experienced a dramatic decline in incidence, associated with infrastructure development (roads, water supplies). It would appear, in most instances, that early, relatively modest increases in socio-economic status are related to critical changes in the environment and/or behavior that brought this about.

Epidemiologic studies have identified personal hygiene and communal sanitation as potentially important determinants of blinding disease. These and other insights resulted in the recently launched *GET 20/20* (Global Eradication of Trachoma by

the Year 2020) and a public-private collaboration, the *ITI* (International Trachoma Initiative). These are based on the (SAFE) **S**(urgery), **A**(ntibiotic), **F**(acial cleanliness/facewashing), **E**(nvironmental Cleanup) strategy: "surgery" to correct triachisis and reduce the burden of existing lid scarring; "antibiotic," particularly highly effective Zithromax, to eliminate an individual's C. trachomatis infection; and "face washing" (to ensure facial "cleanliness") and "environmental cleanup" to reduce the risk of infection/reinfection.

The effectiveness of each of the components of the "SAFE" strategy, alone and particularly in combination, remain poorly documented; a better understanding of the value of these interventions, particularly their timing for maximal synergy, should lead to more effective outcomes.

Five important, generic research issues relate to:

1) Improving surgical outcome of trichiasis surgery. At present, the relapse rate, even for well-trained ophthalmic surgeons, is high.

2) Elucidating the role of acute/recurrent/chronic infection in the pathogenesis of conjunctival scarring.

3) Documenting the dynamics of infection/reinfection (e.g., what serves as the reservoir of C. trachomatis following mass antibiotic treatment; how is it re-introduced into a community; how does it spread between individuals?)

4) Determining what is required to sustain the reduction in prevalence of infection and active disease following antibiotic treatment (and thereby block development of blinding trachoma?)

5) Demonstrating how SAFE can be most effectively delivered

While *ITI* and *GET 20/20* have settled on the SAFE strategy, successful global eradication programs (e.g., smallpox) have demonstrated the critical importance of maintaining a vigorous, parallel research program to enhance program effectiveness and overcome obstacles to interventions that prove ineffective.

Research Opportunities:

A. Trichiasis Surgery

Short-Term:

- Identify factors that influence the recurrence of trichiasis following seemingly successful lid surgery?

- Develop improved surgical approaches (by employing the latest plastic surgery techniques), and test these in clinical trials.

- Identify barriers to surgical uptake and ways to reduce cost and increase access (e.g., minimal equipment and supplies; efficient and effectives procedures and the training of lid surgeons; ways to increase demand/compliance).

- Test simplified systems of surgical audit and evaluation of surgical outcomes.

Medium- to Long-Term:

Identify:

- The pathogenesis of lid scarring (role of infection, immunologic and inflammatory response, etc.)

- The optimal time in the evolution of trachomatous scarring to intervene surgically.

B. Infection and Antibiotics

Short-Term:

Determine the:

- Origins of reinfection (latent infection; re-introduction by visitors or spread from adjacent communities)

- Degree of treatment coverage vs. impact/sustained reduction in infection and progression of disease under differing conditions of endemicity

- Relationship between the frequency of antibiotic (Zithromax) dosing and its duration of impact (reinfection/re-emergence of active or scarring diseases)

- Cost-effectiveness/ cost-benefit of antibiotic use, based on benefits to both ocular and non-ocular diseases (STD, respiratory disease, etc.)

Medium-Term:

- Determine by whom, and for how long and how intensively, should antiobiotics be used for sustained impact (e.g., R/x only children; mothers and children; the family; or the whole community? How often and for how long?)

