ELECTROPHYSIOLOGY
Mouse eyes facilitate assessment of retinal diseases.

GENE TRANSFER
Corneal gene transfer opens doors to new treatments.

PUZZLER
Infiltrates, blurriness and discomfort after LASIK. What is the diagnosis?

NEOPLASIA
Topical mitomycin therapy improves outcomes.

Cole Eye Institute researchers are making progress in their work to identify people at risk of developing age-related macular degeneration such as this. Story, Page 2.
THE FIRST STEP IN PREVENTING AGE-RELATED MACULAR DEGENERATION (AMD) IS FINDING A WAY TO IDENTIFY PEOPLE AT RISK FOR DEVELOPING THE DISEASE, SAYS HILEL LEWIS, M.D., CHAIRMAN OF THE CLEVELAND CLINIC COLE EYE INSTITUTE, WHERE RESEARCHERS CONTINUE TO PURSUE BIOMARKERS THAT CAN PROVIDE SUCH INFORMATION.

In an initial study, John W. Crabb, Ph.D., and colleagues found analysis of plasma reactivity and titers of autoantibodies to carboxyethylpyrrole (CEP) protein adducts (an indicator of oxidative damage) offered promising utility for AMD prognosis. Expanding their research, they are seeing if they can corroborate that finding in a larger sample and studying whether those parameters have value for predicting AMD susceptibility. In addition, they are applying emerging mass spectrometric proteomic profiling methods to search for new low-molecular-mass biomarkers, so-called ion clusters.

“Early identification of people at risk for AMD will allow initiation of interventions that could prevent the disease or slow its progression to minimize the extent of vision loss. Having found that CEP adducts and autoantibody titers in plasma are different for patients with AMD compared with unaffected individuals, we are interested in studying whether that combination of parameters has predictive value,” says Dr. Crabb.

“However, AMD is a very complex disease, and the accuracy and reliability of prognostic methods would be improved by having multiple biomarkers. We hope that the use of mass spectrometric profiling of serum proteomic patterns will facilitate the identification of multiple biomarkers for AMD,” he continues.

The CEP adducts represent oxidative protein modifications generated from docosahexaenoate (DHA)-containing lipids. DHA is a highly oxidizable fatty acid and, while rare in most human tissues, it is abundant in the retina, where it is exposed to high photo-oxidative stress.

Dr. Crabb and colleagues undertook studies measuring CEP plasma reactivity and autoantibody levels based on earlier work showing CEP adducts were present in drusen, and more abundant in AMD donor eyes relative to normal controls.

“The pathogenic mechanisms of AMD remain to be defined, but we are postulating that protein oxidation products, such as the CEP adducts, may be a primary catalyst, acting as an inflammatory stimulus to trigger immune responses that lead to progressive macular damage and vision loss. There is also a genetic connection as certain individuals may be predisposed to increased accumulation of CEP adducts because they have compromised normal protective mechanisms against oxidative stress,” Dr. Crabb explains.

Their study measuring plasma immunoreactivity to CEP and autoantibody levels included 19 of Dr. Lewis’ AMD patients. The results showed that compared with a control group of 19 age-matched individuals having a normal fundus appearance, the AMD patients had significantly higher mean levels of both the CEP adducts and CEP autoantibody titers. Twelve (63%) of the 19 AMD patients exhibited both high immunoreactivity and a high autoantibody titer compared with only 1 (5%) of the 19 age-matched controls. Of 13 people having levels of each marker higher than the mean value for the controls, 12 (92%) had AMD.

The Cole Eye Institute researchers are seeking to corroborate these findings in a much larger study population and are including a third arm consisting of patients at risk of developing AMD defined by the presence of clinically evident drusen but no vision loss or clinical signs of macular degeneration.

“We are speculating that as we follow this at-risk population over time, oxidative modifications, such as the CEP adducts, will gradually increase but be detectable before the onset of retinal pathology,” Dr. Crabb says.

Serum mass spectrometric proteomic pattern analysis will also be conducted in the same study groups. To date, mass spectrometric profiling of serum proteomic patterns has demonstrated significant value in the detection and diagnosis of various types of cancer, including cancer of the prostate, breast, ovaries and pancreas. Interest in using this technique to identify additional AMD biomarkers derives in part from the finding that drusen and Bruch’s membrane in AMD eyes contain oxidative protein modifications other than CEP and is based on substantial evidence implicating the involvement of the vasculature and immunological events in the development of drusen and AMD.

“We propose that signature ion clusters in the blood can be used to identify people at risk for developing AMD prior to onset of retinal degeneration and vision loss. Patterns of ion clusters in the blood may offer higher prognostic accuracy for AMD than any
single biomarker alone. Ultimately, characterization of the ion clusters that differentiate AMD will also prove useful for elucidating the causes of this disease,” Dr. Crabb explains.

