VIEWPOINT

THE DEPARTMENT OF OPHTHALMOLOGY Columbia University
The Edward S. Harkness Eye Institute

Spring 2002

Seeing with Crystal Clarity

Molecular Biologist Lawrence Shapiro

LAST DECEMBER, the Department of Ophthalmology welcomed a new member, Associate Professor Lawrence Shapiro, Ph.D., a molecular biologist who holds two appointments at Columbia—in the department of Ophthalmology and in the Department of Biochemistry and Molecular Biophysics—and collaborates with investigators at the Naomi Berrie Diabetes Center. "Dr. Shapiro is a multi-talented biologist and a brilliant scientist. He is adding a new dimension to our research effort," says Dr. Stanley Chang, Edward S. Harkness Professor and Department of Ophthalmology Chairman.

After he completed his undergraduate degree at New York University, Dr. Shapiro explored several fields, working as a scientific software programmer in Seattle and attending law school at Columbia. He had always been interested in molecular biology, but never felt it would be possible for him to realize these interests in a scientific career. Explaining what factored into his decision to become a scientist, he smiles and says, "I learned to have faith that the world is going to continue to become a much more complicated place."

Once he decided to become a biologist, Dr. Shapiro completed his Ph.D. at Columbia's Department of Biochemistry and Molecular Biophysics in an intensely focused four years, specializing in the structural study of biological molecules. Shortly thereafter, Shapiro was appointed Assistant Professor at the Mt. Sinai School of Medicine in the Department of Physiology and Biophysics, where he built a division of structural biology.

Word of his many talents and accomplishments probing the genetic .

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Photo: Carlos René Perez

Cracking retinopathy's code: Dr. Shapiro studies the genetics of retinal disease.

HIGHLIGHTS

News Brief...

The Director of the National Eye Institute (NEI) Presents The Annual George K. Smelser Lecture

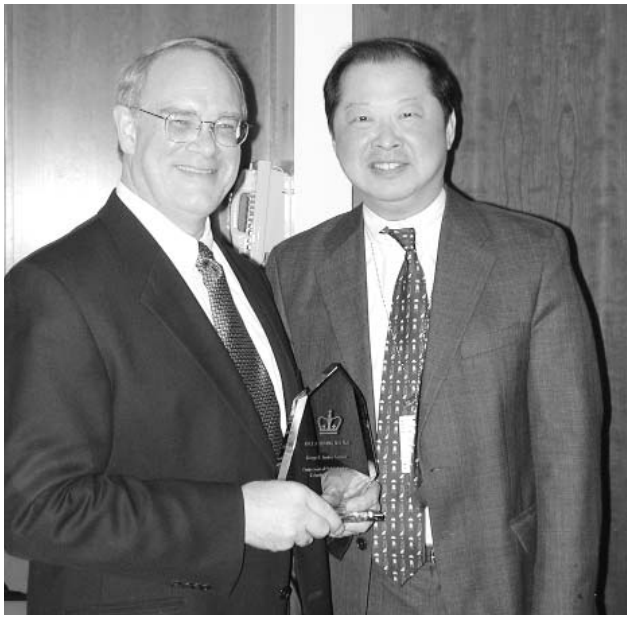

Photo: Kevin Langton

As the Smelser Guest Lecturer, Dr. Paul A. Sieving (left) is presented with the George K. Smelser Award by Dr. Stanley Chang. Earlier in the day, Dr. Sieving attended a series of presentations on departmental research by key faculty members. The George K. Smelser Lecture is endowed by the estate of Virginia Ozanics.

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Viewpoint chronicles fundraising activities of the Department of Ophthalmology and profiles clinicians and researchers supported in part by donor gifts. *Viewpoint* is published twice yearly by the Columbia University Health Sciences Development Office.

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causes of adult-onset obesity and diabetic retinopathy spread quickly, and soon Sloan-Kettering and Columbia were simultaneously recruiting him for their research programs. For Dr. Shapiro, who was not looking for another job, the decision was an easy one. "The opportunity to come back to Columbia was alluring because the intellectual environment it offers to a molecular biologist is one of the best in the world. I'm completely happy being at Columbia," he says.

