VIEWPOINT

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

Spring
1998

Investing in Sight

Business Leaders Fund Retina Research

"*There's never been a time when opportunity for success is greater!*"
Louis V. Gerstner, Jr.
Chief Executive Officer, IBM

Corneal transplants, laser eye surgery, retinal reattachment—today's ophthalmological miracles, must once have seemed like fantasies, requiring such unimaginable skills and surgical delicacy that they could only be dreamed of. Far from being imaginary scenarios, however, these astonishing procedures to improve vision and prevent blindness are now routine, performed throughout the world, seldom causing any particular notice. These and other equally remarkable medical feats are the result of putting an enormous amount of new biological and technological insight at the service of saving and improving the quality of life.

It was this potential for enhancing the efforts of laboratory science and turning its exciting discoveries into new and successful treatments much more quickly than once was expected, that recently gave Columbia expanded opportunities in retinal research. Three prominent New York businessmen, William Acquavella, president of The Acquavella Galleries, Robert L. Burch III, chairman of Jonathan Manufacturing Corporation, and Louis V. Gerstner, Jr., CEO of IBM, each made gifts of $500,000

IN THIS ISSUE

Views from the Chair

Dear Friends,

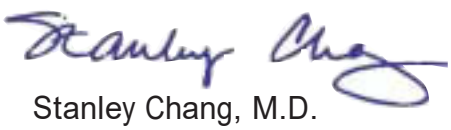
Spring is a time of change and renewal. In this issue of *Viewpoint*, we highlight new and exciting developments in retina research and introduce you to young, talented faculty members—each a future leader in ophthalmology and vision research.

Retinal diseases, particularly age-related macular degeneration and diabetic retinopathy, are among the leading causes of vision loss. As the average life expectancy increases, up to 25% of the population over the age of 75 will be affected by macular degeneration. At Columbia, we are expanding our research effort to increase our ability to understand, prevent, and treat macular degeneration and other retinal diseases. Peter Gouras, M.D., one of the pioneers in the development of transplantation of retinal cells, continues to perfect this technology so that it may someday be used to improve the vision of patients with macular and retinal degenerations. He is joined by Janet Sparrow, Ph.D., who is investigating how aging changes the retinal cells. Our new Scholars Program, established by three prominent benefactors, has allowed the Department to begin a nationwide search for promising young scientists to investigate new treatments for retinal diseases. We are now reviewing applications and interviewing a number of outstanding candidates, attracted by the strength of the medical research community at Columbia.

Diabetic retinopathy remains the leading cause of new cases of blindness in adults under the age of 55. As part of a campus-wide effort in diabetes research, two members of our faculty are collaborating with colleagues in the Departments of Medicine and Surgery to investigate mechanisms causing diabetic retinopathy and to develop new prevention and treatment therapies.

The generosity of friends and patients like you, who are concerned and committed to help find new solutions and treatments through research, has made many of our programs possible. By investing in the future young leaders in our specialty, you have allowed us to move forward at an accelerated pace, renewing our tradition of innovation in the treatment of vision disorders. We are immensely grateful for this strong and united support.

Sincerely,



Stanley Chang, M.D.
Edward S. Harkness Professor and
Chairman of the Department of Ophthalmology

Business Leaders Fund Retina Research, cont.

Louis Gerstner

William Acquavella

Robert Burch

to the Department of Ophthalmology's Research Scholars Program, establishing Acquavella, Burch, and Gerstner Scholars for the exploration of uncharted territory in understanding retinal disease.

Speaking of the reasons behind their decision to support this innovative venture, each of the three philanthropists said he saw an opportunity for opening scientific doors that he found compelling. "As the head of IBM, one of the world's great research institutions, I am convinced that we are on the verge of great breakthroughs in science," said Mr. Gerstner, in making his gift. He also encouraged others to consider the "limited growth in government spending for medical research, which is being applied in narrow areas," adding, "it is up to those of us who have the means to help to support biomedical research."

Expressing his own delight in supporting Dr. Chang's world class research effort at Columbia, Mr. Burch explained, "New York is the capital of

the world. It's logical that young people who are interested in eye research would be attracted here where they can build a vision institution that places emphasis on both basic and clinical studies. I believe we can advance eye research in ways similar to what's been accomplished in other disease research. This is our opportunity." Agreeing, Mr. Acquavella said, "New avenues of research in molecular biology and genetic engineering offer new hope for preventing and treating retinal disease. I'm delighted to help sponsor Columbia's promising initiatives."

