A novel discovery may lead to treatments for wet AMD and diabetic retinopathy.

Patient with recent onset of binocular horizontal diplopia unable to abduct her left eye across the midline.

Clinical trial biases raise questions about comparisons of glaucoma medications.
CLEVELAND CLINIC COLE EYE INSTITUTE
REFRACTIVE SURGEONS AND RESEARCHERS
ARE INVOLVED IN A NUMBER OF PROJECTS
AIMED AT IMPROVING OUTCOMES FOR PATIENTS UNDERGOING REFRACTIVE SURGERY PROCEDURES.

Ronald R. Krueger, M.D., has been using the recently FDA approved Custom-Cornea application for the LADARVision® System to treat patients undergoing primary keratorefractive surgery. He has documented a statistically significant reduction in several types of aberrations, and no increase in other aberrations, with wavefront-guided surgery. He has also discovered how to obtain excellent results without overcorrection in patients requesting upgrades after conventional LASIK, an off-label use.

David Huang, M.D., Ph.D. has developed a mathematical model to predict corneal surface smoothing after excimer laser ablation. By using the information to adjust the ablation pattern, he hopes it will be possible to optimize correction and minimize surgically induced aberrations. Dr. Huang is also involved in the development of dedicated corneal and anterior segment (CAS) optical coherence tomography (OCT) with the goal of producing an instrument that provides high-resolution images together with accurate measurements (see pages 4 and 5).

EXPERIENCE WITH WAVEFRONT-GUIDED CUSTOMIZED ABLATION AT THE COLE EYE INSTITUTE HAS SHOWN THE SYSTEM TO BE SUPERIOR TO CONVENTIONAL LASIK IN MINIMIZING THE INDUCTION OF ABERRATIONS. THIS IS LIKELY THE REASON FOR IMPROVED VISION RESULTS, SAYS DR. KRUEGER, MEDICAL DIRECTOR OF THE DEPARTMENT OF REFRACTIVE SURGERY.

“LASIK corrects myopia and astigmatism, but in the process, generates more aberrations, leading to symptoms such as halo, glare, starburst and double vision. We have recently observed a statistically significant association of these symptoms with certain aberrations – for example, double vision with coma under photopic conditions (p=0.008), and glare and starburst with spherical aberration under scotopic conditions (p≤0.014). This helps us understand the impact of induced aberrations on visual quality,” he explains.

“Our hope was that CustomCornea® would induce fewer aberrations than conventional refractive surgery, and maybe even reduce some preoperative values. This, indeed, has been our experience.”

The Cole Eye Institute was the third center in the United States to begin commercial treatment of patients with CustomCornea following its approval by the FDA in October 2002. From December 27, 2002, to June 1, 2003, Cole refractive surgeons performed custom ablation on 363 eyes. Included in this cohort were patients within one diopter of the full range of correction indicated: up to 7.0 D of...
myopia and 0.5 D of astigmatism. This means their wavefront refraction had to be >8.00 D of myopia and 1.50 D of astigmatism.

Baseline measurements were taken and aberrations were assessed in a subset of patients at postoperative week 1 (n=75) and at 3 months (n=22). Overall, these patients showed a statistically significant reduction in total aberrations, defocus and astigmatism at both time points, says Dr. Krueger.

"At week 1, however, a significant increase in total higher-order aberrations, spherical aberration and other terms was seen (Figure 1). At 3 months, we found no statistical increase in higher-order aberrations, including coma and other terms (Figure 2). This means that about half the eyes we treated had higher-order aberration values that were lower than preoperative levels, and half had values that were higher. That’s good, because higher-order aberration values normally double or triple,” he says.

Dr. Krueger has been exploring further indications for CustomCornea using patients dissatisfied with symptoms or residual correction resulting from LASIK. He discovered that some upgrades result in overcorrection, which he attributes to the large number of pulses required to treat peripheral aberrations and which tend to dry the central corneal tissue, causing excessive tissue to be removed with each pulse.

Dr. Krueger found that using an offset feature in the CustomCornea platform allows him to treat up to 0.5 D less. “We now use it in all our custom upgrades. I also hydrate the surface of the cornea during treatment, which keeps it moist and prevents greater tissue removal with each pulse. With these modifications, I get excellent results with little chance for overcorrection,” he says.

Case study: Use of CustomCornea for reoperation

In May 2003, a 54-year-old male presented at the Cole Eye Institute for re-evaluation. He had undergone H-LASIK in 2001 in both eyes, and although he had good acuity, still noted mild starburst and vertical double vision in the right eye. Despite his low manifest reaction, +0.50 –0.50 x 101° (20/25), Dr. Krueger elected to correct his symptoms due to his notable vertical coma value of 0.37 mm (6.5mm pupil), which was related to his double vision. The offset feature was used to avoid overcorrection, and the cornea was irrigated with BSS after lifting the flap and prior to treatment.

After surgery, the patient’s symptoms were markedly improved, with a manifest refraction of –0.25 –0.25 x 5° (20/25) and a reduction of his coma value to 0.14 µm. “Selective correction of his coma resulted in improved vision,” says Dr. Krueger.

CME Credit

To receive a maximum of 0.5 AMA-PRA Category 1 credits:

- Read the articles on pages 2, 4 and 6
- Go online at www.clevelandclinicmeded.com/ophthupdatef3.htm
- Take the multiple-choice quiz
- Complete the evaluation and registration form

You will then be able to print your CME credit certificate immediately on your own printer. CME credit for this activity will only be available up to January 31, 2004.
The corneal smoothing model was published in *Am J Ophthal.* 2003;135: 267–278.

Corneal smoothing effects change the intended laser correction for weeks after surgery, often leaving patients with less-than-optimal vision. Visual side effects can be particularly pronounced at night and in dim light when the pupil enlarges to accept more light into the eye, leading to problems such as ghosting, glare and halo. Healing-induced aberration is proportional to the amount of laser ablation. Therefore, problems can be particularly profound in patients who undergo higher levels of correction.

