Advances and trends in vision research

Avanços e tendências em pesquisa visual

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I would like to thank the organizing committee of the X Brazilian Congress on Prevention of Blindness for the opportunity to address this group which shares a common goal. That goal is to spare the suffering, frustration, dependency, fear, and economic loss of those who must live out their later years with impairment of vision or loss of sight. In the dynamics of life, fullness, not impairment, should be the reward of living.

The poet Robert Browning had the right idea when he began the poem "Rabbi Ben Ezra" with the lines: "Come, grow old along with me. The best is yet to be, the last of life, for which the first was made". As populations grow larger and their median age rises, more and more people move into the age brackets in which cataract, glaucoma and other age-related diseases tend to strike. For example, it has been estimated that in the United States the frequency of cataract will increase by 160 percent in the next few decades unless preventive measures are found. And in the developing world, the population aged 55 and over will increase about five-fold by the year 2030, with a concomitant increase in all the blinding conditions related to age that can limit the enjoyment of their golden years. Fortunately, recent advances in several areas of vision research offer significant hope that many more people will be able to follow the bidding of Rabbi Ben Ezra and not fear the second half of life, or as he calls it, the heritage of youth.

Progress often has an uneven gait, no matter how doggedly we try to prod it on. However, in vision research, we are seeing some steady but remarkable progress in areas that we dared not imagine a few decades ago. Much of this momentum has come from the interrelatedness of biological research. We have many discrete disciplines in vision research, many with elegant names like molecular genetics, biochemistry, and immunology. All of them, however, have a common goal: the cause, prevention, or treatment of ocular disorders. A scientific finding in one area of research often moves quickly from the laboratory or clinical setting to application in another area, sometimes changing the focus of research in other areas. This dynamic interrelatedness of research has provided the momentum for much of the progress I will be telling you about.

A good example of how scientific findings coalesce for a better understanding of disease is the progress we are making in finding the cause of cataract. An estimated 15 percent of Americans aged 65 to 79 have cataracts. The number is far higher in developing countries where it occurs more often in younger people and remains the major cause of blindness. According to the World Health Organization, about 17 million people in the developing nations are blind from cataract, and as few as 10 percent of all cataracts are removed. Many of these countries have huge backlogs of sight-saving cataract surgeries. As the population ages, more and more cata-

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ract surgery will be needed at a tremendous aggregate cost to individuals and Governments. The ideal solution lies in finding what causes cataracts to develop in the aging process so that we can either prevent or slow the process.

We now know from animal models and laboratory cultures of human lens cells that oxidation - a chemical process - in combination with light, produces highly volatile forms of oxygen that can alter substances in the lens[1]. As a result of these changes, the substances, called crystallins, gradually cause the lens to become opaque. Once we pinpoint just how light and oxygen trigger the cascade of biological events that leads to lens opacification, scientists in pharmaceutical firms should be able to design drugs that will at least slow, if not prevent, the development of cataracts.

If we can delay the need for cataract surgery by just 10 years in each patient, we will be able to decrease the number of patients requiring cataract surgery by approximately 45 percent each year. Moreover, if we can slow cataract development in developing countries so that the level of surgeries will stay about the same over the next decade or two, the nonsurgical intervention will reduce the massive backlog of cataract surgeries and prevent the needless blinding from cataract in millions of these people. By the end of this decade we are hopeful that clinical trials will be under way to test topical medical therapies that will slow the development of age-related cataract so that cataract surgery can level off in both developing and developed countries. Until these medical therapies for cataract development are available, surgery remains the best method to save the sight of most people blinded by cataract.

In many countries of the preindustrialized world, however, a lack of surgical facilities and scarcity of medical practitioners has led to huge backlogs of unoperated cataracts. Unless strong measures are taken to reduce these backlogs, the growing numbers of people reaching the age when cataracts typically develop will only compound the problem. Moreover, if cataracts are not removed reasonably soon after they mature, complications, such as secondary glaucoma, may contribute to irreversible vision loss.

Health care planners agree that any strategy to increase cataract surgeries must be affordable, amenable to mass-scale delivery, and accessible to the people most in need. Cataract surgery should be performed close to the community level so that post-operative followup can be done readily and the patients can avail themselves of family support systems in lieu of protracted hospitalization.

For developing countries, the conventional methods of cataract extraction fortunately have many advantages over the new techniques used in the industrialized world. The older surgeries that do not rely on advanced technologies are far less expensive, can be performed by general practitioners or specially trained medical personnel, and do not need the elaborate surgical setting of large clinics or hospitals.