CME Objective
To describe efforts to develop a blood test for biomarkers of age-related macular degeneration (AMD) susceptibility that will allow identification of individuals at risk for AMD prior to macular degeneration and vision loss.

Immunohistochemical analysis of retinal sections with anti-CEP antibody is shown in the left panels and control tissue sections detected with non-immune sera are in the right panels.

Figure A: Mouse retina shows prominent CEP staining in the photoreceptor outer segments and RPE. Less intense staining is evident in the inner plexiform layer and little, if any, staining is seen in the outer limiting membrane, outer nuclear layer, inner nuclear layer, or ganglion cell layer.

Figure B: Sections from normal human retina.

Figure C: Macula affected by AMD and peripheral photoreceptors immunostained with anti-CEP antibody. More CEP immunoreactivity can be seen in the AMD sample.

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Genetically Engineered Human Corneal Epithelial Clones Provide a Valuable Research Tool

An *in vitro* human corneal epithelial (HCE) cell model developed by researchers at the Cleveland Clinic Cole Eye Institute will provide a valuable system for testing the ocular toxicity of consumer products, believes Rajiv R. Mohan, Ph.D.

“Personal care and other consumer products, including detergents and household cleaners, are required by regulatory agencies to undergo studies to demonstrate their ocular safety, and the most widely used method for performing those evaluations involves the use of animal models. This new HCE cell model will allow initial screening of consumer products to be done *in vitro*, limiting the dependence on animals for research. In addition, it will also enable studies of function and gene regulation in human corneal epithelial cells,” Dr. Mohan explains.

Transfection of the HCE cells with tetracycline-inducible retroviral vectors allowed the Cole Eye Institute researchers to be successful in developing the genetically engineered human corneal epithelial clones where other investigators had failed. The tetracycline-inducible retroviral gene expression system allows gene expression to be turned on and off using tetracycline as a pharmacological switch.

“HCE cells are difficult to culture because they often become senescent. Viral oncogenes have been used effectively to establish long-term cell cultures. However, with that technique, the cells may also begin to proliferate out of control and lose their normal phenotype. A tetracycline-inducible gene expression system allows tight regulation of gene expression and of cell proliferation,” Dr. Mohan says.

The features of the cloned cells were investigated using a variety of techniques. Those studies showed the cells formed multilayers when cultured on a collagen membrane and exhibited normal HCE differentiation, as well as typical HCE morphology and ultrastructural features. Function studies showed the cells responded normally to various growth factors and acted as a significant physical barrier against toxicant penetration.

In follow-up studies, Dr. Mohan and his colleagues are exposing the cultured HCE cells to various known toxicants to evaluate the system’s potential for use in *in vitro* safety testing.
and those four different gene vectors were applied directly to the stroma after creation of a lamellar flap with a microkeratome. A fifth group of animals was treated with BSS to serve as a control.

The rabbits were sacrificed at various time points over the next 10 days and gene expression was evaluated in whole mounts and tissue sections of whole cornea, lamellar corneal bed and flap specimens. Those studies confirmed there was site-specific delivery of the reporter genes into the stromal keratocytes in all four treated groups, although differences were noted between the viral and non-viral vectors with respect to the temporal pattern of gene expression. Gene expression was achieved early, at 4 hours, using the plasmid vector, but disappeared by 3 days. In contrast, using the viral vector, gene expression was first identified at 3 days and was still present at the last evaluation at 10 days.

Now, the researchers are attempting to achieve success with gene transfer using a mouse model and with delivery of the gene-bearing vectors via either microinjection or simple topical application to the scraped ocular surface.

“Recognizing that the epithelium functions to provide a barrier against invasion into the cornea, we wanted to eliminate that obstacle in our initial experiments by introducing the genes under a lamellar flap. However, if a goal of this research is to develop a new technique for controlling wound healing, it will be necessary to show it is possible to achieve gene delivery using a noninvasive or minimally invasive delivery method,” Dr. Mohan says.

Other modifications introduced into the protocol of the new studies include extension of the follow-up period to allow characterization of the longevity of gene expression and use of a third vector – an HIV-based lentivirus carrying a green fluorescent protein gene – that permits in vivo monitoring of the onset and durability of gene expression.