C. Face Washing/Environmental Sanitation

Short- to Medium-Term:

Determine:

- The key personal hygiene/environmental factors that are responsible for infection/reinfection

- The degree to which "F&E" has an additive (synergistic?) benefit when added to treatment with antibiotics

- The long-term impact of alternative "F&E" interventions

- Which factors (behavioral) determine compliance and adoption of personal/community "F&E" interventions

- Whether markers of facial "cleanliness" can identify populations in which the promotion of "face-washing" is unnecessary and redundant

Two Potential (Model) Studies:

1) After reducing the prevalence of infection with baseline systemic antibiotics, compare the impact of alternative F&E strategies. These should cover populations of varying density and over varying distances from a central point in order to trace the rate and route of reinfection. (This will establish whether a wider F&E "cordon sanitaire" more effectively reduces reinfection, by comparing route and reinfection rate from the periphery to the center of the intervention population; and with it, the source of reinfection. Altering the intensity and extent of F&E strategies should reveal the synergy of F&E when added to the use of antibiotics, and the potential value of F&E in sustaining [or maintaining] reduced levels of infection/reinfection.)

2) Once an optimal F&E strategy is identified (in [1] above), combine it with alternative antibiotic dosing regimens (frequency; duration) to identify the ideal F-A-E intervention, for differing levels of endemicity and population density, and the duration of antibiotic use needed before F&E can sustain control on its own.

D. Other

Short-Term:

- Calculate the cost-benefit/cost-effectiveness of alternative interventions

- Refine estimates of the "burden of disease" caused by trachoma, including non-ocular disease

Medium-Term:

- Develop simplified, inexpensive diagnostic tests for infection suitable for program evaluation and monitoring

Long-Term:

- Elucidate the pathobiology of the disease (interactions between microbe and host)

- Develop a vaccine (against infection; against inflammation and blinding scarring)

3. Onchocerciasis

Global programs over the last three decades have dramatically reduced the incidence of new infections with *onchocera volvulus* and their progression to blindness. Through a combination of environmental interventions and widespread treatment with Mectizan, onchocerciasis should cease to be a cause of new blindness reaching a level of "public health significance" by 2010.

This does not mean that further research is not needed. Most modeling studies suggest that at present coverage rates (65%), it will take 40 years before Mectizan distribution can be safely discontinued. At 80-85% coverage, which may prove possible with more intensive and effective delivery systems, the program must still be sustained for more than 25 years. In addition, new drugs are needed that will:

1) Have safe and effective macrofilaricidal activity. Their use would dramatically shorten the need for sustained, repeated microfilaricidal administration
2) Provide a backup to Mectizan should microfilaria develop resistance
3) Prove safer for use in populations with heavy, co-existing infections
4) Allow for treatment of children and pregnant women, thereby increasing coverage (leaving a smaller reservoir of persistent infection)

To enhance and sustain large-scale treatment (to exceed 80 million people annually) requires alternatives to, or strengthening of, the present system of "Community Directed Treatment Intervention" (CDTI).

*A potentially important and recent observation (*Science*, March 8, 2002, "The Role of Endosymbiotic Wolbachia Bacteria in the Pathogenesis of River Blindness") suggests that Wolbachia, an endosymbiotic bacterium present in all developmental stages of* O. volvulus, *are required for production of microfilaria and for much of the inflammatory reaction associated with microfilarial death. As these bacteria are susceptible to antibiotics, it may open a new approach to control of onchocerciasis.*

Research Opportunities

Short-Term (primarily operational research, much of which is already ongoing):

- Investigate serious side-effects of Mectizan among populations in loa loa endemic areas

- Determine the role of interactions between Mectizan, alcohol consumption, and exposure to other toxic substances and serious side-effects observed in those under treatment (especially encephalopathy)

Medium-Term (primarily delivery of drugs):

- Develop ways to ensure long-term sustainability and to increase coverage/compliance of Mectizan treatment programs

- Identify issues related to the use of CDD (volunteer community distributors) and complementary programs addressing other needs that might be added onto this unique delivery system (reaching otherwise underserved populations)

- Follow up preliminary data that suggests increasing the frequency of Mectizan dosing might further block embryogenesis (more fully blocking transmission). Comparisons between alternative treatment regimens might identify ways to reduce the duration required by intervention programs.

Long-Term:

- Develop a safe macrofilaricide

- Develop an alternative to Mectizan in case resistance should develop

- Delineate the role of Wolbachia in the pathogenesis of river blindness, and the potential role of alternative interventions (antibiotics that destroy the bacteria; drugs that block its inflammatory effects; etc.)