Such generous investments in ophthalmologic research are not only becoming more frequent, says Dr. Stanley Chang, chairman and Edward S. Harkness Professor of Ophthalmology, but, he adds, "Enlightened benefactors like Bill Acquavella, Bob Burch, and Lou Gerstner are helping us to win the war on retinal disease." By appointing young scientists with expertise in molecular biology and genetic engineering as new research scholars, Dr. Chang hopes to hasten, "the identification of genes that cause macular and retinal degeneration." This, he believes will be critical to developing treatments at an increased level of success in preventing and managing this group of diseases. By identifying and isolating genes shown to cause retinal diseases, Dr. Chang anticipates that the potential for finding and monitoring patients at risk will become far greater than is possible at present.

Angiogenesis, or new blood vessel growth, will be the equally promising assignment given

"Enlightened benefactors like Bill Acquavella, Bob Burch, and Lou Gerstner are helping us to win the war on retinal disease."

to another of the Department's new retinal research scholars. "Finding agents that can inhibit the formation of new, unwanted blood vessels," Dr. Chang points out, "can be crucial in saving the eyesight of patients with "wet" macular degeneration or diabetic retinopathy."

Joining a growing team of basic scientists and clinicians in Columbia's Department of Ophthalmology, the Acquavella, Burch, and Gerstner scholars will mesh their efforts with this extended commitment to preventing vision loss caused by retinal disease. Dr. Janet R. Sparrow, associate professor of Ophthalmic Science and associate professor of Anatomy and Cell Biology, and Dr. Gaetano R. Barile, assistant professor of Clinical Ophthalmology, the two most recent retina specialists in the Department, were appointed to Columbia's faculty in 1997.

A Push to Prevent Age-Related Macular Degeneration

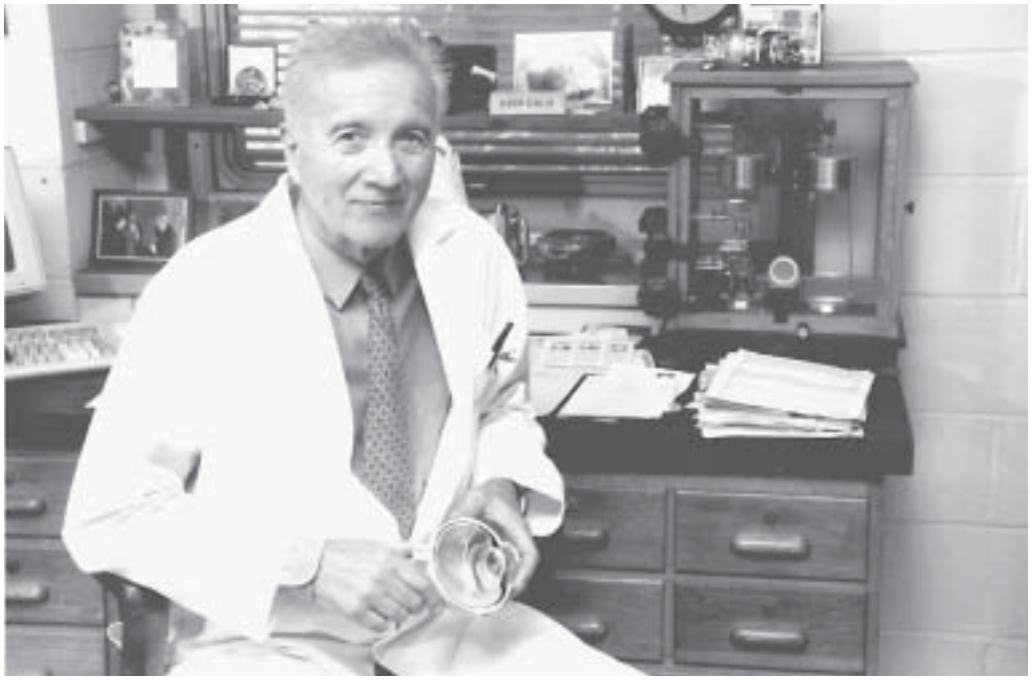
When older people lose their central cone of vision, although retaining peripheral sight, the cause is age-related macular degeneration, or AMD. More than 300,000 people have damaged sight because of this condition—the leading cause of severe vision damage in people over the age of 60. As more Americans live longer and longer, AMD will be even more common in the population and is expected to strike as many as six million people by the year 2030.