Once the gene transfer techniques have been refined, Dr. Mohan and his coworkers in the laboratory directed by Steven E. Wilson, M.D., have plans to begin several other studies. In the area of modulating corneal wound healing, they will be investigating the effects of gene transfer of hepatocyte growth factor and transforming growth factor-β. In the area of corneal dystrophy studies, they will be trying to develop animal models for disorders associated with mutations in the genes BIG-H3 and CHST6, genes critical to the function of the normal cornea and associated with several corneal diseases in humans.
With electrophysiology, electrodes are placed upon the cornea to measure the electrical response of various cell types within the retina. The light-evoked responses are recorded in an electroretinogram (ERG).

“This technology allows us to analyze the visual consequences of retinal diseases, measuring degree and nature of visual loss. Since the eye is not damaged in our approach, changes that occur over time can also be monitored,” Dr. Peachey explains.

Electrophysiology permits characterization of animal models that are targeted to understanding a retinal disease, he explains. Much of his work involves mouse models of retinal disease. Although the mouse retina has many similarities to human retinas, there are certain key differences. Electrophysiology helps elucidate the specifics of those differences, such as the fact that mice have UV cones that human do not possess.

“We are able to follow the course of a disease and therapies in mouse models and then work to apply them to humans,” Dr. Peachey says. “As more genes are identified as causing retinal degenerations, labs across the country use that information to create a mouse model, inserting or deleting the appropriate genes to study their function further. One of our jobs is to validate how closely these mice re-create the human disease.”

His lab was the first to examine the status of cones in mouse models of retinitis pigmentosa (RP). By applying findings about human rod and cone involvement in RP to mouse models, he was able to determine that cones do become involved secondarily in the disease’s progression.

“A major goal of RP research is to find a way to save the cones so patients maintain a useful level of vision,” Dr. Peachey explains. “These findings indicate that mice will be very useful in this effort.”

Electrophysiology also provides a convenient outcome measurement for experimental treatments and is a useful tool in identifying additional mutant models for human retinal disease. It is also useful in determining where a problem is occurring in patients with otherwise unexplained visual loss, Dr. Peachey says. It is particularly valuable in the study of conditions such as congenital stationary night blindness (CSNB), in which the retinal tissue appears healthy even though the patient has decreased vision.

“ERG allows localization of defects to confirm the cause of blindness,” he explains. “In CSNB, there is a defect in retinal transmission. This is a rare disease, but fascinating to study because the retina appears normal in many respects, suggesting that it would be a good candidate for gene therapy.”
A 38-YEAR-OLD MAN PRESENTED AT THE COLE EYE INSTITUTE FOR CORRECTION OF MYOPIA IN BOTH EYES. THE PATIENT DENIED OCULAR HISTORY AND HIS MEDICAL HISTORY WAS SIGNIFICANT ONLY FOR HIGH BLOOD PRESSURE UNDER CONTROL WITH BENAZEPRIL.

Cycloplegic refraction was -3.75 +0.50 x 81; 20/20 in his right eye, and -5.00 -1.25 x 83; 20/20 in his left eye. Corneal thickness was 559µm in his right eye and 553µm in his left eye. His corneal topography and wavefront maps were normal and his pupil sizes were 4.0 and 5.5 mm under standardized photopic and scotopic conditions of illumination, respectively.

On external examination and slit-lamp microscopy, there was moderate plugging and inflammation of the meibomian glands and scruff and moderate debris at the base of the lashes. The cornea was otherwise normal with no epithelial defects or infiltrates. The patient was instructed to perform lid scrubs daily for one week prior to surgery and in general terms was considered a good candidate for refractive surgery.

The patient had simultaneous, bilateral wavefront-guided LASIK, aiming for monovision on the left eye (-1.00 D).

On postoperative day 1, his undercorrected visual acuity (UCVA) was 20/25 in both eyes with a normal slit-lamp examination. Four days after surgery, his slit-lamp examination revealed three small infiltrates in the left cornea, peripheral to the flap edge, with a clear cornea zone between the peripheral cornea and the limbus (Figures 1 and 2). At the stromal interface, mild diffuse nonspecific cells were noted in both eyes, more prominent on the left. At this time, his uncorrected vision was 20/25 in the right eye and 20/40 on the left. The patient reported mild blurriness and discomfort in the left eye.

What is the diagnosis? See Part II on Page 10.

THE CONJUNCTIVAL EPITHELIAL TUMORS REPRESENT A SPECTRUM RANGING FROM MILD DYSPLASIA TO INVASIVE SQUAMOUS CELL CARCINOMA INVOLVING THE CONJUNCTIVA AS WELL AS THE CORNEA, AND ARE GROUPED AS OCULAR SURFACE SQUAMOUS NEOPLASIA (OSSN). The presence of a perilimbal circumscribed fleshy growth is typical of OSSN. Associated prominent feeder vessels and surface leukoplakia are characteristic findings. The differentiation between conjunctival/corneal intraepithelial neoplasia (CCIN) and invasive squamous cell carcinoma (SCC) is made by careful histopathologic evaluation to determine extension of the tumor beyond the basement membrane.