“By anticipating this healing process in the preoperative ablation calculations, surgeons can compensate for it and avoid inducing higher-order aberrations,” explains Dr. Huang.

He believes that combining his formula, which he calls Advance Healing Adjusted Ablation (AHAA), with state-of-the-art flying spot lasers with tracking and adequately sized treatment zones will greatly improve overall refractive surgery outcomes.

“The ability to avoid aberrations may be even more clinically significant than the use of wavefront imaging to detect and try to correct aberrations once they have been induced,” he says. “Without a time machine, wavefront-guided laser treatment can only correct pre-existing aberrations. Even with state-of-the-art wavefront treatment, post-surgical aberration still exceeds pre-existing aberration in most patients. Only a predictive algorithm such as AHAA can pre-compensate for induced aberration.”

Dr. Huang believes the AHAA algorithm is complementary to current advances in wavefront sensing. “By combining wavefront sensing and AHAA, both pre-existing and induced aberrations can be treated, leading to better results than with either method alone.”

The Cleveland Clinic has filed a patent application based on the Advance Healing Adjusted Ablation invention. Dr. Huang maintains a proprietary interest in the technology.
New High-Speed
OCT Prototype Enters
Clinical Evaluation

DR. HUANG IS ALSO A PIONEER IN THE DEVELOPMENT OF NON-CONTACT, HIGH-SPEED CAS OCT IMAGING. WORKING WITH A TEAM OF OTHER ACADEMIC-BASED RESEARCHERS, HE INITIALLY DESIGNED A PROTOTYPE SLIT LAMP-MOUNTED WIDE-FIELD CAS OCT SCANNER, SHOWN IN PILOT TESTING TO BE QUITE VERSATILE WITH UTILITY IN MEASURING CORNEAL THICKNESS, PROFILING THE ENTIRE LASIK FLAP (FIGURE 1), AND PERFORMING ANTERIOR CHAMBER BIOMETRY (FIGURE 2).

With interest in the commercialization of CAS OCT to allow its widespread clinical application, Dr. Huang has been collaborating with scientists and engineers at Carl Zeiss Meditec in instrument design, and they have introduced a prototype that entered clinical trials in July.

The investigational system features a 1.3-micron wavelength able to penetrate through highly scattering tissues, such as the limbus and sclera, while allowing video-rate imaging. It obtains 2000 axial scans per second and incorporates an internal fixation target to optimize centration on the cornea.

In one initial study, the OCT device was used in pre- and postoperative evaluation of patients undergoing LASIK to profile the thickness of the cornea and the LASIK flap. In their ongoing research, the development team is working to expand the capabilities of the system so that it can capture three-dimensional corneal anatomy and produce maps of corneal topography, thickness and internal layers.

“So far we have concentrated on getting measurements and other information from single, cross-section images, but a three-dimensional depiction will have the greatest value for the refractive surgeon performing excimer laser ablative vision correction procedures,” Dr. Huang says.

Unlike existing Placido ring-based corneal topography systems that produce only anterior cornea elevation maps, the CAS OCT scanner has the potential to characterize both the anterior and posterior surfaces of the cornea. In that regard, the CAS OCT device is similar to the Orbscan slit-scanner. However, with its higher axial resolution, the CAS OCT device may offer greater reliability in evaluating the posterior surface. CAS OCT also has the unique capability of noncontact mapping of the flap and posterior stromal bed thickness after LASIK.

Anterior chamber biometry is another potential use of the CAS OCT scanner, and studies are also being planned to evaluate the performance of the new prototype system in that application. Dr. Huang points out that the ability of this technology to directly measure the recess-to-recess anterior chamber width along with such other parameters as anterior chamber depth and crystalline lens vault could have important implications for improving the safety of refractive surgery using angle-supported phakic IOLs, a type of anterior-chamber IOL (AC-PIOI).

“Safety has been a prominent concern relating to the phakic IOLs. By allowing these direct measurements, CAS OCT may at least permit more accurate sizing of AC-PIOIs and thereby reduce complications as pupil ovalization, which occurs when the implant is too large, or PIOl dislocation, which can develop if the device is too small,” he explains.

Looking to the future, Dr. Huang notes that as AC-PIOIs move into the next generation of easy-to-implant foldable devices, the ability to select an appropriately sized implant can be a key factor in determining the suitability of the technology for widespread use in the treatment of high ametropias.

“Thus, the new CAS OCT system may be an important enabling technology for the adaptation of phakic AC-PIOIs into clinical practice,” Dr. Huang says.
Natural Protein Found to Inhibit Angiogenesis

A NOVEL DISCOVERY BY RESEARCHERS AT THE CLEVELAND CLINIC COLE EYE INSTITUTE INTO HOW THE BODY PREVENTS ANGIogenesis MAY LEAD TO NEW TREATMENTS FOR OCULAR DISEASES SUCH AS THE EXUDATIVE FORM OF AGE-RELATED MACULAR DEGENERATION AND DIABETIC RETINOPATHY.

TIMP-3, or tissue inhibitor of metalloproteinases-3, is one of a family of four proteins naturally produced by the body that are able to prevent the breakdown of specific cellular barriers. The Cole researchers, led by Bela Anand-Apte, M.B.B.S., Ph.D., have learned that TIMP-3 also works to prevent abnormal blood vessel growth.

“For angiogenesis to occur, a molecular lock must be opened,” says Dr. Anand-Apte. “Scientists have known for some time that the body seeks to prevent this from occurring by producing a number of proteins, one of which is TIMP-3. What wasn’t known, and what we have found, is how TIMP-3 actually works.”

Her team discovered that TIMP-3 blocks the binding of vascular endothelial growth factor (VEGF) to its receptor. In other words, the VEGF “key” no longer is able to open its VEGF-2 receptor “lock,” which initiates events leading to abnormal blood vessel growth. This inhibits downstream signaling and angiogenesis.

“This may be our body’s natural defense to stop tumor growth,” says Dr. Anand-Apte, who has been with The Cleveland Clinic since 1996. “This insight will help us to better explore its potential in medical treatments.”