"The Eye Institute is renewing its commitment to basic research," says Dr. Shapiro. "It's exciting to be part of that."

Dr. Shapiro has pioneered the molecular study of a gene known as "tubby," which is linked to adult-onset obesity, hearing loss, and retinal degeneration. He conducts his research using a specially bred strain of obese mice that carry a mutation in the tubby gene. Because of the similarities its genome shares with ours, the mouse is an ideal model for researchers to use in studying how genetic mutations might cause retinal disease in humans.

The protein molecules created or "encoded" by genes are the focus of Dr. Shapiro's work on tubby. Composed of about 5,000 non-hydrogen atoms, a protein carries out a gene's instructions by interacting chemically with molecules in body tissues such as the retina. When the gene carries a mutation, its proteins can be highly destructive, causing diseases like *retinitis pigmentosa,* a potentially blinding disease of the retina's photoreceptor cells affecting one million people in the U.S.

Because the family of proteins associated with the tubby gene, referred to as "tubby-like proteins," or TULPs, differ significantly from other known proteins, scientists have not been able to determine their chemical function using traditional methods of analysis. Dr. Shapiro uses a 3-D imaging technique called *X-ray crystallography* to crack their chemical code. The images produced reveal the details of these proteins' highly complex structure, such as sequences of atoms, "binding surfaces," and "folds," all of which are key to a protein's chemical behavior.

"Determining function through structure essentially turns the paradigm of molecular biology on its head," says Dr. Shapiro. In the past, molecular biologists would discover a molecule's function by beginning with traditional biochemical and molecular biological methods, and at the end, following up with structural studies to work out the details.

"What we're doing is the opposite: starting with structure and working toward function," he says. Changes in techniques of structural determination and the perfecting of imaging methods, together with a large body of accumulated information about the chemical behavior of proteins, have made this shift possible, and have reduced the process of analyzing biological molecules from a period of years to several weeks.

Structural analysis has played an important part in molecular biology's medical breakthroughs. The study of the structure of the HIV protease enzyme, for example, has allowed scientists to develop HIV protease inhibitors, which offer a useful strategy in the treatment of the disease.

As basic research that investigates the most fundamental levels of living systems, Dr. Shapiro's study of the TULPs has powerful potential for many clinical applications, including in diabetes and in eye disease. "The Eye Institute is renewing its commitment to basic research," says Dr. Shapiro. "It's exciting to be a part of that." **JT**

Photo courtesy of Russ and Angelica Berrie

Russ and Angelica Berrie were instrumental in funding Dr. Shapiro's recruitment.

Gentle Tactics for the War on Age-Related Macular Degeneration

Spotlight on Vision's Old Foe

Age-related macular degeneration (AMD), the blurring or loss of vision in the central part of the retina, is caused by the progressive loss of function in the photoreceptors—the rod and cone-like cells that capture light and convert it into nerve impulses.

Researchers speculate that environmental, behavioral and genetic factors, such as smoking and aging, combine to contribute to AMD's development, but they do not yet know why photoreceptor cells gradually lose function or die off, nor whether the toxic waste products that accumulate in the retina as part of the aging process represent a symptom or a cause of the disease. The work of two experts in the diagnosis and treatment of AMD at the Department of Ophthalmology may help shed light on this conundrum.

R. Theodore "Ted" Smith, M.D., Ph.D., Associate Clinical Professor in the Department of Ophthalmology, and his Columbia colleague, Gaetano "Guy" R. Barile, M.D., Assistant Professor of Clinical Ophthalmology, are testing a powerful new laser scanning device, the Heidelberg Retinal Analyzer, to study AMD and identify its precursors.

Traditionally, the tell-tale sign of AMD has been the accumulation of *drusen*—yellowish deposits of uncertain origin in the tissue beneath the retina—which crowds out healthy tissue, and disrupts the delivery of nutrients to the photoreceptors and the elimination of waste from them. The result is the gradual death of photoreceptors and eventually, macular degeneration.