While excision of the lesion is the mainstay of treatment, incomplete initial excision is the most important risk factor for recurrence. More than 20 years ago, Fraunfelder and Wingfield reported improved tumor control when excision was combined with cryotherapy as compared with excision or cryotherapy performed alone. Although recurrence rates of more than 50% have been previously reported, rates of 5% to 10% are generally accepted now.

Currently there is interest in use of topical chemotherapy (interferon, mitomycin C, and 5-fluorouracil) for management of OSSN. Topical chemotherapy with mitomycin has been advocated for postoperative use in cases where tumor excision is incomplete, both for primary and recurrent tumors. Excellent response to topical mitomycin alone in cases with small conjunctival or diffuse corneal intraepithelial neoplasia has also been reported.

We recently used mitomycin 0.04% eye drops in a patient with extensive CCIN preoperatively with a view to induce “chemoreduction” of the tumor. Following partial tumor regression, excision of the residual tumor with tissue sparing was achieved.

**Case**

A 68-year-old white male was evaluated for redness of the right eye for 3 months. On examination, his visual acuity was 20/40 and 20/20. A nodular growth, 6 x 5 x 3 mm, was observed at the temporal limbus overriding the cornea for about 2 mm (Figure 1a). The lesion demonstrated corneal extension circumferentially for 120° from 7 to 11 o’clock (Figure 1b).

Preoperative treatment with 0.04% mitomycin eye drops four times a day (one-week-on, one-week-off cycle) was initiated. Punctal plugs were inserted.
and the patient signed a consent form as required by the Institutional Review Board. The patient was evaluated every two weeks. Marked reduction in size of the conjunctival tumor was observed by the end of two cycles (Figure 2a) with complete clearing of all corneal involvement and replacement by normal epithelium (Figure 2b). The patient tolerated therapy well.

Following completion of three cycles of treatment, excision of the residual conjunctival tumor and double freeze thaw cryotherapy to the conjunctival margins were performed. Histopathologic study of the residual conjunctival tumor confirmed the lesion to be CCIN with mild to moderate dysplasia (Figure 3). Postoperatively, there was excellent healing and no evidence of tumor recurrence at the six-month follow-up visit (Figure 4).

**Comments**

In general, surgical excision supplemented with cryotherapy, where feasible, offers the advantage of potential cure in more than 90% of cases and provides tissue for histopathologic diagnosis. The limitation of surgical excision is a potential for partial excisions and possibility of stem cell failure when large areas of limbal epithelium are excised. The advantage of topical chemotherapy is its application in cases with diffuse CCIN where surgery may not be feasible. The disadvantages of topical mitomycin C are local side effects such as reversible keratoconjunctivitis after prolonged use.

By using limited cycles of topical chemotherapy preoperatively to reduce the tumor volume followed by excision of residual mass (supplemented with cryotherapy), the advantages of surgical excision and of chemotherapy can be exploited in the most effective way. By this technique, the surgical excision is limited, histopathologic diagnosis can be confirmed and the risk of postoperative tumor recurrence may be reduced. ■

*Dr. Singh is director of the Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic Foundation.*

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**CME Objective**

To examine the role of topical mitomycin therapy in the treatment of conjunctival/corneal intraepithelial neoplasia.

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**References**

Differential diagnosis

The patient presented with marginal catarrhal keratitis infiltrates on the left eye a short time after LASIK. In addition, the patient developed stage I diffuse lamellar keratitis (DLK) in both eyes. Microbial keratitis must be considered and ruled out when corneal infiltrates are present. Corneal cultures for bacteria, fungus and acanthamoeba were obtained. Gram staining was also performed from a scraping from the left cornea overlying the infiltrates.

The peripheral location and multiple infiltrates suggested that the condition was most likely a noninfectious inflammatory condition related to the meibomian gland dysfunction and blepharitis, but because of the potential for rapid dissemination of infection along the lamellar interface, a decision was made to started fortified vancomycin (50 mg/ml) and Amikacin (15 mg/ml) along with prednisolone acetate 1% every hour. Treatment was also started with doxycycline 100 mg twice a day with continued lid hygiene.

There was marked improvement of the infiltrates over the next three days and during this interval, the antibiotics were tapered to four times per day. Initially, DLK became a little worse during the two days after vancomycin and Amikacin were started, but improved significantly when the frequency of the antibiotic treatment was decreased. Prednisolone acetate 1% was slowly tapered over the next month. Treatment with oral doxycycline 100 mg each day, FML four times a day OU and lid hygiene was continued for an additional two months.