“This important discovery at the Cole Eye Institute could lead to the prevention of the two most common causes of severe visual loss and blindness in the western world, the exudative form of AMD and proliferative diabetic retinopathy, by preventing the growth of abnormal blood vessels around and within the retina,” says Hilel Lewis, M.D., director of the Cole Eye Institute. “It could also have dramatic implications beyond ophthalmology, such as in cancer.”


The next step on the road to what may ultimately be synthetic drugs and gene therapies to control angiogenesis is for Dr. Anand-Apte’s team to try to learn which part of TIMP-3 binds to the VEGF-2 receptor and which domain of the receptor is involved.

Cleveland Clinic researchers who have worked on this project include Jian Hua Qi, Ph.D., Quteba Ebrahem, M.D. and Nina Moore, Ph.D. (former CCF staff). External collaborators include Gillian Murphy of Cambridge University in the United Kingdom, Lena Classson-Welsh of Uppsala University, Sweden, Mark Bond of the University of Bristol, U.K., and Andrew Baker of the University of Glasgow, U.K.

This research is funded by the National Institutes of Health, the Foundation Fighting Blindness and The Cleveland Clinic Cole Eye Institute.

▲ CME Objective of Natural Protein Found to Inhibit Angiogenesis: To study how a natural protein may someday be used to block the abnormal growth of blood vessels in the eyes.
IVth Retina Summit
a Worldwide Success

RETINAL CLINICIANS AND RESEARCHERS FROM ACROSS THE UNITED STATES AND AS FAR AWAY AS JAPAN, CENTRAL AMERICA AND AUSTRALIA ATTENDED THE IVTH RETINA SUMMIT AT THE COLE EYE INSTITUTE ON MAY 2 AND 3, 2003. IN ADDITION TO OFFERING EXCITING, THOUGHT-PROVOKING CLINICAL AND RESEARCH PRESENTATIONS, THIS YEAR’S CONFERENCE TOOK AN INNOVATIVE TURN BY BROADCASTING SURGERY LIVE ON THE INTERNET.

On Friday, Hilel Lewis, M.D., performed proliferative vitreoretinopathy surgery, which was narrated for the live and electronic audience by Peter K. Kaiser, M.D. During the procedure, Dr. Lewis answered questions emailed from ophthalmologists as far away as Japan and Israel. More than 3,000 physicians, health professionals and consumers viewed the surgery over the Internet.

On Saturday, conference attendees watched Jonathan Sears, M.D., remove a large ciliary body tumor. This procedure was teleconferenced to physicians in Bogota, Colombia at their request. Three overflow seating areas enabled Cole Eye Institute staff, fellows, residents, nurses and technicians to watch the procedure on large-screen televisions and monitors outside the James P. Storer Conference Center.

The popularity of the Retina Summit will require the meeting to move from state-of-the-art meeting facilities at the Cole Eye Institute to larger high-tech accommodations. The next Retina Summit will be held across the street in the new InterContinental Hotel and Conference Center, where a larger number of participants can take advantage of what the meeting offers.

2003 ARVO
Abstracts from Cole Eye Institute Staff

Cleveland Clinic Cole Eye Institute researchers and clinicians submitted more than 75 papers and posters to the 2003 Association for Research in Vision and Ophthalmology (ARVO) meeting. While the largest number of submissions dealt with retinal disease, abstracts on cataract, glaucoma, refractive surgery, pediatric ophthalmology and uveitis were also published.

All abstracts are available on www.ccf.org/eye/research. Click on retina research, refractive research or other research on the left-hand menu. The researchers may be contacted directly by calling the Cole Eye Institute at 216/444-2020, or 800/223-2273, ext. 42020.

Ophthalmic Puzzler

By Linda A. Lam, M.D. and Careen Y. Lowder, M.D., Ph.D.

A 29-year-old female presented with intermittent binocular horizontal diplopia of two days’ duration. On the day of her visit she was unable to abduct her left eye across the midline. She denied changes in vision, pain, flashes, photophobia, or history of trauma. She had a 2-week history of painless left-sided facial numbness, particularly over her left lip. Her ocular history was significant only for hyperopia of her right eye since childhood, without patching. Her medical history was significant for relapsing polychondritis and hypertension. She had a history of recurrent sinusitis and underwent a nasal biopsy. Current medications included prednisone, methotrexate, Nexium, Norvasc, Flonase, folic acid, calcium, and multivitamins. No eye medications. For 9 months she had been drinking frequently and urinating up to 6 liters daily. She was born in China, and had come to the United States one year earlier to attend college.

The patient’s best-corrected visual acuity was 20/25 in the right eye and 20/20 in the left eye. Intraocular pressure was 20 mm Hg in each eye. Pupillary reflexes, visual fields, and color plates were normal. Her right eye demonstrated full range of extraocular movements. Slit lamp examination of the anterior segment and the dilated fundus exam were normal in both eyes.

What is the diagnosis? Turn to Page 8
Differential diagnosis
Vasculopathies are a common cause of isolated sixth nerve palsy, particularly in patients with diabetes or hypertension. When multiple cranial nerves are involved, Wegener’s, Churg-Strauss, temporal arteritis, and Kawasaki disease should be considered. Arteriovenous malformations, cavernous sinus thrombosis, carotid aneurysm, and stroke may also be factors.

Infectious etiologies in immunosuppressed patients must be ruled out. Herpes, syphilis, tuberculosis of the cavernous sinus, Lyme, mumps-measles-rubella vaccinations, meningitis, Gradenigo syndrome, and sinusitis have all been implicated. Sarcoid, myasthenia gravis, and Guillain-Barré, as well as intracranial tumors may cause abducens palsy. Nasopharyngeal carcinoma, lymphoma and leukemia have been implicated in multiple cranial neuropathies.