Even though the effective surgical procedure is fairly simple, problems surrounding the treatment are more complicated - namely, deployment of treatment personnel and surgical resources; fear, ignorance, or fatalistic attitudes of the cataract blind; and logistics and economic barriers impeding patients from treatment and post-treatment care.

One very successful attempt to overcome these impediments to treatment is the cataract-free zone program that has reached an encouraging number of people with cataracts here in Brazil and in other parts of South America[2]. The cataract-free zone plan was first discussed in 1985. The goal was to reduce by 70 percent the level of cataract blindness in a limited population within a specified period of time. Chimbote, Peru, and Campinas, Brazil, were selected for the pilot studies, which began in the latter half of 1986, just a little more than one year from plan conception.

These programs were not designed to replace or interfere with existing eye care delivery in either country. Instead, each was to be an addition to regional eye care programs and were carefully tailored to serve specific target communities - for example, poorer urban people who had no or limited access to organization-supported health care. After the backlogs of unoperated cases are reduced substantially, both programs continue to treat new cases to keep cataract-caused blindness to the designated minimum.

In Peru, the program was organized by dr. Francisco Contreras with a goal to reach the general population who were 40 years or older with a visual acuity of 20/200 or worse in the best eye. Of the more than 30,000 persons surveyed door-to-door by trained community workers, almost 75 percent consented to the home screening. If the visual test revealed a possibility of cataract, the team encouraged the person to have an examination by an ophthalmologist. Of those recommended for an examination, an imprensive 93 percent completed the exam at a clinic or mobile examination unit. Some of the cataract blind persons were ineligible for surgery for various reasons, but of those eligible, about 65 percent had the surgery[3]. These response rates are very encouraging.

Although the Brazil plan, under the direction of dr. Newton Kara José, had the same goal and encouraging response rates, the program had several differences. The door-to-door survey was conducted among low-income persons who were 50 years or older. The survey found 9,732 in this

age group. Blindness from unoperated cataracts accounted for 50 percent of the blindness among those surveyed. Over 80 percent completed the home screening. Of those recommended for examination by an ophthalmologist, more than 78 percent completed the exam, and 65 percent of those recommended for cataract removal had the surgery[4]. As a result of the program. the number of blind who have had cataracts removed increased from 58 percent to 82 percent in less than two years.

Both programs used health center ophthalmic examinations, out-patient surgery,.and post-operative followup, which was done mostly in the home. Appropriate optical spectacles were provided at no cost to patients. The experience gained in using outpatient surgery in both settings should play an important role in reducing the cost and inconvenience of cataract surgery, making it easier to achieve the program goal of 70 percent reduction in cataract blindness.

At present, Peru, Brazil and other Latin American countries have developed other cataract-free zone programs in their countries. These zones are based on the pilot program, but modified according to the insights learned from the first programs. These experiences in operations research are valuable tools for solving the most formidable problem of delivering the medical care to the cataract blind.

As with other major ocular diseases, we have devoted both laboratory and clinical research to finding the cause of and treatment for age-related macular degeneration, one of the leading causes of blindness among older people. Molecular biology and biochemistry can help us understand the harmful changes that occur in the macula, the small area of the retina that we use for sharp, straight-ahead vision. These changes can lead to either the earlier dry form in which small areas of the macula atrophy, or die, or to the more advanced wet form in which weak, new blood vessels develop.

Clearly, one tissue involved in at least the dry form of this disease is the retinal pigmented epithelium layer, which lies over and nourishes the hard-working retina. We currently have no treatment for the slower-developing, but less sight-threatening dry form. However, scientists are studying how the pigmented epithelium cells of the macular differ from those in other parts of the retina. In the next decade, biochemists, molecular biologists, and molecular geneticists will provide us with important information about what these differences are and how the differences make the macular epithelium more vulnerable to the degeneration. Once again, if we determine what causes the changes, we should be able to find ways to intervene in the process.

A much greater threat to vision loss arises when the dry form of macular degeneration gives way to the wet or neovascular form. New, leaky blood vessels grow beneath the macula, causing the irreplaceable light-sensitive cells near them to weaken and die. Although we do not understand yet what causes the change, we do have a treatment that can preserve vision for most people with this type of macular degeneration. The Macular Photocoagulation Study demonstrated that prompt laser treatment that seals the leaking vessels can prevent as much as 89 percent of blindness cause by this disease[5].