"New blood vessel growth is not an undesirable event in all physiologic circumstances—for example, cardiologists are looking at ways of promoting it in cases of coronary artery disease," explains Dr. Barile. "But in the case of wet AMD, it is the principal factor behind severe vision loss."

With the new Retinal Analyzer, Dr. Smith and Dr. Barile will be looking to identify early markers of macular degeneration, particularly a family of compounds related to *drusen*, known collectively as *lipofuscin,* which are by-products of photoreceptor metabolism that accumulate beneath the retina.

Lipofuscin has been invisible to

Photo: Kevin Langton

Dr. Ted Smith says HRA analysis is similar to doing a biopsy on retinal tissue, but without damaging the retina.

conventional techniques for examining the retina, but when illuminated by the HRA, *lipofuscin* "fluoresces," or emits distinctive patterns of light, which may enable researchers to isolate areas in the macula beginning to undergo disease, thus paving the way for early detection of AMD.

The Retinal Analyzer's screening capabilities may also be able to help doctors discern different types of *liposfuscin* compounds in the retina, each of which may be associated with different forms of macular degeneration. "Identifying the various compounds that accumulate in the retina will help us define and classify the different types of AMD," says Dr. Barile.

Once the different types of AMD have been defined, researchers may be able to match them with the various genetic mutations that contribute to the disease's onset. Studies are underway under the direction of Assistant Professor of Ophthalmic Science Rando Allikmets (in Ophthalmology and Pathology) and the Louis V. Gerstner Jr. Scholar in Ophthalmology to identify those genetic culprits.

Dr. Smith says HRA analysis is similar to conducting a biopsy on retinal tissue, which is impossible to do without damaging the retina. "The HRA is potentially a very important instrument," says Dr. Smith. "There is no other way to study the retina with such clarity. This technique will contribute to retinal disease research across the board."

Restoring Sight without Surgery

Dr. Barile, in partnership with NYC-based drug developer Eyetech Pharmaceuticals, is testing a new method for treating wet AMD, a less common but highly damaging type of macular degeneration.

The "wet" form of age-related macular degeneration (AMD), in which abnormal new blood vessels leak fluid under the retina, causing it irreparable damage, accounts for only about fifteen percent of cases of macular degeneration, but represents the chief cause of blindness from the disease. "The retina needs to be relatively dry for it to function and capture light signals, like the film of a camera," says Dr. Barile. "Otherwise, images get wavy and distorted."

In wet AMD, poorly formed new blood

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vessels invade the dense network of photoreceptor-nourishing blood vessels beneath the retina—the region with the highest blood flow in the body—and leak their contents. The buildup of the fluids there exerts pressure on the retina and causes visual loss.

Conventional therapies for wet AMD include the use of laser coagulation, a surgical procedure in which a laser is used to destroy abnormal blood vessels. Since vision loss cannot be reversed by this procedure, early detection of wet AMD is key. Photodynamic therapy may also help stabilize vision when blood vessels grow under the center of the retina, but most cases are neither eligible for this treatment, nor responsive to it.

Dr. Barile is testing a nonsurgical method of inhibiting new and existing blood cell growth in the macula. After identifying a substance known as vascular endothelial growth factor or VEGF, which is associated with many types of new blood vessel formation in the eye, Eyetech researchers developed an anti-VEGF compound that may both block growth of the new blood vessels and halt ongoing leakage of faulty ones.

In a short procedure, Dr. Barile and his colleagues inject the anti-VEGF compound into the eye so as to reach the affected area directly. The therapy is repeated again after six weeks, so as not to aggravate or damage the retina. In pre-clinical models, it has been effective in checking growth of unwanted blood vessels. If the trial is successful, ophthalmologists will have a new tool for curbing blood vessel growth and restoring diseased tissue to health in patients with wet AMD.