Evaluation
The patient was admitted and evaluated by the neurology, rheumatology, and endocrinology services. On physical examination, she had bilateral nasal mucosal crusting and congestion. She had severe tenderness over her maxillary and frontal sinuses bilaterally, especially over the left side. No lymphadenopathy was found. Neurologic exam was normal, except for left lower facial hypesthesia and inability to abduct the left eye. Complete blood count, metabolic profile, sedimentation rate, C-reactive protein, thyroid function tests, anti-neutrophilic cytoplasmic antibodies (ANCA), and urinalysis were obtained. All serologic and urine laboratory results were normal except for an elevated C-ANCA, T4, and thyroid microsomal antibody.

Neuroimaging demonstrated normal brain parenchyma, cavernous sinus structures, and meninges. However, the left mandibular branch of the trigeminal nerve in its course from the cavernous sinus to the foramen ovale was thickened (Figure). Mucosal thickening was also found in the maxillary, sphenoid, and ethmoid sinuses, indicating extensive sinus inflammation. Head MRA and venogram were normal. A thyroid ultrasound showed an enlarged homogenous thyroid gland. Water deprivation test confirmed diabetes insipidus.

Diagnosis
The cranial neuropathies in this patient were most likely due to Wegener’s granulomatosis, which had been diagnosed one year earlier with a nasal biopsy. Hyperthyroidism is present in 3% of patients with Wegener’s, and diabetes insipidus occurs due to enlargement of the pituitary gland by inflammatory infiltrates.

Classic Wegener’s granulomatosis was first described as a triad featuring disease in the upper and lower respiratory tracts and kidneys. Biopsy specimens show necrotizing vasculitis, granuloma formation, eosinophilia, and tissue necrosis. Pulmonary involvement occurs in more than 90% of patients. Renal involvement has been reported in 77% of patients, and is the major cause of mortality. Neurologic complications have been reported in up to 50% of patients. The most common neurologic manifestation of Wegener’s is peripheral neuropathy. Cranial neuropathies, ophthalmoplegia, Horner’s syndrome, papilledema, hearing loss, headaches, meningitis, and strokes have also been described. Cardiac involvement in the form of pericarditis and vasculitis occurs in about 8% of patients. Cranial nerve palsies have been described as the initial manifestation in the limited form of Wegener’s granulomatosis, which involves the upper and/or lower respiratory tract without renal disease. These patients have a better prognosis than those with the classic diffuse form of disease.

Seroserological testing is of value in the diagnosis of Wegener’s; however, pathologic confirmation is key. Cytoplasmic or cANCA is a highly specific marker for Wegener’s, being positive in 90% of patients with classic Wegener’s, 65% in patients with limited form, and 30% of patients in remission.

Involvement of the orbit or eye is seen in 25%-58% of patients with Wegener’s. They may have limited extraocular movements, proptosis, diffuse or necrotizing scleritis, and peripheral ulcerative keratitis. Retinal findings occur in about 10%-18% of patients in the form of retinal hemorrhages, edema, or cotton-wool spots. Branch and central retinal artery occlusions and branch retinal vein occlusion have been reported as complications. Uveitis, often in the form of vasculitis, occurs in 10% of patients.

Untreated, Wegener’s is a rapidly progressive, fatal disease. For severe systemic disease or patients with glomerulonephritis, the most effective treatment regimen is a combination of cyclophosphamide and prednisone. The prognosis with this regimen is good, with 90% of patients achieving improvement and 75% achieving remission.
Bennie H. Jeng, M.D., joined the staff of The Cole Eye Institute in July after completing a fellowship in cornea and external diseases at the Francis I. Proctor Foundation at the University of California San Francisco. Dr. Jeng completed his internship and residency at The Cole Eye Institute in 2002, serving as chief resident in his final year. He received his medical degree from the University of Pennsylvania School of Medicine in Philadelphia.

Dr. Jeng’s primary interests are in corneal transplantation, ocular surface disease, limbal stem cell transplantation, and artificial corneas. He plans to spend about 75 percent of his time in patient care, with the remainder devoted to research. He is particularly interested in finding ways to improve eyebanking techniques that will increase the health and viability of donor tissue, leading to improved transplantation success rates.

He says the dynamic environment he experienced during his residency at CCF is what motivated him to return after his fellowship. “The Eye Institute has always impressed me with its continuous upward movement in a time when other institutions are struggling to expand,” he comments.

Dr. Jeng is a member of the American Academy of Ophthalmology, the Association for Research in Vision and Ophthalmology, the American Society of Cataract and Refractive Surgery, and the Contact Lens Association of Ophthalmologists.

After five years as professor and chair of ophthalmology and the holder of the Grace E. Hill Chair in Vision Research at the University of Washington in Seattle, Steven E. Wilson, M.D., has returned to the Cole Eye Institute as director of corneal research.

Dr. Wilson received his M.S. in molecular biology and biochemistry from the University of California, Irvine, and M.D. from the University of California, San Diego. He served his residency at the Mayo Clinic, and his fellowship in cornea, external disease, and refractive surgery at the Louisiana State University Eye Center in New Orleans. He then joined the Department of Ophthalmology at the University of Texas Southwestern Medical Center in Dallas.

Dr. Wilson is recognized as one of the world’s leading cornea and refractive surgery specialists. An NIH-funded investigator, he leads a research laboratory that explores cellular and molecular interactions in the cornea involved in development, homeostasis, wound healing, and disease. He is the author of more than 130 peer-reviewed clinical and research papers.

Dr. Wilson is currently a trustee of the Association for Research in Vision and Ophthalmology. He serves on the executive board of ISRS-RSIG, the program committee for the American Academy of Ophthalmology, and the editorial boards for Experimental Eye Research, The Journal of Refractive Surgery, and Cornea. He is the chief medical editor of Review of Refractive Surgery.
To map the genes for inherited eye diseases. To screen candidate genes for mutations in a variety of genetic ocular disorders, including ocular malformations, congenital cataracts and retinal dystrophies. 

**GENETICS**

**STUDIES OF THE MOLECULAR GENETICS OF EYE DISEASES**

**Objective** To map the genes for inherited eye diseases. To screen candidate genes for mutations in a variety of genetic ocular disorders, including ocular malformations, congenital cataracts and retinal dystrophies. 