Dr. Janet Sparrow

Age-related macular degeneration is as prevalent as it is destructive. But, scientists have not yet been able to understand why AMD waits until we grow older, attacking our precious sight just as we're about to retire, enjoy our grandchildren, or finally have the leisure to travel, read, and garden to our heart's content. But Columbia's ophthalmology researchers are building a clearer picture of AMD and its causes in the hope of learning to prevent the disease's onset and reverse its terrifying consequences.

Why is Aging Bad for Your Eyes?

"When the eye's retinal pigment epithelium (RPE)—a special layer of 'nursing' cells in the retina is healthy," explains Associate Professor Janet Sparrow "the light-sensing part of the macula that is essential to central vision is



Dr. Peter Gouras

also healthy. But, when RPE fails, there is corresponding damage to photoreceptor, or light-sensing cells." One of Columbia's new retinal disease investigators, Dr. Sparrow is dedicated to understanding how aging affects the eye. Because her work emphasizes the role of RPE in removing unwanted debris from retinal tissue, she is also analyzing the link between AMD and lipofuscin, a metabolic byproduct that accumulates in the eye as it ages. Collaborating with Drs. James Dillon, associate professor of Ophthalmology, Norman Kleiman, assistant professor of Ophthalmology, and Centennial Professor of Chemistry Koji Nakanishi, Dr. Sparrow points out that lipofuscin, also known as "aging pigment," is the most characteristic feature of the aging retina. For a 40-year-old, she says, lipofuscin accounts for only a tiny part of RPE, "But, by the time a person reaches the age of 80, it occupies an entire fifth of the RPE cell." To learn more about the effects of this little understood compound on retinal tissue, Dr. Nakanishi's laboratory recently created a synthetic form of lipofuscin. They hope that this significant achievement will lead to new AMD prevention and treatment therapies.

Mysterious, undesirable retinal deposits, called drusen, are common in patients with AMD. A clinical trial to test laser surgery as a method of reducing or removing these particles is being conducted by Dr. R. Theodore Smith, assistant professor of Clinical Ophthalmology, while research fellow, Dr. Joanna Urbanowicz, working with Drs. Sparrow and Dillon, is running his results through computer analysis. They hope this research will answer—once and for all—questions about the effectiveness of laser treatments in eliminating drusen and the problems it can cause.

Gene Altering Therapies To Save Sight

Green fluorescent protein. It may sound like a slimy, harmful bacterium or a space-age vegetarian dinner, but it is actually a revolutionary genetic tag scientists are using in cutting edge gene therapy research at Columbia.

The question of how to reverse destructive, new blood vessel growth in the eyes of patients with AMD or diabetes has long perplexed researchers and clinicians, looking for ways to treat retinal disease. Now, new treatments involving genetically engineered cells may soon be used to eradicate unwanted growth of blood vessels in the human retina.

Led by Dr. Peter Gouras, professor of Ophthalmology and Dr. Stephen Goff, Stephen P. Higgins Professor of Biochemistry and Molecular Biophysiology, Columbia researchers have been able to deliver a powerful agent that stops blood vessel growth, angiostatin, in the genetic structure of living retinal tissue. When green fluorescent protein, a naturally fluorescent product derived from jellyfish is delivered along with the angiostatin-producing gene, it serves as a monitoring agent that lets scientists actually watch genetic protein expression as it occurs.

"We're just at the beginning," says Dr. Gouras. "But through new technologies, we can now observe genes working in the living retina, which is just like seeing into the human brain."

What is AMD?

Try to imagine the horror of having your vision slowly begin to erode. You can't look up a phone number, drive a car, discern facial expressions of loved ones, or read a book. That is what it's like to have advancing AMD, a disease that results from damage to the macula, a tiny collection of cells that lie in back of the retina. If AMD gets worse, it can lead to a significant loss of vision.

There are two types of AMD. Most people with the disease have the "dry" kind, believed to be caused by a breakdown of light sensing cells in the retina. As the disease progresses, new blood vessels may begin to grow under the macula. Fluid and blood leaking from the fragile, new blood vessel growth is responsible for "wet" AMD, which accounts for the majority of AMD-caused blindness.