- Evaluate the long-term impact of Mectizan on the incidence and severity of retinitis/optic neuritis

4. Xerophthalmia

Xerophthalmia was traditionally a major cause of visual disability among young children, particularly in South and Southeast Asia and in Africa. Recent studies confirm it is also prevalent, primarily as night blindness, among women of reproductive age. The discovery that vitamin A deficiency (VAD), the cause of xerophthalmia, is far more prevalent than clinically evident ocular complications, and that mild levels of deficiency dramatically increases infectious morbidity and mortality, have resulted in global initiatives (UNICEF, WHO, USAID) to control micronutrient malnutrition. As a result, over 70 countries have launched VAD

control programs. UNICEF estimates these reach 80% of their target childhood populations in over 40 countries. As a result, many countries have witnessed a dramatic decline in the incidence of xerophthalmia and related blindness (formal assessment in Indonesia suggests a 92% reduction in the prevalence of active disease).

The primary constraint to VAD control is a cost-effective method for improving vitamin A status. We now know that one cannot normalize vitamin A status by simply changing dietary habits of populations dependent upon a vegetable diet, because the bioavailability of vitamin A from carotene-containing fruits and vegetables is much lower than previously thought.

Fortification of dietary staples would provide a cost-effective means of supplementing diets with additional vitamin A. Unfortunately, few centrally processed products, in which vitamin A is stable, are consumed by high risk populations. Identification of such potential vehicles for fortification remains a high priority.

The single most important intervention strategy remains periodic administration of high-dose supplements (generally once every 3-6 months). The supplements themselves are extremely inexpensive, but distributing them is not. Many countries have successfully grafted vitamin A distribution onto NIDs ("National Immunization Days") utilized to eradicate polio through mass immunization. As many countries have successfully eradicated polio, NIDs are being phased out and alternative delivery schemes need to be adopted. Increasingly, other micronutrient deficiencies are being recognized as important targets for control, and wherever possible, combined with vitamin A supplementation. But there is little data on the potential interactions between co-administered multiple micronutrients.

Research Opportunities

Short- to Medium-Term:

- Develop better tools for population assessment of vitamin A status

Medium-Term:

- Develop and test alternative supplementation strategies (e.g., use of market forces to propel and sustain programs)

- Generate additional information on the role of vitamin A status in determining maternal mortality, and the impact of control of VAD

- Conduct population-based trials to elucidate micronutrient-micronutrient interaction, and to establish appropriate supplementation and fortification strategies for populations with different degrees/states of micronutrient deficiency

Medium- to Long-Term:

- Determine the impact of very early (birth) vitamin A supplementation on the developing immune system, as this may have enormous consequences for morbidity and mortality, and thus for the justification of vitamin A control programs

- Develop, refine and evaluate the value of crops bio-engineered to produce beta-carotene and/or retinol

5. The Glaucomas

Collectively, glaucomatous optic nerve damage accounts for a significant amount of global visual impairment and blindness. Of the many types of glaucoma, only primary angle closure glaucoma (PACG) is sufficiently prevalent (primarily in "Asian" eyes), and opportunities for intervention sufficiently promising, to have engaged the Committee's considerations.

Until such time as the potential cost-benefit advantages of intervention for the other glaucomas becomes competitive with those for cataract, trachoma or onchocerciasis, they are left to future consideration. Indeed, there is considerable concern that even if cost-effective strategies become available for identifying patients with open-angle glaucoma, the complications associated with surgical intervention and failure to produce immediately discernible benefits could well lead unsophisticated populations to become discouraged from seeking any surgical interventions (including cataract surgery).

Research Opportunities – PACG

Strategies that may make preventing PACG more relevant in third-world settings:

Short- to Medium-Term:

- Develop practical techniques for effectively screening populations to identify eyes at high risk of visual impairment and blindness from angle closure glaucoma

- Determine the value of laser iridotomy as long-term prophylaxis in those who never previously suffered angle closure

- Evaluate the cost-efficiency of screening and prophylaxis interventions in populations of varying risk

Research Opportunities – Primary Open Angle Glaucoma

Only with the discovery of better tools and techniques will POAG become a practical target for population-based intervention in third world settings. This is, by necessity, a medium- to long-term research agenda.