**Eligibility Criteria** Participants must have at least two family members who have been diagnosed with macular degeneration and who are willing to participate in our study. There is no age limit, and it does not matter if you have the wet or dry type of AMD. 

**Contact** E. Traboulsi, M.D., 216/444-4363 or S. Crowe, C.O.T., 216/445-3840

**GENETICS AND MOLECULAR ANALYSIS OF RETINAL DISEASES**

**Objective** The Cole Eye Institute is recruiting patients with a family history of macular degeneration to participate in a genetic study. Our goal is to find the gene that causes macular degeneration. 

**Eligibility Criteria** Participants must have at least two family members who have been diagnosed with macular degeneration and who are willing to participate in our study. There is no age limit, and it does not matter if you have the wet or dry type of AMD. 

**Contact** H. Lewis, M.D., 216/444-0420, or E. Simpson, R.N., 216/445-9886

**THE GENETICS OF STRABISMUS**

**Objective** To discover the genes that cause some strabismus syndromes, including those for accommodative esotropia, congenital esotropia, congenital ocular fibrosis syndrome, intermittent exotropia, Brown syndrome and Duane syndrome. 

**Contact** E. Traboulsi, M.D., 216/444-4363 or S. Crowe, C.O.T., 216/445-3840

**GLAUCOMA**

**GLAUCOMA DIAGNOSIS BY OPTICAL COHERENCE TOMOGRAPHY ANALYSIS OF RETINA AND OPTIC NERVE**

**Objective** The purpose of this study is to evaluate the ability of the Optical Coherence Tomography Unit Model 2010 to accurately measure and reproduce measurements of the optic nerve head excavation, retinal fiber thickness layer and the perifoveal retinal thickness in patients suspected of having glaucoma or patients with glaucoma. 

**Contact** S. Smith, M.D., M.P.H., 216/444-1995, or R. Scott, 216/444-0680

**PEDIATRICS AND STRABISMUS**

**COMPARISON OF LEA GRATING PADDLES WITH TELLER ACUITY CARDS FOR EVALUATION OF VISUAL ACUITY IN PREVERBAL PATIENTS**

**Objective** Pediatric ophthalmologists are investigating a new method of checking visual acuity in preverbal children. This method uses the principle of preferential looking. Infants' acuity is tested using Teller acuity cards and Lea Grating Paddles during the same clinical visit. The investigators are trying to determine if Lea Grating Paddles are accurate and if they offer any advantage over the widely accepted Teller Acuity Cards. 

**Contact** E. Traboulsi, M.D., 216/444-4363 or D. Peralta, M.D., 216/444-4363

**COLOR SORT TEST**

**Objective** This project compares an individual’s performance on four tests of color vision. 

**Contact** E. Traboulsi, M.D., 216/444-4363

**REFRACTIVE SURGERY**

**THE EFFECT OF CREATING A LASIK FLAP AS DETERMINED BY WAVEFRONT ANALYSIS**

**Objective** To determine the effect of creating a LASIK flap. 

**Eligibility Criteria** Subjects more than 18 years of age and eligible for LASIK. 

**Contact** R. Krueger, M.D., 216/444-8158, or R. Scott, 216/444-0680

**USE OF WAVEFRONT DEVICE FOR DIAGNOSTIC MEASUREMENTS**

**Objective** The CustomCornea Wavefront Device from Alcon/Summit Autonomous will be evaluated for repeatability and accuracy of measurements as compared with manifest refraction and topography. 

**Eligibility Criteria** Must be 18 years of age or older. Participants will have eyes dilated. Must be eligible for LASIK, PRK or AK.

**VISION THERAPY: A PROGRESSIVE CONTROLLED STUDY ON THE EFFECTIVENESS OF VISION THERAPY IN ELIMINATING ASTHENOPIA IN A SYMPTOMATIC POPULATION**

**Eligibility Criteria** Patients who are 18 to 35 years old and have any of the following symptoms: eye strain, occasional blurred vision when using a computer or performing other near work, occasional headaches, have words run together or fall asleep when doing prolonged computer work or near work. If eligible, participation will involve approximately three visual assessments at the Cleveland Clinic Division of Ophthalmology at Beachwood and required equipment for therapy. Compensation of $100 will be allotted for travel expenses. 

**Contact** D. Tucker, O.D., 216/831-0120, or K. Danko, C.O.T., 216/831-0120

**RETINAL DISEASES**

**DIABETIC MACULAR EDEMA IMPLANT STUDY (CDS FL-007)**

**Objective** This 4-year multi-center controlled study is designed to evaluate the safety and efficacy of an intravitreal fluorocine laser and Retisert, in patients with diabetic macular edema. Patients will be randomly assigned to one of three study groups:

1. Vitrectomy with Retisert implant;
THE CLEVELAND CLINIC COLE EYE INSTITUTE IS PROUD TO PRESENT THE 2003 DISTINGUISHED LECTURE SERIES, WHICH PROVIDES A FORUM FOR RENOWNED RESEARCHERS IN THE VISUAL SCIENCES TO PRESENT THEIR LATEST RESEARCH FINDINGS. THIS SERIES OF LECTURES WILL FEATURE ADVANCES IN MANY AREAS OF OPHTHALMIC RESEARCH PRESENTED BY NOTED BASIC AND CLINICAL SCIENTISTS FROM THROUGHOUT THE WORLD. AMPLE OPPORTUNITY FOR QUESTIONS AND DISCUSSION WILL BE PROVIDED.

PLEASE JOIN US FOR THESE INSIGHTS INTO OPHTHALMIC RESEARCH AND THE PROMISES THEY HOLD FOR PATIENT CARE. NO REGISTRATION IS REQUIRED. CALL 216/444-5832 WITH QUESTIONS.

ALL PROGRAMS ARE HELD AT THE CLEVELAND CLINIC COLE EYE INSTITUTE’S JAMES P. STORER CONFERENCE CENTER FROM 7 TO 8 A.M. ATTENDEES SHOULD PARK IN THE EAST 102ND STREET PARKING LOT (FACING THE FRONT OF THE COLE EYE INSTITUTE) OR THE VISITORS’ PARKING GARAGE AT EAST 100TH STREET AND CARNEGIE AVENUE. WE WILL VALIDATE YOUR PARKING TICKET.