The RAGE in Diabetic Retinopathy

"I vividly remember meeting two diabetic women during my fellowship—both students in their early 20's, who had juvenile-onset diabetes," recalls Dr. Gaetano Barile, assistant professor of Clinical Ophthalmology at Columbia. "The two young women suffered from a particularly aggressive form of diabetic retinopathy and ultimately went blind, despite all current medical and surgical interventions," says Dr. Barile. "It's obviously moving for anyone to witness such sad events and motivates us to do more for the future."

Diabetes, the leading cause of blindness in young adults, is responsible for as many as 24,000 new cases of vision loss each year. A "head to toe," systemic disease, that is also the principal cause of lower limb amputations in the United States, diabetes is not only often associated with blindness, but also heart, kidney, and nervous system damage, dental and gum disease, stroke, high blood pressure, and pregnancy complications.

In its early stages, diabetic retinopathy, the main cause of diabetes-related vision impairment, tends to be of the "nonproliferative" or "background" type, occurring when retinal blood vessel walls balloon outward, leaking fluid into the eye, to blur central vision. The more advanced disease stage, "proliferative" retinopathy, is characterized by rampant new blood vessel growth within the retina. Particularly fragile and easily ruptured, if the new blood vessels leak their contents into the eye, light may be prevented from reaching the retina, resulting in complete vision loss. Scar tissue or swelling that often develops may result in further complications including retinal detachment—a condition in which the retina is separated completely from the back of the eye.

Drs. David Stern and Anne Marie Schmidt

Until recently, little was understood about the mechanisms causing the debilitating complications associated with diabetes. But now, two Columbia researchers, Dr. David Stern, professor of Physiology and Cellular Physiology, and Dr. Anne Marie Schmidt, assistant professor of Medicine and Surgical Science, have identified a receptor that is likely to have a central role in diabetic retinopathy as well as many of the other disorders associated with diabetes. Their research is offering hope for preventing, treating, and possibly even reversing the complications of diabetes.

Why the RAGE?

When the body's proteins are exposed to sugars as part of the metabolic process, they undergo a series of modifications that forever alter their characteristics. Similar to the way foods become brown when cooked, the bodily changes that occur in the presence of high lev-

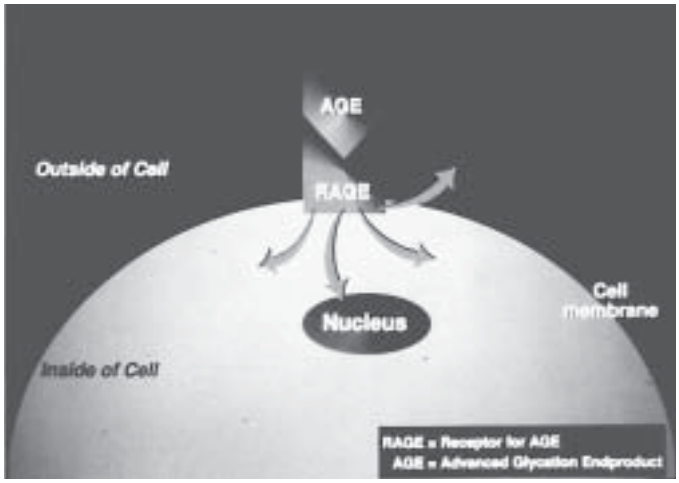


Diagram of AGE-RAGE interaction

els of blood sugar, result in the formation of caramelized proteins, called Advanced Glycation Endproducts, or AGEs. Accumulating gradually in all of us as we grow older, AGEs accrue at a markedly accelerated rate in patients with diabetes.

In 1990, Drs. Stern and Schmidt identified a receptor, located on the surface of cells, which binds to AGEs, much in the way a lock accepts the right key. Calling the molecule that develops from this combination, RAGE, for Receptor for AGE, the researchers suggest that its formation triggers ever-increasing amounts of AGEs and new cell surface RAGE to be expressed in a spiraling cycle that is largely irreversible. Once developed, say Drs. Stern and Schmidt, the AGE-RAGE interaction is present for life, and its presence may play a key role in the destruction of blood vessels in diabetic patients.

How does RAGE do its damage?

Normally, the cells lining the inside of blood vessels form a tightly connected wall that acts as a barrier to prevent blood seepage. When AGE attacks the lining of blood vessels, it erodes that natural barrier, creating crevices through which blood components can leak. In the eye, this system breakdown may lead to the excessive growth of new blood vessels, also prone to leakage, which may result in varying degrees of vision impairment, ranging from blurred eyesight to complete blindness.