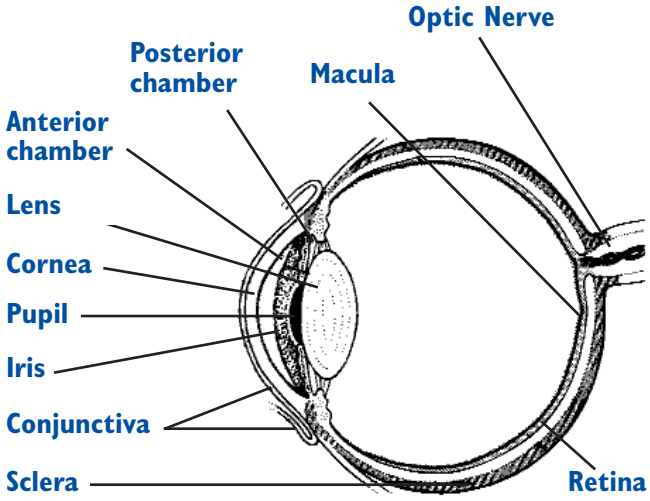
Tobacco: The Smoking Gun in AMD?

For decades, public awareness campaigns have warned us that smoking causes diseases ranging from cardiovascular complications to lung cancer. Ophthalmologists know that smoking is a risk-factor for age-related macular degeneration and nuclear cataracts—cloudy spots in the nucleus of the lens that scatter light. What is not yet fully understood is how smoking inflicts its damage on the body. The work of David Paik, M.D., in the Department of Ophthalmology at Columbia, is helping to unravel that mystery.

Dr. Paik has shown that nitrite, a by-product of cigarette smoke, may damage critical tissues in the body, including those found in the retina and lens of the eye. Nitrite, a compound of oxygen and nitrogen, is a by-product of gases in cigarette smoke that is also found in foods such as cured meats, including hot dogs. A precursor of nitrite, nitric acid, a gas formed naturally in the body, plays a vital role in inflammation, which helps

the body purge badly injured or dead tissue before it begins the healing process. But scientists have also documented the adverse effects nitrites can have on health. Nitrites gained notice in the 1970s, when they were discovered to play a role in the formation of cancer-causing compounds.

What Dr. Paik has learned is that nitrite reacts harmfully with three types of proteins in the body—collagen, elastin, and alpha-crystallin—that make up the connective tissues in the skin, bones, tendons, arteries, and organs, such as the lungs and eyes. "Collagen is like a scaffolding that makes up our framework. It is the most abundant protein in the body," explains Dr. Paik. Alpha crystallin is found in the lens of the eye, while collagen and elastin are found in the membranes beneath the retina. Nitrite may cause damage to the structural integrity of these proteins through a chemical process called non-enzymatic nitration. Collagen, which is ordinarily strong and flexible, becomes rigid when exposed to nitrite, while elastin becomes cracked and fragmented, like an old rubber band, and alpha-crystallin clumps and scatters light. This is precisely the kind of damage that occurs in the tissues of the eye in macular degeneration and nuclear cataracts, obscuring vision and causing blindness.



Cross-section of the eye.

"These reactions between connective tissue proteins and nitrite may explain the contribution of cigarette smoke to a range of diseases, including AMD and nuclear cataracts," Dr. Paik says. "This is not the only cause of age-related macular degeneration, but it is one potential mechanism that may explain the contribution of smoke-related damage that occurs in the tissue of the eye." He adds that it may be the accumulation of nitrites in the body, over a period of years and from different sources, that eventually causes this damage. Any prescriptions? "You can buy meat products that do not have nitrite," suggests Dr. Paik. "And either smoke cigarettes with lower nitrite yields or—stop smoking."

RA

Therapy for Thinning Nerves

The news in treatment for glaucoma

A cable-like bundle of more than a million filaments, the optic nerve transports visual images from our eyes into our brains. Without this final connection in the vision pathway, our sense of sight would not be possible. Glaucoma, a sight-threatening disease characterized by chronic degeneration of the optic nerve, afflicts one in 25 Americans, and is one of the leading causes of blindness in the United States today.

"We have a talented group of clinical investigators who will help in the discovery of future treatments for glaucoma," says James C. Tsai, M.D., Director of the Glaucoma Division, Associate Professor of Ophthalmology, and Homer McK. Rees Scholar in glaucoma research at the Harkness Eye Institute. Together with his colleagues in the Division, Dr. Tsai is undertaking clinical and scientific studies that he hopes will improve our understanding of the causes of and treatments for this debilitating disease.