At four months after surgery, the patient was found to have overcorrection to +1.00 + 0.50 x 110 in the left eye and a decision was made to perform LASIK enhancement. Preoperatively, the patient was instructed to continue the doxycycline 100 mg per day and lid hygiene and start prednisolone acetate 1% four times a day in the left eye two days prior to the procedure. After the LASIK enhancement, there was mild recurrence of the peripheral infiltrates without signs of DLK.

Postoperatively, the patient was instructed to use ofloxacin and prednisolone acetate 1% six times a day. At the one-week postoperative examination, manifest refraction was -1.25 D sphere and uncorrected visual acuity was 20/30 with clear corneas on slit-lamp examination.

Discussion

Marginal catarrhal infiltrates are usually attributed to a localized corneal hypersensitivity reaction to toxins produced by bacteria colonizing the eyelid margins, especially in cases of blepharitis and meibomian gland dysfunction. The lesions are sterile and probably represent local deposition of antigen-antibody complexes and attracted inflammatory cells in the peripheral corneal stroma.

Secretions from the meibomian glands may also be a triggering factor for some sporadic cases of DLK. These irritating factors can also trigger cytokine (for example, interleukin-1 alpha [IL-1α]) release from the corneal epithelium. IL-1α binds to keratocyte receptors and keratocytes respond to IL-1 receptor activation by producing proinflammatory chemokines (such as monocyte chemotactic and activating factor and granulocyte stimulating factor), which are responsible for attracting inflammatory cells into the cornea from the limbal vessels and the tear film. The inflammatory cells likely accumulate along the lamellar interface (to produce DLK) because the lamellar interface is a potential space, creating a path of least resistance to cell movement after LASIK. The localized peripheral or catarrhal infiltrates are likely related to the localized deposition of antigens, such as bacterial toxins, in the context of the normal inflammatory response associated with LASIK.

Treatment of both the catarrhal infiltrates and DLK involves the intensive use of topical corticosteroids and requires careful observation. Preoperative screening is a key factor for success in these cases and the prophylactic pretreatment with lid scrubs, hygiene and doxycycline are recommended in patients with blepharitis and meibomian gland dysfunction.

Since we first described catarrhal infiltrates associated with LASIK, we have found that prophylactic treatment with prednisolone acetate 1% beginning two days prior to surgery is highly effective in preventing or limiting the severity of this post-LASIK disorder. Recurrence is likely with LASIK enhancement and can be attenuated by similar treatment prior to the reoperation.

References


THE CLEVELAND CLINIC COLE EYE INSTITUTE IS PROUD TO PRESENT THE 2004 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 ANSWERS WILL BE PROVIDED.

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ALL PROGRAMS WILL BE HELD IN THE JAMES P. STORER CONFERENCE CENTER OF THE COLE EYE INSTITUTE 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 VISITOR’S PARKING GARAGE AT EAST 100TH STREET AND CARNEGIE AVENUE. WE WILL VALIDATE YOUR PARKING TICKET.

June 10, 2004
TOWARD AN UNDERSTANDING OF AGE-RELATED MACULAR DISEASE
Alan C. Bird, M.D.
Department of Clinical Ophthalmology
Institute of Ophthalmology
Moorfields Eye Hospital
London, England

July 15, 2004
EXPERIMENTAL GENE-BASED THERAPY FOR RETINAL DEGENERATIONS
Matthew M. LaVail, Ph.D.
Professor
Department of Anatomy & Ophthalmology
Beckman Vision Center
University of California, San Francisco School of Medicine

August 19, 2004
IMMUNOLOGIC MONITORING OF HERPES SIMPLEX VIRUS LATENT AND LYTIC INFECTIONS
Robert Hendricks, Ph.D.
Professor, Departments of Ophthalmology, Molecular Genetics and Biochemistry, & Immunology
Director, Ophthalmology and Visual Sciences Research Center
University of Pittsburgh

September 16, 2004
NEURAL REMODELING IN RETINAL DEGENERATIONS
Robert E. Marc, Ph.D.
Professor, Department of Ophthalmology & Visual Sciences
Adjunct Professor, Department of Physiology
John A. Moran Eye Center
University of Utah School of Medicine

October 21, 2004
CHANGING YOUR MIND: MECHANISMS OF RAPID PLASTICITY IN DEVELOPING VISUAL CORTEX
Michael P. Stryker, Ph.D.
Professor and Chair
Department of Physiology
University of California, San Francisco

November 18, 2004
G PROTEIN SIGNALING IN PHOTORECEPTORS
Vadim Y. Arshavsky, Ph.D.
Associate Professor of Ophthalmology & Neuroscience
Howe Laboratory of Ophthalmology
Harvard Medical School
Massachusetts Eye and Ear Infirmary