Certain persons with either the dry or wet form of age-related macular degeneration are eligible for a new 10-year clinical trial that is investigating whether a combination of two protective elements will reduce the damage of photo volatile oxygen radicals, namely supplemental vitamin E and vitamin C. This is another study that has resulted from laboratory work on the degenerative effects of light and oxygen and on the possible value of antioxidants, such as vitamin E and vitamin C, to counteract or repair the damage[6].

Research on diabetic retinopathy has made significant progress in the past two decades. In an early multicenter clinical trial called the Diabetic Retinopathy Study, we found that lasers effectively seal, or photocoagulate, the leaky, new blood vessels that develop in advanced diabetic retinopathy[7,8]. With thatunderstanding, the National Eye Institute began another clinical study called the Early Treatment Diabetic Retinopathy Trial to test whether the same laser treatment would be more effective if begun earlier in the disease process[9-12]. The results from this study show that:

- Focal treatment is effective for macular edema;
- Scatter laser treatment reduces the risk of severe visual loss. The rates of severe visual loss are low whether the treatment is given early in the disease process or deferred until the development of high-risk proliferative retinopathy; and
- Aspirin treatment does not alter the progression of diabetic retinopathy.

In addition to these studies, findings from another National Eye Institute sponsored clinical trial has changed our thinking about when to use vitrectomy for patients who fail laser therapy. In vitrectomy, the vitreous gel in the center of the eye that has been clouded by hemorrhage is surgically removed and replaced whit a clear gel. Conventional management had been to delay vitrectomy for about a year. The recent findings from the Diabetic Retinopathy Vitrectomy Study, however, showed that with early vitrectomy, more patients either regain lost vision or retain better vision than do those who have the vitrectomy delayed[13].

In research with animals that have a condition that mimics human diabe-

tes, scientists have clarified how opacities form in diabetic cataract[14]. This is a good example of scientific cross-pollination. Biochemical studies haven shown that at normal levels of blood sugar, the breakdown of cellular components works properly. However, when the blood sugar level rises, as in diabetes, an enzyme called aldose reductase converts this sugar to another substance called sorbitol, which is slow to leave the cells. When sorbitol concentrations build up, water is forced down the fibers of the lens. The lens fibers then swell and burst, causing cataract to develop. Again, once we understand the cause, we can intervene in the destructive action of the aldose reductase.

Does this hypothesis of the role of aldose reductase also apply to the retinal vessels? We know from the elegant studies of Cogan and Kuwabara that there are two types of cells in the retinal capillaries, the mural cells and the endothelial cells[15]. We also know that the first change that occurs in the diabetic retina is a selective loss of the mural cells. This appears to trigger the entire chain of events that leads to microaneurysms and eventually to exudates, hemorrhages, nonproliferative retinopathy, and eventually proliferative diabetic retinopathy.

Immunohistochemical staining has shown that the enzyme aldose reductase is present in the mural cells but not present in the endothelial cells. Therefore, it is quite conceivable that the same mechanism that brings about the death of lens fibers can also bring about the death of the mural cells: sugar alcohol accumulates in the cell, then water moves along its osmotic gradient into the cell, forcing the mural cells to swell and burst, thereby causing their death.

Another ubiquitous aspect of diabetes that occurs in humans as well as experimental animals is the thickening of the capillary basement membrane. We now know that an aldose reductase inhibitor administered to rats completely blocks the membrane thickening[16-17]. Based on this very strong laboratory evidence of the role of aldose reductase, the hypothesis has been advanced that aldose reductase is involved in the development of diabetic retinopathy. Clinical trials and laboratory studies have indicated that aldose reductase inhibitors can reverse the progressive slowing of motor and sensory nerve conduction that occur in diabetic neuropathy[18-19].

With this information, the National Eye Institute began the Sorbinil Retinopathy Trial several years ago to determine whether diabetic retinopathy and diabetic neuropathy could be slowed or prevented in early diabetes. Sorbinil is an aldose reductase inhibitor. This trial was an interesting collaboration between the private sector represented by Pfizer and the government represented by the National Eye Institute whereby the National Eye Institute was responsible for the scientific design and surveillance of the study while Pfizer was responsible for providing the resources enabling the trial to be conducted. At the conclusion of this clinical trial in 1990, the results indicated that it is unlikely that sorbinil administered at a dose of 250 mg daily for three years has a clinically important effect on the course of retinopathy in adults with Type I insulin-dependent diabetes[20].