"The mechanisms underlying optic nerve damage in glaucoma are not well understood," says Dr. Tsai. "However, a significant risk factor is known to be elevated intraocular pressure (IOP), which occurs when the fluid inside the eye is unable to exit in a normal fashion and becomes trapped. The resulting higher pressure within the eye damages the optic nerve and causes permanent vision loss."

Dr. Tsai and his colleagues are pursuing research in the area of neuroprotection—defense against nerve degeneration—and are investigating certain recombinant proteins that may benefit the optic nerve. "One of our theories is that genetic deficiencies in the receptors linked to these proteins may explain why some patients develop glaucoma while others don't," explains Dr. Tsai. "We are pursuing research funding to investigate these receptor deficiencies both in animal models and in the clinical setting. We are also collaborating with other researchers to identify new potential medications that may prove beneficial in protecting the optic nerve from glaucoma-associated damage."

Dr. Tsai is also conducting clinical investigations of a family of drugs called prostaglandins that are already being widely used by physicians to treat glaucoma patients. These drugs are very effective in lowering IOP and have been approved by the Food and Drug Administration (FDA) for treatment in patients with glaucoma.

Racial and ethnic diversity is an important component in drug studies, since African-Americans are four times more likely than Caucasians to develop glaucoma. Due to an earlier onset and greater severity, glaucoma is the leading cause of irreversible blindness in African-Americans. Dr. Tsai explains that the Glaucoma Division's affiliation with the Department of

Ophthalmology at Harlem Hospital is extremely valuable in providing the necessary ethnic diversity for clinical trials intended to benefit the African-American community.

Because its symptoms are unnoticeable in the early stages, only half of those afflicted with glaucoma are aware that they have the disease. Although current treatment options can arrest progression of the disease, they cannot reverse blindness acquired from glaucoma. Early diagnosis provides the best chance of reducing vision loss.

In order to detect and track progression of glaucoma damage in patients, physicians have come to depend on several cutting-edge diagnostic imaging techniques that analyze the optic nerve and nerve fiber layer of the retina in exquisite detail. **Optical Coherence Tomography** (OCT) measures the thickness of the nerve fiber layer and may detect the thinning associated with early glaucoma damage. The **Heidelberg Retinal Tomograph** (HRT) can take 32 separate layer-by-layer images of the optic nerve, capturing its contour to detect and measure deepening of the cup where the optic nerve emerges from the back of the eye, another sign of glaucoma damage. The **Heidelberg Retinal Flowmeter** (HRF) measures blood flow in the superficial capillaries near the optic nerve head, which may prove to be very useful

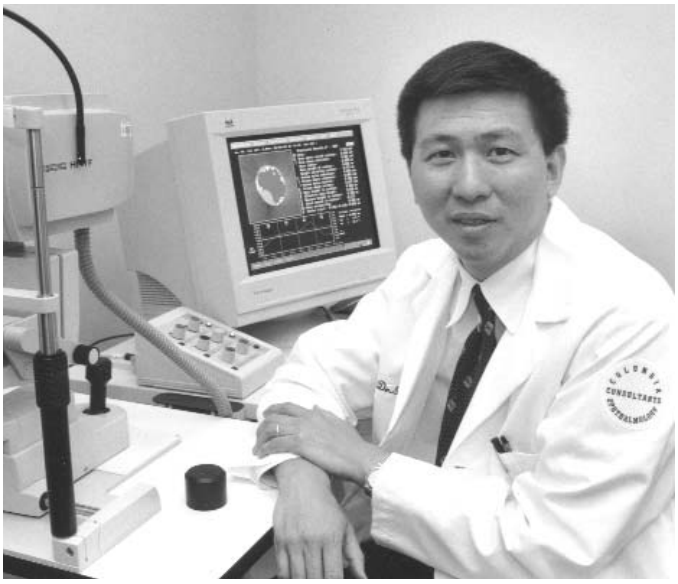


Photo: Carlos René Perez

Tracking glaucoma's toll: James Tsai, M.D., with the Heidelberg Retinal Tomograph.

information since reduced optic nerve blood flow is thought to be a non-IOP factor in glaucoma damage. Dr. Tsai's research team is evaluating these three methods for their accuracy and applicability to the diagnosis of glaucoma.