December 16, 2004
CONNE VISUAL PIGMENTS: STRUCTURE AND FUNCTION
Rosalie K. Crouch, Ph.D.
Professor of Ophthalmology and Biochemistry
Provost Emerita
Research to Prevent Blindness Senior Scientific Investigator
Medical University of South Carolina
PHYSICIANS ARE CORDIALLY INVITED TO ATTEND THE FOLLOWING OPHTHALMIC CONTINUING MEDICAL EDUCATION COURSES AT THE CLEVELAND CLINIC COLE EYE INSTITUTE. ALL COURSES ARE HELD IN THE JAMES P. STORER CONFERENCE CENTER ON THE FIRST FLOOR OF THE COLE EYE INSTITUTE, UNLESS OTHERWISE NOTED.

For more information, contact Jane Sardelle, program coordinator, at 216/444–2010 or 800/223–2273, ext. 42010, or sardelj@ccf.org. View the entire 2003–2004 course catalog at http://www.clevelandclinic.org/eye/physician_info or go to the Cleveland Clinic web site at www.clevelandclinicmeded.com.

Saturday, May 22, 2004
UPDATE ON GLAUCOMA: CURRENT KNOWLEDGE AND NEW DEVELOPMENTS IN ANGLE-CLOSURE GLAUCOMA

Course Co-Directors
Scott D. Smith, M.D., M.P.H.
Edward J. Rockwood, M.D.
Glaucoma Department
Cole Eye Institute

Guest Faculty
Nathan G. Congdon, M.D., M.P.H.
Associate Professor of Ophthalmology
Dana Center for Preventive Ophthalmology
The Wilmer Eye Institute
Johns Hopkins University School of Medicine
Baltimore, MD

David S. Friedman, M.D., M.P.H.
Associate Professor of Ophthalmology
Dana Center for Preventive Ophthalmology
The Wilmer Eye Institute
Johns Hopkins University School of Medicine
Baltimore, MD

Content & Objectives:
This course will provide a comprehensive update on angle-closure glaucoma. Although less common in the United States than primary open-angle glaucoma, primary and secondary angle-closure glaucomas present unique diagnostic and therapeutic challenges. Cole Eye Institute staff and guest consultants will present current guidelines on diagnosis and management, as well as their future vision of the treatment and prevention of angle-closure glaucoma.

At the conclusion of this course, participants should be able to:
• Describe the pathophysiology of angle-closure glaucoma and how this influences methods of disease treatment and prevention.
• Understand the epidemiology of angle-closure glaucoma and demonstrate how this influences methods for diagnosis of the condition.
• Distinguish among the medical treatments available for primary and secondary angle-closure glaucoma and prepare a treatment plan individualized to the needs of a specific patient.
• Describe the recent developments in ophthalmic imaging, and how these may be useful in the diagnosis of and screening for angle-closure glaucoma.

Friday and Saturday, June 18–19, 2004
REFRACTIVE SURGERY SUMMIT 2004: TOMORROW’S MAINSTREAM VISION CORRECTION PROCEDURES

Course Co-Directors
Ronald R. Krueger, M.D., M.S.E.
Department of Refractive Surgery
Cole Eye Institute
Cleveland, OH

Scott M. MacRae, M.D.
Professor of Ophthalmology and Visual Science
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Rochester, NY

Jean-Marie Parel, Ph.D.
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John Vukich, M.D.
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Assistant Professor in Research
University of Utah Salt Lake City, UT

Guest Faculty
Stephen F. Brint, M.D., F.A.C.S.
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Francesco Carones, M.D.
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Liliana Werner, M.D., Ph.D.
Assistant Professor in Research
University of Utah Salt Lake City, UT

Content & Objectives:
Refractive intraocular lenses (IOLs) and customized corneal correction have been available internationally for several years and are being introduced to the United States after rigorous FDA-sanctioned clinical trials. These innovations are both characterized by higher quality of vision compared with conventional laser vision correction. We believe they represent the next mainstream options for refractive surgeons in the United States. This summit will present these
important state-of-the-art procedures and examine how they will fit into the clinical practice in the United States, as well as how they will benefit patients. At the conclusion of the course, participants should be able to:

• Identify patients who are likely to benefit from customized corneal correction.
• Identify patients who are likely to benefit from refractive IOLs.
• List the advantages and limitations of customized corneal correction.
• List the advantages and possible adverse effects of refractive IOLs.
• Distinguish between the various customized corneal correction technologies.
• Distinguish between the various refractive IOL options.
• Discuss current and prospective methods of presbyopia correction and their potential limitations.