So far, scientists don't know for sure how to stop the AGE/RAGE interaction. But, Drs. Stern and Schmidt have developed a form of RAGE, called sRAGE or soluble RAGE, which acts as a decoy to block AGE-RAGE from interacting. Their encouraging findings may lead to improved control of many of the complications associated with disease of both small and large blood vessels in diabetes, including kidney failure, wound healing, periodontal disease, atherosclerosis, neuropathy, and retinopathy.

Dr. Gaetano Barile

Department of Ophthalmology faculty, including Drs. Barile, and Janet R. Sparrow, associate professor of Ophthalmic Science and associate professor of Anatomy and Cell Biology, are collaborating with Drs. Stern and Schmidt to study the development of diabetic retinopathy and its relationship to RAGE. "No current research therapies are available to help patients who have lost their vision to advanced disease," says Dr. Barile. "The best hope for the future is to develop therapies to prevent or control retinal blood vessel leakage and aggressive proliferative growth."

REM Sleep May Have More to do With Vision than with Dreams

"Rapid eye movement (REM) sleep has been considered to be the domain of disciplines ranging from psychology to neuropharmacology and it has not received attention from ocular physiologists," says Dr. David Maurice, professor of Ocular Physiology at Columbia University. Now, Dr. Maurice has carried out research that seems to show that REM sleep may have more to do with vision than with dreams.

In the 1950s, researchers found that sleepers could often recall a dream if they were awakened during the REM part of their sleep, when their eyes appeared to be darting around beneath their eyelids. Scientists theorized that during this REM sleep, the brain is processing information gathered while awake, "rather like a store closing for business during its taking inventory," according to Dr. Maurice. His research, reported in *Experimental Eye Research*, last February, suggests that the aqueous humor, the clear watery liquid just behind the cornea, needs to circulate to bring oxygen to the cornea from blood vessels in the iris. When the eyelids are closed during sleep, the circulation slows dramatically, and the motion of rapid eye movement simply serves to "stir" the aqueous humor and prevent corneal suffocation.

Dr. Maurice developed his theory when he learned of a young man whose eyes had been immobilized by an accident and whose corneas had become laced with blood vessels, presumably to supply the corneas with oxygen. Dr. Maurice knew that when the eyes are closed, oxygen can reach the cornea from the iris only by diffusion across the stagnant liquid. Using mathematical calculations, he established that under these circumstances the oxygen supplied will be insufficient and could result in corneal suffocation. He suggests that REM sleep may have evolved with the primary purpose of "stirring up" the aqueous to protect the cornea.

And what of our dreams? Dr. Maurice does not deny that REM sleep is associated with such phenomena as dreaming, a rise in brain temperature, penile erections, and EEG changes. But he cannot see any physiological significance in these phenomena and suggests that they may result from the partial arousal necessary for REM to occur. "In any case," he writes, "my interests are in the plumbing, and I am happy to leave dreams to others."

IN FOCUS

New Full-Time Faculty Expanding Programs and Care at Columbia

We'd like you to meet some of the new rising stars on our faculty—each recently appointed assistant clinical professor. Having studied at leading universities and trained at top hospitals and academic medical centers, they have each distinguished themselves through their achievements in research and their expertise in patient care.

Gaetano R. Barile, M.D.

Retina Division

Guy Barile received his medical education from Cornell University Medical College after graduating magna cum laude from Haverford College. After completing his internship at the Columbia-Presbyterian Medical Center and his residency at Manhattan Eye, Ear and Throat Hospital, Dr. Barile also undertook a retinal surgery fellowship with Dr. Stanley Chang, Columbia chairman of Ophthalmology and Edward S. Harkness professor, and a medical retina fellowship at London's Institute of Ophthalmology and Moorfields Eye Hospital.

"Controlled clinical trials have demonstrated the benefit of laser surgery in stabilizing the natural course of diabetic retinopathy," says Dr. Barile. "Advancements in surgical techniques, such as those pioneered by Dr. Chang, have also improved outcomes. But, there are always individuals who, despite all current interventions, develop progressive or recurrent retinopathy and associated complications." He is currently collaborating in diabetic retinopathy studies with Dr. David Stern, professor of Physiology and Cellular Biophysiology, and Dr. Anne Marie Schmidt, assistant professor in Medicine, in an effort to gain increased understanding of the events leading up to vision impairment in order to develop new prevention and treatment therapies.