The Glaucoma Division currently handles a large patient volume and is recruiting another full-time glaucoma specialist. "Our vision is a Glaucoma Center at Columbia that will serve the major metro New York area and the surrounding region," says Dr. Tsai. "Our goal is to offer the most comprehensive, innovative and compassionate glaucoma care for patients afflicted with this sight-threatening disease. With Dr. Chang's strong support, faith and confidence in us, we're at the beginning of a long but really exciting and fulfilling journey." **JT**

Controlling Macular Edema

"Putting medications directly into the eye is the treatment method of the future for many eye diseases," says Irene Barbazetto, M.D., Daniel Kirby Clinical Research Fellow in Ophthalmology, who is the clinical coordinator of a phase 2 clinical trial of a new technique for treating macular edema. The trial, which will conclude next fall, includes approximately 285 patients from more than 25 leading ophthalmic centers in the U.S., including the Eye Institute at Columbia. Dr. Stanley Chang is the principal investigator of the Columbia site.

"Putting medications directly into the eye is the treatment method of the future for many eye diseases."

—Irene Barbazetto, M.D.

Macular edema, the swelling of the central retina (macula), is a symptom of several different eye conditions and diseases. It affects more than 600,000 people in the U.S. and is a leading cause of visual disabilities and legal blindness. If the disorder is caught in time, before chronic and permanent cystic changes develop that may render the condition untreatable, steroids, known for their anti-inflammatory benefits, can be used to control macular edema. The drugs have traditionally been administered as eye drops, in pill form, or under the tissue that surrounds the eyeball, but because none of these methods deliver the medication efficiently enough, large doses have been required, causing severe systemic side effects.

The new technique, pioneered by the Oculex Company, involves a tiny tablet made of a time-release polymer substance called Posurdex. The tablet, known as a "delivery system," is infused with the required medication and inserted into a tiny slit in the sclera, or "white," of the anesthetized eye. The tablet dissolves completely, releasing the medication gradually, over a period of approximately five weeks. No follow-up surgery or removal is required, as has been the case with other direct-to-eye delivery systems in the past. The benefit of this novel system is that it delivers a much smaller dose directly to the area to be treated, with equal or greater effect than traditional methods.

Dr. Barbazetto reports that the results of the previous, stage 1, trial have been very promising, providing patients with relief,

and perhaps just as important, with fewer side effects.

Dr. Barbazetto completed her ophthalmology training at the Department of Ophthalmology in Lubeck, Germany. She was a vital member of the team that pioneered the development of photodynamic therapy for age-related macular degeneration in Europe. However, romance brought her to New York when she met her husband, an American, in Germany. She is currently preparing to obtain her medical license in the U.S., but will have to repeat a residency program here.

Dr. Barbazetto is supported by a generous grant from the Eye Surgery Fund. This foundation was started by the family of Dr. Daniel B. Kirby, a former faculty member at the Eye Institute and former Chairman of Ophthalmology at N.Y.U. Medical Center. Dr. Kirby is known for establishing the first basic science laboratory in vision science at Columbia. The Kirby family that includes Mr. and Mrs. Peter Mullen, Mr. Dukes Wooters, and Sister Joan Kirby, have continued Dr. Kirby's legacy through support of vision research.

JT

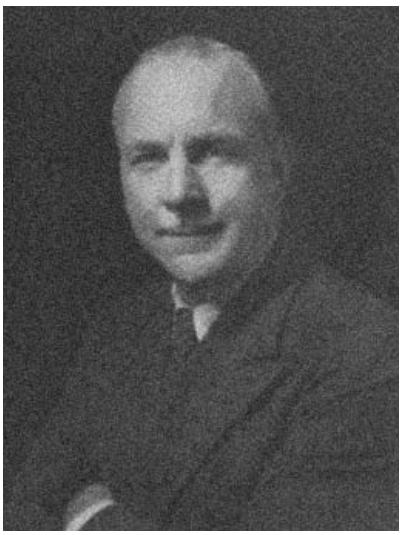


Photo: Courtesy of Augustus C. Long Health Sciences Library, Columbia University

Dr. Daniel B. Kirby (1891-1953) former faculty member at the Eye Institute.