- To become relevant to third-world populations, screening techniques are needed that identify subgroups at particularly high risk of disease (genetic markers?)

- Early treatment/prophylaxis interventions must make a long-term difference in the risk of glaucomatous visual impairment and blindness

- Epidemiologic studies may identify environmental/behavioral factors that contribute to (seemingly) societal variations in risk

- Simplified and sensitive measures of progression of optic nerve damage would dramatically improve the ability to test alternative interventions and improve the benefits of intervention/management

- New and novel treatment approaches, particularly neuroprotection (beyond medical and surgical approaches targeting IOP), would offer new options for control of blinding disease

6. Diabetic Retinopathy and Age-Related Macular Degeneration

These two conditions are becoming increasingly important everywhere as populations "age." AMD is already a major cause of blindness in wealthy countries, and increasingly important among middle class and wealthy urban populations of the developing world. Intervention options for AMD, however, remain rudimentary and expensive everywhere.

Diabetic retinopathy is a rapidly growing problem, even in developing countries. Increasingly, populations are obtaining insulin and therefore surviving IDD, while the global epidemic of obesity is fueling a dramatic increase in the incidence of NIDD. Treatment of diabetic retinopathy is effective, and in wealthy countries (as well as for the urban elite of poor countries) affordable and cost-effective. Operations research may make it cost-effective even for poor populations, particularly if targeted to those at high risk because of genetic or nutritional factors.

Research Opportunities

Short- to Long-Term:

- Documenting population variations in risk (AMD, DR) may help elucidate genetic and environmental markers/pathogenetic mechanisms

- The nature of angiogenesis and its relation to antioxidant intake may better be studied in micronutrient poor populations

- Better tools are needed for defining risk, early disease, and tracking progression

- Operational research provides opportunities for extending retinal photocoagulation to poor populations suffering from diabetic retinopathy

7. Refractive Error

Refractive error is the most common ocular abnormality, a situation exacerbated in many poor countries by lack of access to refractive services and low-cost spectacles. In some countries, this relates to artificial political and legal constraints (only ophthalmologists can prescribe glasses, effectively disenfranchising the vast majority of the rural poor); and in other countries, to cost. These limitations are eminently responsive to careful cataloguing and operations research, though in the final analysis (as for most conditions), the limiting factor for effective solutions will prove to be "political will."

In India, for example, it is that untreated or under-treated refractive error is responsible for 40 million individuals having visual impairment of 20/60 or less, and 3 million with vision less than 20/200.

The two major refractive disorders impacting on employment and quality of life are myopia and presbyopia (aside from surgical aphakia).

Research Opportunities

Short- to Medium-Term:

- Identify social and cultural constraints to utilizing refractive services and spectacles

- Develop protocols for the education, training, and certification of low-cost spectacle providers

- Experiment with alternative organizational systems and infrastructural support for the sustainable provision of appropriate low-cost spectacles (e.g., micro-credit enterprises, formal refraction vs. patient self-selection from among spectacles of varying correction, individually ground lenses vs. snap-in spherical equivalents)

- Enroll high risk populations into epidemiologic studies and randomized clinical trials seeking environmental/behavioral etiologic

factors and effective strategies for reducing the incidence/progression of refractive error

- Analyze the cost-benefit and cost-effectiveness of alternative interventions (including spectacles), considering their economic impact on education (and subsequent earning power)

- Investigate the value of social marketing of refraction/spectacles

Medium- to Long-Term:

- Identify the origins of myopia

- Investigate alternative interventions for reducing the incidence/progression of refractive error

- Apply evolving technologies to the treatment of refractive error in poor populations.

CLOSING CONSIDERATIONS

All ocular conditions and diseases would benefit from intensified research. Much of the needed research will ultimately provide a better understanding of the etiology of the conditions and ultimately ways to prevent them. This is as critical for ARM and glaucoma as it is for cataract and diabetic retinopathy. While there are effective interventions for the latter, they are costly in human and capital resources, even when these are available. Preventing these conditions would be far preferable to treating them by the millions. This represents a long-term, basic research agenda. It should be advanced by advocacy and initiatives that facilitate the exchange of information and biologic materials, and fosters international collaboration enhancing the ability to bring science to the location of the problem, and vice versa.