Thursday and Friday, June 24-25, 2004

ANNUAL RESEARCH, RESIDENTS & ALUMNI MEETING

Course Co-Directors
Hilel Lewis, M.D.
Chairman, Division of Ophthalmology
Director, Cole Eye Institute
Cleveland, OH

Careen Y. Lowder, M.D., Ph.D.
Uveitis Department
Cole Eye Institute
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Keynote Speaker
Thomas J. Liesegang, M.D.
Louis and Evelyn Kreuger Professor of Ophthalmology, Mayo Clinic Jacksonville
Editor-in-Chief, American Journal of Ophthalmology
Editor, Transactions of the American Ophthalmological Society
Senior Secretary for Education, American Academy of Ophthalmology
Jacksonville, FL

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

Bela Anand-Apte, M.B.B.S., Ph.D.
John W. Crabb, Ph.D.
Marc A. Feldman, M.D.
Philip Goldberg, M.D.
Fronzie A. Gutman, M.D.
Stephanie A. Hagstrom, Ph.D.
Joe G. Hollyfield, Ph.D.
David Huang, M.D., Ph.D.
Bennie Jeng, M.D.
Peter K. Kaiser, M.D.
Gregory S. Kosmorsky, D.O.
Ronald R. Krueger, M.D.
Roger H.S. Langston, M.D.
Michael S. Lee, M.D.
Careen Y. Lowder, M.D., Ph.D.
Andreas Marcotty, M.D.
Alan D. Marmorstein, Ph.D.
David M. Meisler, M.D.
Michael Millstein, M.D.
Neal S. Peachey, Ph.D.
Victor L. Perez, M.D.
Julian D. Perry, M.D.
Edward J. Rockwood, M.D.
Allen S. Roth, M.D.
Jonathan E. Sears, M.D.
Arup D. Sholiton, M.D.
Arun D. Singh, M.D.
Scott D. Smith, M.D., M.P.H.
Elias I. Traboulsi, M.D.
Steven Wilson, M.D.

Residents: First Year
Pawan Bhatnagar, M.D.
Anat Galor, M.D.
Pankaj Gupta, M.D.
Sunita Radhakrishnan, M.D.

Residents: Second Year
Susie Chang, M.D.
Sai Chavala, M.D.
Albert Dal Canto, M.D., Ph.D.
Alex Melamud, M.D., M.A.

Residents: Third Year
Eric Baylin, M.D.
Brian Kim, M.D.
Rachel Kuchtey, M.D., Ph.D.
Egbert Saavedra, M.D.

Fellows
Sophie Bakri, M.D.
Leonid Lerner, M.D., Ph.D.
Vitreoretinal Surgery

Ko Nakata, M.D.
Vitreoretinal Research

Maria Regina Chalita, M.D.
Refractive Surgery Research

Content & Objectives:
This program provides a scientific forum to present clinical and basic science research of the residents, fellows, alumni, staff (Cole Eye Institute, Division of Ophthalmology, Cleveland Clinic Foundation), and invited ophthalmologists.

The goal of this meeting is to pursue and present the highest-quality, original thought-provoking clinical research papers. In addition to the educational aspects of the program, this event offers an excellent opportunity to make and renew friendships, meet current residents, fellows, new faculty and invited ophthalmologists and learn about new and ongoing investigations within the Cole Eye Institute.
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.
Contact E. Traboulsi, M.D., at (216) 444-4363 or S. Crowe, C.O.T., at (216) 445-3840

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., at (216) 444-4363 or S. Crowe, C.O.T., at (216) 445-3840

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 Cards during the same clinical visit. The investigators are attempting to determine if Lea Grating Cards are accurate and if they offer an advantage over the widely accepted Teller Acuity Cards.
Contact E. Traboulsi, M.D., at (216) 444-4363 or D. Peralta, M.D., at (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., at (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 Must be at least 18 years old and eligible for LASIK.
Contact R. Krueger, M.D., at (216) 444-8158 or R. Scott at (216) 444-0680

CUSTOM CORNEA LASIK SURGERY
Objective To evaluate the ability of the Custom Cornea Device in its ability to improve keratorefractive surgery. Custom Cornea is a new method of measuring the visual system of the eye. These measurements are used in conjunction with the excimer laser system to customize the application of the laser beam to the individual’s needs. This allows the excimer laser to reshape the cornea so that light entering the eye is properly focused. If this technology proves reliable, it stands to improve keratorefractive surgery by minimizing or eliminating common postoperative side effects such as glare, halos, double vision, night vision difficulties and residual refractive error.
Contact R. Krueger, M.D., at (216) 444-8158 or R. Scott at (216) 444-0680