Vitamin Therapy: Cure for Aging Eyes?

A growing number of people in the U.S. are taking nutritional supplements to treat disorders of all kinds, although the benefits of these supplements are not generally well understood.

On March 29, the Department of Ophthalmology presented a conference addressing the ways in which such supplements benefit vision. Janet Sparrow, Ph.D., Associate Professor of Ophthalmic Research, who was one of the conference organizers, explains that the conference was timely since "positive effects of supplements on age-related macular degeneration and cataract formation in the elderly have recently been reported."

A recent clinical trial has shown that a combination of vitamin C, vitamin E, beta-carotene and zinc, taken in high doses, can slow the progress of intermediate age-related macular degeneration and age-related cataract. The trial was conducted by the National Eye Institute at the National Institutes of Health.

The conference, "Vitamins, Nutrition, and Eye Disease," was held on the Columbia Health Sciences campus. It featured a discussion of the trial and its findings by its principal investigator, Frederick L. Ferris III, M.D., Director of the Division of Epidemiology and Clinical Research, National Eye Institute, together with a series of presentations on related topics, such as nutrition and cataract, the role of carotenoids in retinal health, vitamin A's central importance to the vision process, and smoking-related eye damage.

Photo: Courtesy of Ambassador John L. Loeb, Jr.

Ambassador John L. Loeb, Jr. provided support for the conference on "Vitamins, Nutrition, and Eye Disease."

Ambassador John L. Loeb, Jr., a member of the Board of Advisors at the Department of Ophthalmology, who provided support for the conference, says he is encouraged by the dialogue on complementary medicine it offered. "I've always had an interest in the question of whether vitamins and nutrition played a role in the health of the eye in general and macular degeneration in particular. I'm delighted that Dr. Chang helped to organize this seminar to examine recent developments in this area of ophthalmology and nutrition," he says. **JT**

Planned Giving for Columbia Health Sciences

GIVING Well

Creating a Charitable Gift Annuity for Ophthalmology

Q: What is Giving Well?

A: Giving Well is the Columbia University Health Sciences planned gifts program, through which the Health Sciences Development Office can assist you in making gifts to the Department of Ophthalmology. We can help you to review and clarify the financial, estate, and tax implications of your gift, and assist you and your advisors in selecting the amount and type of gift that will best accomplish your charitable goals.

Q: What types of gifts can I make?

A: Gifts of appreciated securities, real estate or other property, closely-held stock, gifts in trust, life income gifts, and those created through a provision in your will are some examples. Each way of giving offers different advantages, and we can help you determine which is most advantageous for you.

Q: What kinds of advantages can a planned gift to Columbia's Department of Ophthalmology provide for me?

A: Gifts to Columbia's Department of Ophthalmology are tax-deductible, of course. The type of property you give, how long you have held it, and whether you give it outright, through a trust, or in your will, can determine the type and amount of that tax deduction.

Q: Are there any additional benefits?

A: Yes. For example, a life income gift, such as a charitable gift annuity, a pooled income fund contribution, or a gift in trust not only can provide you with a tax deduction, it will also pay lifetime income to you or those you name. A gift in your will, a bequest, may help to reduce estate taxes and can even establish a trust to benefit your heirs.

Q: How can I make certain that I maximize the benefits of Giving Well?

A: Call, write, fax, or e-mail us, or have your tax or legal advisor do so. We can provide you with illustrations and support to help you to give well...and wisely.

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You may forward your gift in the envelope found in the center section of this newsletter, or feel free to contact Susan Taylor, at 212-304-7225, to discuss your interests and gift opportunities. Gifts may be in the form of cash, securities, or one of a variety of planned giving vehicles and may be directed for current use funds or endowed gifts.

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