Glaucoma is another insidious, sight-impairing disease that affects millions of people, almost all of them middle-aged or older, and many of them black. The exact cause of open-angle glaucoma, the most common kind of glaucoma, remains unclear. Although open-angle glaucoma cannot be cured, it can usually be controlled by medication and blindness can be prevented if detected and treated early. Although some practitioners may start treatment immediately while others may observe the patients on a regular basis without treatment, the person at high risk for and the person with glaucoma needs professional eye examinations and must follow recommendations for follow-up visits.

Fortunately, we are making progress in research, especially on glaucoma medications that do not cause toxic side effects. For example, scientists are now developing an antiglaucoma medication that becomes active only when it reaches the corneal membranes for which it is targeted. They can do this because earlier research had clarified how the corneal membrane - which allows drugs to be absorbed into the eye - differs from two nearby tissues - which allow drugs to be absorbed into the bloodstream. The specificity of the target should reduce the amount of drug in the bloodstream and the consequent toxicities and shouldenableclinicians to control the amount of drug that gets into the eye. When these drugs that contain a carbonic anhydrase inhibitor become widely available, clinicians and their patients must be made aware of their value, so that the thousands of patients who cannot tolerate their current antiglaucoma drugs can be given these less toxic medications that may save their vision.

To help those people whose glaucoma cannot be controlled with medications alone, we are currently evaluating the effectiveness of different surgical interventions in three multicenter clinical trials. In the Glaucoma Laser Trial[21], the argon laser was used to make tiny scars around the spongy tissue that allows the fluid to drain from the eye. The scars seem to stretch the tissue, allowing for better drainage. Sometimes, however, the procedure must be repeated when intraocular pressure starts to build again. The study group concluded that during the two-year folowup period, argon laser treatment was safe and effective in lowering intraocular pressure and reducing the need for additional medication when compared with

initial topical medical therapy with timolol[22]. The results showed:

- Patients treated with laser had less exposure to glaucoma medicine and less trouble achieving and maintaining pressure control;
- First treatment worked in 44% of eyes when the treatment was laser compared with 30% when the initial treatment was timolol; and,
- Eyes first treated with laser maintained intraocular pressures 2 mmHg lower on average than those initially treated with medication.

Long term follow up of these patients is continuing.

Although laser surgery has become popular, another type of therapy, called filtering surgery, also relieves intraocular pressure. A surgeon makes a tiny flap in a layer of eye tissue near the drainage area to allow the fluid to flow better. Sometimes, however, the normal healing forces of the body react to the incision as if it were a would and so begins to scar over the incision. To offset this action, we started the multicenter Fluorouracil Filtering Surgery Study to test whether the use of an antimetabolite - a drug to slow this healing action - would keep the drainage flap open longer. The drug is called 5-fluorouracil, or 5-FU for short.

Results from the 5-FU study were announced in December 1989[23]. One-year followup data demonstrated a 50 percent improvement in surgical control of glaucoma using 5-FU in patients at high risk for blindness. Of the 105 operations on eyes treated with 5-FU, 73 percent were successful at least 1 year, compared with 50 percent of the 108 eyes in the standard therapy group.

Because glaucoma patients sometimes must return for further surgical treatments, we need to know more about how these surgeries should be sequenced. Is it better to start with filtering surgery and follow laser or vice versa? We have begun the Advanced Glaucoma Intervention Study to examine this question and to determine whether surgery is superior in enabling patients to retain their vision. This important clinical trial will complete patient recruitment in November of this year, but results will not be available for 3-4 years because of the long-term follow up required.

Although the precise cause of glaucoma is still unknown, some scientists suspect that the culprit causing the changes in cataracts - namely, oxidation - is also responsible for the development of glaucoma. Some exciting work that has been reported may be what these scientists need to confirm or repudiate their suspicions for both diseases or, for that matter, for many other eye diseases. For a long time, scientists have been able to study intact eye tissue that is removed during surgery or after the death of a person. But these small bits of tissue may not be the most suitable for certain investigations because the tissue may be either damaged at the time of surgery or changed at the time of death. Now scientists have found a way to grow eye tissues outside of body in the laboratory[24-25]. It is exciting to think about the opportunities for research into disease causes and consequent new treatments that this tool may provide. Again, we have a good example of research cross-pollination.

Thus far, I have discussed advances that have been made in preventing and treating the four major diseases that cause visual loss and blindness. Now let us briefly look at two potentially blinding diseases that can be prevented by very simple measures.