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**September 25, 2003**

**UPDATE ON THERAPIES FOR AGE-RELATED MACULAR DEGENERATION**

Joan W. Miller, M.D.
Professor of Ophthalmology
Harvard Medical School, Boston, Mass.

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**October 16, 2003**

**STRATEGIES FOR RPE REPLACEMENT IN PATIENTS WITH AGE-RELATED MACULAR DEGENERATION**

Marco A. Zarbin, M.D., Ph.D.
Professor and Chair
Institute of Ophthalmology and Visual Science
New Jersey Medical School
University of Medicine and Dentistry of New Jersey, Newark, N.J.

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**November 20, 2003**

**ENERGY METABOLISM IN RETINAL NEURONS AND GLIA: IMPLICATIONS FOR PHYSIOLOGY AND PATHOLOGY**

Barry S. Winkler, Ph.D.
Professor of Biomedical Sciences
Eye Research Institute
Oakland University, Rochester, Mich.

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**Thursday, December 11, 2003**

**FISHING FOR NOVEL GENES**

John E. Dowling, Ph.D.
Llura and Gordon Gund Professor of Neurosciences
Department of Molecular and Cellular Biology
Harvard University, Cambridge, Mass.
### Staff

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<th>Name</th>
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<td>Stephanie A. Hagstrom, Ph.D.</td>
<td>Ophthalmic Research Department, Research Interests</td>
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<td>Michael Millstein, M.D.</td>
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<td>Cornea and External Disease and Refractive Surgery Departments, Research Interests</td>
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<td>Edward J. Rockwood, M.D.</td>
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<td>Careen Y. Lowder, M.D., Ph.D.</td>
<td>Uveitis Department, Research Interests</td>
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<td>Andreas Marcatto, M.D.</td>
<td>Pediatric Ophthalmology and Strabismus Department, Research Interests</td>
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**Specialty Interests**

- Vitreo-retinal surgery
- Cornea and external disease, corneal transplantation, ocular surface disease, limbal stem cell transplantation, artificial corneas, eyebanking
- Refractive surgery
- Cataract, glaucoma, refractive surgery
- General ophthalmology
- Oculoplastics
- Refractive surgery
- Cataract, prevention of eye disease, international ophthalmology
- Contact lens research, general ophthalmology
- Ocular diseases of children, pediatric ophthalmology, strabismus, retinoblastoma, congenital cataracts, childhood glaucoma
- Corneal and external disease, corneal transplantation, refractive surgery, corneal healing
- Aesthetic facial surgery/fat transplantation and repositioning, acellular human dermal graft matrix, new bovine hydroxyapatite orbital implant, thyroid eye disease/trauma, strabismus after decompression surgery for dysthyroid orbitopathy
- Emetic therapy, exotropia, external strabismus, endophthalmitis, posterior vitreoretinal detachment and trauma, age-related macular degeneration, diabetic retinopathy, retinal photoagulation, instrument development
- Age-related macular degeneration, inherited retinal diseases
- Retinal vascular diseases, laser therapy, diabetic retinopathy
- Inherited forms of retinal degeneration, including macular degeneration and retinitis pigmentosa
- Retinal degeneration, retinal diseases
- Kerato-refractive surgery, instrumentation and equipment development, corneal disease, cataract/anterior segment surgery
- Corneal transplantation, ocular surface disease, limbal stem cell transplantation, artificial corneas, eyebanking
- Vitreo-retinal diseases, age-related macular degeneration, retinal detachment, diabetic retinopathy, endophthalmitis, posterior vitreoretinal surgery for complicated retinal detachment and trauma
- Refractive surgery, lasers, refractive corneal pathology, lamellar corneal transplants, investigational clinical trials
- Corneal and external disease, corneal transplantation
- Pediatric ophthalmology, optic neuropathies, double vision
- Uveitis, intraocular inflammatory diseases, pathology
- Pediatric ophthalmology and retina, adult strabismus
- Cataract, glaucoma, refractive surgery
- Visual loss associated with hereditary retinal degeneration
- Medical and surgical treatments of autoimmune inflammatory conditions of the cornea and ocular surface, uveitis, corneal transplantation, cataract surgery
- Aesthetic facial surgery/fat transplantation and repositioning, acellular human dermal graft matrix, new bovine hydroxyapatite orbital implant, thyroid eye disease/trauma, strabismus after decompression surgery for dysthyroid orbitopathy
- Corneal and external disease, corneal transplantation, refractive surgery, cataract and implant surgery
- Pediatric and adult vitreoretinal diseases, pediatric retinal detachment, inherited vitreoretinal disorders, retinopathy of prematurity, other acquired proliferative diseases
- Cataract and implant surgery, glaucoma, oculoplastics
Ophthalmic Continuing Medical Education

Programs in Ophthalmic Education September 2003–March 2004

Physicians are cordially invited to attend the following ophthalmic continuing medical education courses at the Cleveland Clinic Cole Eye Institute. All courses will be held in the James P. Storer Conference Center on the first floor of the Cole Eye Institute, unless otherwise noted.

For more details, contact Jane Sardelle, program coordinator, at 216/444-2010 or sardelj@ccf.org. View the entire course catalog online at http://www.clevelandclinic.org/eye/physician_info.

Saturday, September 6, 2003
CONJUNCTIVAL INFLAMMATION: A STEPLADDER APPROACH IN DIAGNOSIS, TREATMENT AND OCULAR SURFACE SURGICAL RECONSTRUCTION

Course Co-Directors
Victor L. Perez, M.D.
David M. Meisler, M.D.
Cole Eye Institute

Guest Faculty
Claes H. Dohlman, M.D., Ph.D.
Professor of Ophthalmology
Cornea and External Disease Service
Massachusetts Eye & Ear Infirmary
Harvard Medical School
Boston, Mass.