Richard Braunstein, M.D.

Cornea Division

Graduating from the University of Pennsylvania, magna cum laude with Honors in Biochemistry, Richard Braunstein received his medical education at Columbia University's College of Physicians & Surgeons. After completing his ophthalmology residency at Columbia's Edward S. Harkness Eye Institute and a fellowship in cornea and external disease at Johns Hopkins Wilmer Eye Institute, he joined Columbia's faculty in 1994 as instructor in Clinical Ophthalmology.

Dr. Braunstein is currently principal investigator in two clinical trials to treat corneal disorders: he is studying the use of excimer laser surgery for patients who are farsighted with astigmatism; and he is investigating the safety and effectiveness of a new antibiotic eyedrop to treat conjunctivitis, a common eye infection. Dr. Braunstein recently completed a study using a highly precise waterjet to surgically remove superficial layers of the cornea. This new technology may have important applications in corneal refractive surgery. He has also lectured and published extensively on the diagnosis and treatment of corneal disease.

Thomas E. Flynn, M.D.

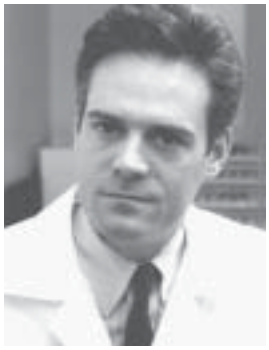
Uveitis, Retina Division

Tom Flynn graduated from Harvard College and received a Masters in Physiology from Georgetown University before completing medical studies at George Washington University School of Medicine. Interning at Providence Hospital in Washington, DC, and completing a residency in Ophthalmology at New York Hospital, Dr. Flynn also completed fellowships at Johns Hopkins' Wilmer Eye Institute, where he studied inflammatory eye diseases and ocular immunology, and in vitreoretinal diseases at Cornell University Medical Center. In 1996, the New York Academy of Medicine honored Dr. Flynn with its David Warfield Research Award.

An expert in diagnosing and treating eye inflammations caused by autoimmune diseases such as lupus and rheumatoid arthritis, Dr. Flynn has also specialized in treating patients with AIDS-related eye infection. He is currently collaborating with Dr. David Maurice, Columbia professor of Ocular Physiology, in a study on improving drug delivery directly into the eye and is also conducting research on new drug therapies to treat infectious and inflammatory retinal disease.

Steven A. Odrich, M.D.

Glaucoma Division



Steve Odrich, a graduate of both Columbia's College of Physicians & Surgeons and Columbia College, completed a fellowship in glaucoma studies at Mount Sinai Medical Center after his residency at Columbia's Edward S. Harkness Eye Institute and an internship at Washington University's Jewish Hospital. The 1992-93 recipient of a Fight for Sight National Society for the Prevention of Blindness Postdoctoral Research Grant, Dr. Odrich was also honored with the Robert E. McCormick Scholar's Award for Outstanding Research in Ophthalmology by Columbia's College of Physicians & Surgeons.

Dr. Odrich is studying the effects of laser correction to treat nearsightedness in patients with glaucoma. "Laser correction of nearsightedness may make measurements of pressure within the eye inaccurate," he says. "We hope that this work will allow patients with glaucoma, many of whom are nearsighted, the option of laser correction—a choice they do not currently have."

William M. Schiff, M.D.

Retina Division

Bill Schiff graduated from New York University's School of Medicine after receiving a BA from Cornell University. He completed postdoctoral fellowships at Columbia's College of Physicians & Surgeons and Cornell University Medical College, fellowships and a residency at the New York Eye and Ear Infirmary, as well as an internship at St. Luke's Hospital Center. Honored with Fison's Grants for Research in Ophthalmology in 1991 and 1993, Dr. Schiff was the 1994 recipient of the Louis Girard Award for Outstanding Research from the New York Eye and Ear Infirmary, where he also served as chief resident.

Dr. Schiff, who trained with Dr. Stanley Chang, Columbia chairman of Ophthalmology and Edward S. Harkness professor, specializes in the treatment of retinal disorders, including diabetic retinopathy, macular degeneration, and complicated retinal detachment, such as giant retinal tears. He is currently developing a screening program to detect early-stage retinopathy in diabetic patients.

Giving Well

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 the Director of Planned Giving, 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.

Please contact:

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