GLAUCOMA
ADVANCED IMAGING FOR GLAUCOMA
Objective Advanced Imaging for Glaucoma (AIG) is a multi-center bioengineering partnership sponsored by the National Eye Institute (NEI). The goal of the partnership is to develop advanced imaging technologies to improve the detection and management of glaucoma. The advanced imaging technologies include optical coherence tomography (OCT), scanning laser polarimetry (SLP) and scanning laser tomography (SLT). The technologies will be evaluated in a longitudinal 5-year clinical trial composed of glaucoma suspects, glaucoma patients and normal subjects.
Contact D. Huang, M.D., Ph.D., at (216) 444-0848 or K. Schach (216) 444-2566

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 measure accurately and reproducibly optic nerve head excavation, retinal fiber thickness layer and the perifoveal retinal thickness in patients suspected of having glaucoma or known to have glaucoma.
Contact S. Smith, M.D., M.P.H., at (216) 444-1995 or R. Scott at (216) 444-0680

NEURO-OPHTHALMOLOGY
LEBER’S OPTIC NEUROPATHY
Objective To evaluate the safety and vision-sparing efficacy of brimonidine-Purite 0.15% administered four times a day in the unaffected eye of patient with unilateral visual loss due to Leber’s optic neuropathy.
Contact G. Kosmorsky, D.O., at (216) 444-5888 or K. Schach (216) 444-2566

PROTOCOL B7A–MC–MBDL REDUCTION IN THE OCCURRENCE OF CENTER–THREATENING DIABETIC MACULAR EDema
Objective The primary objective of this study is to test the hypothesis that oral administration of 32 mg per day of ruboxistaurin for approximately 36 months will reduce, relative to placebo, the occurrence of center-threatening diabetic macular edema as assessed by fundus photography in patients with non-clinically significant macular edema and nonproliferative diabetic retinopathy at baseline.
Contact P. Kaiser, M.D., at (216) 444-6702 or C. Rosal, R.N., B.S.N., at (216) 445-1256

All studies have been approved by the Institutional Review Board.
## Cole Eye Institute Staff

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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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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.

Ophthalmic Pearl

What to Tell Patients Considering Blepharoplasty

By Julian D. Perry, M.D.

WHILE INSTRUMENTATION FOR UPPER BLEPHAROPLASTY HAS IMPROVED RESULTS AND MINIMIZED RECOVERY, THE MOST IMPORTANT ASPECT OF BLEPHAROPLASTY SURGERY IS STILL THE PREOPERATIVE EVALUATION AND DISCUSSION WITH THE PATIENT.

Because aging typically results in fat deflation, removal of too much fat during blepharoplasty can hasten these aging changes and produce an aged or skeletonized appearance rather than a rejuvenated one. This concept of fat preservation is especially important in the lower lids. Repositioning of the fat into the hollow area overlying the orbital rim can lead to a smoother lower eyelid, often with no excision of fat at all.

While many cases do require excision of a small amount of fatty tissue, the surgeon must carefully consider skin excision in a patient with horizontal eyelid laxity. Laxity must be corrected if skin is excised. Lateral canthal resuspension adequately addresses the laxity and minimizes the chances of postoperative lower eyelid retraction.

During the evaluation, the surgeon must note the degree to which brow ptosis contributes to fullness of the upper eyelids. The surgeon should resect only the redundant eyelid skin. Any remaining skin must be addressed through brow-lifting techniques.

I explain to patients that removing all of the skin of the upper eyelids will simply sew the eyelashes to the eyebrows and they will be unable to close their eyelids. I explain that if they have brow ptosis, they should expect some skin overhang after surgery, which can only be addressed through brow ptosis repair. If the patient declines brow surgery, I will often sculpt the retro orbital orbicularis oculi fat (ROOF) to minimize the effect of the brow ptosis. However, even this technique will not sufficiently address larger amounts of brow ptosis. Larger amounts may be corrected medically with botulinum toxin, or surgically via a direct brow lift, mid-forehead incision or endoscopic approach.

The surgeon should leave enough fatty tissue in the medial area to prevent skeletonization, an uncommon occurrence that is better to avoid than to treat. Asymmetry of the lid creases can be avoided by leaving a small amount of fat between the orbicularis and levator muscle to prevent an untoward high lid crease. This is especially true for patients with an Asian eyelid configuration. A softer lid crease is formed by avoiding the incorporation of deeper tissues into the cutaneous closure. Should the surgeon desire a harder lid crease, the levator muscle may be incorporated into the cutaneous closure. Great care must be taken with these “supertarsal fixation” techniques to achieve symmetry.

Using these techniques, the surgeon can confidently produce reliable and symmetric results.