More immediately, operations research provides multiple opportunities to increase access to, and the effectiveness of, ocular disease control strategies, by developing more efficient and cost-effective interventions. NGOS and others involved in delivering services can play a greater role in advancing knowledge and developing more effective intervention paradigms, and in so doing enhance the delivery of services worldwide. Institutions and formal constructs are needed for identifying and thinking through the major research questions and opportunities. Widely shared and coordinated agendas and protocols would greatly facilitate work in neglected research areas by leveraging already existing programs and investments. Planning meetings between research institutions and NGOs could advance this opportunity.

At present, the highest priority for ICO advocacy is operational research directed at increasing access to cataract surgical services. Cataract is the single greatest cause of global blindness, while operational research receives little financial support or rigorous research attention. Suitable, organized investments and work can have a profound, almost immediate impact on the cataract problem, and therefore on global blindness.

Periodic symposia at major meetings, particularly ARVO, would serve to highlight, inform, update and refine the research agenda outlined in this report.

APPENDIX 1:

Distinguishing Characteristics of Persistent Ocular Diseases

	Prevalence/ Incidence		Contribution to visual Impairment (e)		Effectiveness of Rx/Px		Resources available for control (a)		
	OECD Countries	**Poor Countries**	**OECD Countries**	**Poor Countries**	**OECD Countries**	**Poor Countries**	**OECD Countries**	**Poor Countries**	**Attractive Opportunity Near-Term Research (d)**
Cataract	5	5	1	5	5	5	4	2	A
Trachoma	NA	5	NA	5	5	3	NA	3	Rx/A
Onchocerciasis	NA	2	NA	2	4	4	NA	4	A
Xerophthalmia	NA	2	NA	2	5	5	NA	2	A
Glaucoma	4	4	3	4	3	1	4	1	-
AMD	4	2	5	3	1	1	4	1	-
Diabetic Retinopathy	4	3	4	3	4	4	4	1 (b)	A
"Childhood" (c)	3	3	3	2	3	2	3	1	E/A
Refractive Error [4]	5	5	1	4	5	5	5	1	E/A

a. Resources include infrastructure, human capital, and financing.

b. Diabetic retinopathy is a classic example of a growing problem in the developing world (3); where effective Rx and Px exists (4); and where infrastructure in poor countries is inadequate to deliver effective Rx/Px to most of those who need it (1), but special groups (urban elite) often have full access to care. The same is true of cataract.

c. "Childhood" reflects retinopathy of prematurity in OECD countries; xerophthalmia, injury, congenital cataract and glaucoma in poor countries.

d. Attractive near-term opportunities for etiologic (E), treatment (Rx), or operational ("applied") (A) research.

e. Several entities are transitioning towards different endpoints. Onchocerciasis is presently "controlled"; in several decades it may be eradicated. Xerophthalmia is partially controlled; it may someday be "eliminated" as a public health problem, but as vitamin A deficiency can reoccur, unlike complete elimination of a parasite, the condition can never be "eradicated."

5= "to greatest degree" (e.g, prevalence/incidence high; very important contribution to visual impairment; very effective treatment or prevention modality; resources adequately available)

1= "to the least degree" (converse of "5")

NA= not applicable because successfully controlled

APPENDIX 2:
Research Goals: Prioritization
and the Means to Move Forward

"Research," by definition, is the systematic discovery of new knowledge. While major, fundamental insights often arise from the unfettered search for new knowledge, the ICO's more urgent and achievable goals of reducing global visual impairment and blindness will be best served by focusing global action in poorer countries on a) the systematic elucidation of their major causes of needless visual impairment, and b) a shared, coordinated, energetic and innovative approach toward understanding and overcoming obstacles to their resolution.