Bennie Jeng, M.D.
Anterior Segment/Cornea Department
Cole Eye Institute
Cleveland Clinic Foundation
Cleveland, Ohio

Francis S. Mah, M.D.
Assistant Professor
Department of Ophthalmology
Cornea and External Disease and Refractive Surgery
University of Pittsburgh Medical Center
Pittsburgh, Pa.

Julian D. Perry, M.D.
Ophthalmic Plastic & Orbital Surgery Department
Cole Eye Institute
Cleveland Clinic Foundation
Cleveland, Ohio

E. Lee Stock, M.D.
Professor of Ophthalmology
Cornea-External Disease Service
Eye Institute
Medical College of Wisconsin
Milwaukee, Wis.

Scheffer C. G. Tseng, M.D., Ph.D.
Associate Professor
University of Miami/Bascom Palmer Eye Institute
Ocular Surface Center and Ocular Surface
Research & Education Foundation
Miami, Fla.

Conjunctival inflammation is one of the most common diseases evaluated and treated by ophthalmologists. The differential diagnosis is broad, complex and includes local or systemic diseases that can lead to significant ocular morbidity and blindness. Moreover, the etiology of the inflammation will determine the appropriate course of action and treatment that will prevent progression and complications. The goal of this course is to present ophthalmologists with a comprehensive review of the different causes that should be considered when evaluating a patient with conjunctival inflammation. These include infections, immune-mediated inflammation, trauma, malignancies and other disorders presenting as a masquerade syndrome.

The course will provide updated information with regard to the medical and surgical management of conjunctival inflammatory disorders. Experts in the field will review the new information available for the role and use of the new family of anti-microbials and immunomodulation therapy available for specific conjunctivitis. In addition to these, our guest faculty will present the most recent surgical techniques available for the vision rehabilitation and treatment of these diseases, including the latest concepts in conjunctival resection, amniotic membrane grafts, limbal stem-cell grafting and keratoprosthesis.

At the conclusion of this course, participants should be able to:
• Describe the different clinical manifestations of conjunctival diseases.
• Identify the newest anti-microbial treatment of infectious conjunctival inflammation.
• Recognize other non-infectious causes of conjunctival inflammation and approaches to treatment.
• Summarize the newest development in amniotic membrane and limbal stem-cell grafting and keratoprosthesis.

Saturday, October 11, 2003
UPDATE ON DIABETIC RETINOPATHY: CURRENT KNOWLEDGE, NEW DEVELOPMENTS AND CASE PRESENTATIONS

Course Director
Hilel Lewis, M.D.
Chairman, Division of Ophthalmology
Director, Cole Eye Institute

Guest Faculty
Thomas R. Friberg, M.D.
University of Pittsburgh
Eye and Ear Institute
Pittsburgh, Pa.

Thomas W. Gardner, M.D.
Professor of Ophthalmology and Cellular and Molecular Physiology
Pennsylvania State College of Medicine
Hershey, Pa.
nosis and management that will allow the participant to identify distinct features of diabetic retinopathy, interpret the clinical angiographic and OCT findings and manage and treat common and difficult cases.

At the conclusion of this course, participants should be able to:

- Recognize biochemical mechanisms and implication for pharmacologic therapies.
- Summarize evidence on the role of diabetic control and medical therapy in the prevention and treatment of diabetic retinopathy.
- Recognize the role of serum lipids as a predictor of macular edema.
- Determine the role of OCT in the diagnosis and treatment of diabetic macular edema.
- Describe the indications, approaches and techniques for laser photocoagulation for both diabetic macular edema and proliferative diabetic retinopathy.
- Describe new and experimental treatment options, such as the use of intravitreal steroids.
- Identify indications for surgery.

Some patients complain of vision loss without apparent ocular abnormalities. Functional vision loss, however, is a diagnosis of exclusion. This course will present clinical approaches to the patient with a “normal” eye examination and reduced visual acuity.

At the conclusion of this course, participants should be able to:

- Incorporate strategies to test patients with functional vision loss.
- Localize sources and causes of visual decline in the setting of a normal-appearing eye.

Friday to Monday, February 13-16, 2004
INTERNATIONAL COURSE:
NEW INSIGHTS, ADVANCES AND PRACTICAL APPROACHES IN OPHTHALMOLOGY
Cabo San Lucas
Baja California, Mexico
(Hotel: Presidente InterContinental)

Course Co-Directors
Hilel Lewis, M.D.
Chairman, Division of Ophthalmology
Director, Cole Eye Institute
The Cleveland Clinic Foundation
Cleveland, Ohio, USA

Hugo Quiroz-Mercado, M.D.
Director, Vitreoretinal Department
Asociacion Para Evitar La Ceguera En Mexico, IAP
En Mexico, IAP

Peter K. Kaiser, M.D.
Vitreoretinal Department
Cole Eye Institute
Cleveland Clinic Foundation
Cleveland, Ohio

Leonid Lerner, M.D., Ph.D.
Vitreoretinal Department
Cole Eye Institute
Cleveland Clinic Foundation
Cleveland, Ohio

S. Sethu Reddy, M.D.
Chairman
Department of Endocrinology
Cleveland Clinic Foundation
Cleveland, Ohio

Jonathan E. Sears, M.D.
Vitreoretinal Department
Cole Eye Institute
Cleveland Clinic Foundation
Cleveland, Ohio

This program is designed to provide comprehensive ophthalmologists and retina specialists with a comprehensive review of prevention and treatment of diabetic retinopathy and its complications. New information on the biochemical mechanisms and the implications for pharmacotherapy will be presented. In addition, new information from prevention, such as the role of diabetic control and the role of lipids, will be discussed and interpreted. Special topics will include the role that optical coherence tomography plays in the diagnosis and management of complications from diabetic retinopathy; new laser strategies for diabetic macular edema; and the role of intravitreal steroids and vitreoretinal surgery in the treatment of diabetic macular edema. Current clinical trials will be discussed and interpreted.