Trachoma has been virtually elliminated in industrialized countries. However, about 500 million people in preindustrial countries are still infected with trachoma, and between 6 and 9 million are blind as a result of the infection. Unfortunately, the numbers of blind may more than triple by the year 2020 because in many countries the populations are growing explosively in rural areas where trachoma is still a major problem. Accompanying this rapid population growth, are the usual crowded living quarters, poverty, and consequent unsanitary conditions that increase the spread of the disease. As a result, numbers of trachoma blind will soar in ten and twenty years when the infected children reach the age when the disease causes visual loss and eventual blindness.

Trachoma can be treated with antibiotic salves and other drugs; however, unless unhealthy behavioral and environmental factors are corrected, infection almost inevitably recurs. We know from studies in other countries that very simple behavior modifications can eliminate the spread of trachoma, but knowing which protective practice the people will accept and follow is another story. For example, in Egypt, scientists have been looking for one or two simple hygienic practices that rural Egyptians can adopt to stop disease spread. To find out what behavioral modification would be culturally acceptable and yet pratical and effective, the team's medical anthropologist spent weeks visiting rural families in their homes, learning what practices these people could and would follow to protect themselves against disease spread. Moreover, the team gained important insights about how the disease is spread in Egyptian rural homes. As a result, the team has inaugurated a vigorous education program promoting daily face washing with soap[26].

In addition to behavior modification to prevent disease spread, scientists are also working on a vaccine to prevent both the venereal infection and the blinding disease caused by the trachoma microorganism. A convenient diagnostic kit that can be used easily in the field is already available for identifying endemic areas that need special efforts to combat the di-

sease.

Another potentially blinding disease that can be prevented by very simple measures is xerophthalmia, a condition brought on by prolonged vitamin A deficiency. Tragically, severe xerophthalmia also shortens life by increasing a person's risk for lethal infections. It most often blinds young people who live in impoverished conditions. In Asia alone, 250,000 children are blinded by xerophthalmia and millions more have their sight impaired, either temporarily or permanently. We are now finding that some African and Latin American countries also have significant levels of blindness from the disease.

Once again we have a disease that is preventable, and, if identified early, amenable to a simple therapy. Vitamin A is added to the diet either through vitamin-rich natural foods or through food fortification. High-dose vitamin supplements are sometimes needed to relieve acute situations or provide a transition to the time that long-term measures become effective.

We are moving away from routinely distributing vitamin A capsules, however, and are now focusing on the reeducation of mothers to recognize the value of dark green leafy vegetables in the diet of their children. In many countries where blinding malnutrition is endemic, rich sources of vitamin A grow well, often as weeds along the roadside.

Finally, if we look the future, we see three areas that are and will play a major role in advancing clinical research in ophthalmology.

Molecular biology can help us understand the dry form of age-related maculopathy so that we can develop new treatment. Clearly, one tissue that is primarily involved in this disease is the retinal pigmented epithelium (RPE). Researchers are now focusing on this layer of cells, looking at its biochemical and molecular biology, to determine how the RPE in the macula differs from the RPE found elsewhere. In the next decade the biochemists, the molecular biologists, and the molecular geneticists will provide us with very important information concerning the etiology of diseases of the RPE with secondary involvement of the sensory retina.

Molecular genetics is a powerful research tool for understanding the bases of a number of diseases. We are all familiar with the major strides that have been made in understanding retinoblastoma. This understanding has affected both vision research and cancer etiology in general. We have known about oncogenes for year, but the story of retinoblastoma has clearly shown that some tumors can occur only if genes are quiet rather than active[27]. These "recessive" genes should play a very important role, not only in retinoblastoma, but in other tumors as well.

Neurobiology is another field that has been focusing on two aspects critical to an understanding of central nervous system pathology. This greater understanding will lead to the treatment of diseases arising from disorders of the central nervous system. We are learning more and more about the plasticity of the central nervous system-how this plasticity can be maintained, not lost, during maturation. Research in nerve regeneration is also moving forward very rapidly. When we learn how to maintain plasticity and bring about nerve regeneration, our treatment of amblyopia and strabismus patients will be markedly improved. Moreover, the treatment should ensure good vision for the life time of the patient.

In conclusion, if it were not for the healthy fusion of basic and clinical research, I would not have been able to tell you about the significant progress that vision researchers have made, especially in the past decade. From these few examples I have described, you can see whathopeful prospects lie ahead. Or, again to use the words of Rabbi Ben Ezra, "the best is yet to be."

Thank you.

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