A. **Evaluative Research**

1. **Burden of Visual Impairment**

   Knowing the primary causes of visual impairment is critical to prioritizing the interests of the eye care community, mobilizing resources, and influencing policy. Given the large number of "blindness" surveys conducted during the past two decades, few countries need to carry additional ones out. Countries that have can serve as reasonably valid indices for those with similar characteristics that haven't.

2. **Quantifying the "Burden" of Pathology**

However, in this day and age, mere "prevalence" of disease is inadequate to move policymakers or even affect research or programmatic allocations. Health priorities are now established on the basis of "burden of disease," a concept that more dynamically captures visual impairment. To be meaningful for ophthalmic conditions, one needs to know:

a. The distribution of visual impairment (for most practical purposes, in the better eye) by severity and age. The younger the onset, and the more severe the impairment, the greater its "burden." Permanently impaired vision in a young child will cause a greater "burden of disease" because this burden will be born for more years than when the impairment had its onset in old age. Hence senile cataract, which may appear to be the overwhelming cause of visual impairment, can become less important, relatively, to childhood causes like injuries or xerophthalmia, or mid-adult causes like trachoma.

b. The impact of different levels of visual impairment, at different ages, on "quality of life." Very little work has been done in this regard, though a start had begun over the past decade and a half. Almost all of the (meager) correlations between vision, impairment, and quality of

life come from studies on older individuals (primarily with cataract) in wealthier countries. A better delineation of these relationships is critical to establishing "burden of disease" estimates.

Action Item: Regional consortia, composed of countries with similar characteristics, should pool resources and opportunities for developing data needed to estimate "burden of disease" created by their common ocular ailments.

B. **Operational Research**

At least two major issues are critical to dealing with "avoidable" visual impairment:

1. Generating the capacity to meet the population's need for interventions, whether cataract surgery or treatment for trachoma. In most developing countries, unoperated cataract remains the single most common cause of visual impairment and blindness (more sophisticated data is still needed to determine its relative "burden of disease"). Enormous progress has been made in reducing the time, cost, and complexity of cataract surgery, for example, and in ways to motivate populations to seek care. But the gap between needed care and available care remains, for most poor countries of Asia and Africa, enormous. For most of the rural, poor countryside, there will never be adequate access to fully qualified ophthalmic expertise if one relies on the procedures and techniques employed in wealthy countries.

   Action Item: There is a continuing need to refine approaches to cataract surgery (trichiasis remediation, etc.) to simplify the procedure; reduce the need for sophisticated equipment, facilities, and supplies; and minimize the training and experience required by the operating "surgeon" but remain compatible with high-quality outcomes.

2. Capacity and quantity of activity is not itself adequate. Outcomes, whether of cataract surgery or trachoma intervention, must be successful and approach "international" standards and expectations. These improvements must address both short- and long-term results, and "quality of life" indicators of the recipient populations.

   Action Item: There is still a paucity of data on the outcome of ophthalmic interventions in developed and developing countries alike. But the limited resources of developing countries make it imperative that resources are not wasted. Every country needs to monitor outcomes of its interventions, primarily to identify where and why these might fall short, and thereby prompt remedial intervention. It makes sense for countries with similar characteristics to jointly develop, test, and refine common protocols, as a spur to action and as a means for sharing "lessons."

C. **Discovery Research**

Nearly every ocular condition would benefit from basic discoveries related to etiology, treatment, and prevention: from macular degeneration, for which little can presently be done, to cataract, where prevention might well prove far more cost-effective and reduce dependence on readily accessible care. All countries can participate in discovery research, though most such work will be funded and conducted by investigators in wealthy nations (where appropriate, in collaboration with colleagues from poorer countries). "Discovery research," while critically important, is probably of tertiary relevance to the funding priorities of poorer countries: Investments in evaluative and operational research are likely to provide more immediate returns. However, developments or discoveries in wealthy countries that impact on ocular conditions in poorer countries are important: Azithromycin for trachoma and Ivermectin for onchocerciasis are two examples.

Action Item: A consortium of ophthalmic scientists from wealthy and poor countries should systematically monitor new drugs, discoveries, and technologies for potential testing and application in the developing world.