A special practical and clinically oriented approach utilizing case presentations will emphasize details of diagnosis and management that will allow the participant to identify distinct features of diabetic retinopathy, interpret the clinical angiographic and OCT findings and manage and treat common and difficult cases.

At the conclusion of this course, participants should be able to:

- Recognize biochemical mechanisms and implication for pharmacologic therapies.
- Summarize evidence on the role of diabetic control and medical therapy in the prevention and treatment of diabetic retinopathy.
- Recognize the role of serum lipids as a predictor of macular edema.
- Determine the role of OCT in the diagnosis and treatment of diabetic macular edema.
- Describe the indications, approaches and techniques for laser photocoagulation for both diabetic macular edema and proliferative diabetic retinopathy.
- Describe new and experimental treatment options, such as the use of intravitreal steroids.
- Identify indications for surgery.

Some patients complain of vision loss without apparent ocular abnormalities. Functional vision loss, however, is a diagnosis of exclusion. This course will present clinical approaches to the patient with a “normal” eye examination and reduced visual acuity.

At the conclusion of this course, participants should be able to:

- Incorporate strategies to test patients with functional vision loss.
- Localize sources and causes of visual decline in the setting of a normal-appearing eye.

Saturday, November 1, 2003
UPDATE ON NEURO-OPHTHALMOLOGY:
VISION LOSS WITH A "NORMAL” EYE EXAMINATION

Course Co-Directors
Michael S. Lee, M.D.
Gregory S. Kosmorsky, D.O.
Cole Eye Institute

Guest Faculty
Randy H. Kardon, M.D., Ph.D.
Associate Professor
Department of Ophthalmology
University of Iowa Hospitals
Iowa City, Iowa

Simmons Lessell, M.D.
Professor of Ophthalmology
Director, Neuro-Ophthalmology Unit
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, Mass.

Nancy Newman, M.D.
Leo Delle Joley, Professor of Ophthalmology
Professor of Ophthalmology
and Neurology
Instructor, Neurosurgery
Emory University School of Medicine
Atlanta, Ga.
This international course will provide a comprehensive review of new developments in clinical practice and will emphasize state-of-the-art management, problem-solving, case presentations and evaluation of new interventions and technology. There will be ample time for questions and answers and the faculty will be available throughout the course for informal consultation and discussion.

At the conclusion of this course, participants should be able to:

- Describe the pathogenesis of different ocular disorders.
- Evaluate and utilize new diagnostic and surgical techniques.
- Develop effective management strategies.

Accreditation

The Cleveland Clinic Center for Continuing Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Cleveland Clinic Center for Continuing Education designates this educational activity for a maximum of 0.5 Category 1 credit toward the AMA Physician’s Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This activity may be submitted for American Osteopathic Association Continuing Medical Education Credits in Category 2.

Faculty Disclosure

Current guidelines state that participants in CME activities should be made aware of any affiliation or financial interest that may affect the faculty’s presentation(s) and/or who will be discussing off-label therapies.

The following faculty have indicated that they have a relationship which, in the context of their presentations, could be perceived as a potential conflict of interest:

- **David Huang, M.D., Ph.D.**
  The Cleveland Clinic has filed a patent application based on the Advance Healing Adjusted Ablation invention. Dr. Huang has a proprietary interest in the technology.

- **Ronald R. Krueger, M.D.**
  Grant/Research Support and Speaker’s Bureau – Alcon.

The following faculty will be discussing therapies that are not yet labeled (FDA approved) for the use under discussion, or the products are still investigational:

- **David Huang, M.D., Ph.D.**
- **Ronald R. Krueger, M.D.**

The following faculty have indicated they have no relationship which, in the context of their articles, could be perceived as a potential conflict of interest:

- **Bela Anand-Apte, Ph.D.**
Ophthalmology Update, a publication of The Cleveland Clinic Cole Eye Institute, provides information for ophthalmologists about state-of-the-art diagnostic and management techniques and current research. Please direct any correspondence to:

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The Cleveland Clinic Foundation is an independent, not-for-profit, multispecialty academic medical center. It is dedicated to providing quality specialized care and includes an outpatient Clinic, a hospital with approximately 927 staffed beds, an Education Division and a Research Institute.

Ophthalmology Update is written for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

Physicians who wish to share this information with patients need to make them aware of any risks or potential complications associated with any procedures.

Release date September 1, 2003
Expiration date February 29, 2004
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Advances in the medical therapy of glaucoma have produced a variety of options for the treatment of glaucoma. Is one agent better than another? Poorly designed studies make it difficult to accept data from pharmaceutical companies at face value.

When selecting an effective treatment regimen for patients, we are often faced with choosing from among medications without having seen a direct comparison of the relative efficacy and safety of each agent. Pharmaceutical representatives frequently present us with data from clinical studies comparing their medication to others. However, these data always highlight the benefits of their particular product. Such studies should be viewed with extreme skepticism. Here is one example why:

Recently, I was shown the results of a “study” that purported to show that drug A was better than drug B in lowering intraocular pressure (IOP). The study involved switching patients from drug B to drug A, and compared IOP before and after this switch. A “statistically significant” reduction in IOP after switching to drug A had been found.

While this seems simple enough, I asked the pharmaceutical representative why patients were switched from drug B to drug A. I wondered if this was a clinical trial in which patients were switched as part of a study protocol or switched because their doctor felt the IOP was too high. As it turns out, patients were switched because their IOP was felt to be too high.

This fact alone makes the “study” results impossible to interpret. We are all aware that patients experience periodic fluctuations in IOP. Selecting only those patients with high IOP virtually guaranteed that the average IOP on the following visit would be lower, regardless of whether the medication was switched or not. The competitor could have done the same study, switching from drug A to drug B, and would have found their drug to be “better.” This well-known phenomenon, called regression to the mean, is a form of selection bias that frequently affects clinical studies. Such forms of bias are abundant in clinical studies that are not properly designed.

Until you see a randomized, blinded clinical trial specifically designed to eliminate bias, you should maintain a healthy skepticism about comparative studies of glaucoma medications.

– Scott D. Smith, M.D., M.P.H.