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Welcome to an expanded special edition of Ophthalmology Update. We hope you find the information on our ongoing clinical and basic science investigations to be interesting and helpful in your everyday practice.

In addition, we have included a special addendum that provides an overview of the exciting and cutting-edge capabilities and programs that are available here at the Cole Eye Institute. The sections in it are:

- Innovation: What makes us different
- Staff: Who we are
- Education and Training: Our commitment to professional development
- Research: Our relentless pursuit of answers

We are very excited about the work that is being done by our clinicians and researchers and remain committed to forging partnerships between the two groups. We have found this to expedite the process of turning an idea into the highest quality clinical practice.

This issue also describes our 2006-2007 Programs in Ophthalmic Education, one of the largest hospital-based continuing medical education programs in the country, and our Distinguished Lecture Series, featuring some of the biggest names in eye research. We hope you will be able to join us at one or more of these events this year.

Please do not hesitate to contact us with questions about our events or for more information on how we can help you as you care for your patients.

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Director, Cole Eye Institute
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Investigations

When the lines between research and patient care blur, doors open and excellence flourishes.
Cole Eye Researchers Aiming to Elucidate Physiological and Pathological Roles of TIMP3

Identification of the role of vascular endothelial growth factor (VEGF) in the development of choroidal neovascularization (CNV) has led to exciting advances in treatment for exudative age-related macular degeneration (AMD). However, understanding of the pathogenesis and regulation of ocular neovascularization is still very limited.

At the Cole Eye Institute, Bela Anand-Apte, M.B.B.S., Ph.D., has been conducting research aiming to characterize the physiological role of tissue inhibitor of metalloproteinase-3 (TIMP3) and to elucidate the mechanisms by which it might regulate angiogenesis in eyes with AMD and Sorsby’s fundus dystrophy (SFD).

Starting off with the basic knowledge that proteolytic degradation of capillary basement membrane by matrix metalloproteinases (MMPs) is an initiating event in the development of new blood vessel growth, Dr. Anand-Apte and colleagues focused their attention on the TIMPs that inhibit MMP function. Their interest was directed to TIMP3 because in contrast to other members of the TIMP family, TIMP3 uniquely binds to extracellular matrix. While these studies were under way, independent researchers linked mutations in the TIMP3 gene to SFD.

“Although TIMP3 is ubiquitous throughout the body, patients with SFD have only ocular symptoms. Therefore, it made sense that as a bound protein, TIMP3 would have a localized effect,” Dr. Anand-Apte explains.

Experiments conducted so far in a mouse model of laser-induced CNV show that TIMP3 is a potent inhibitor of angiogenesis. Additional studies indicate that its mechanism appears to involve inhibition of VEGF action by preventing VEGF from binding to its receptors. Ongoing studies are examining what effect TIMP3 might have on the progenitor cells that are known to be involved in the development of CNV in the mouse model.

The researchers are also aiming to understand the role of the mutated TIMP3 in SFD with the hope that information generated will provide clues to its participation in AMD-related CNV pathogenesis. Preliminary results from functional studies show that the mutated protein does not inhibit angiogenesis like the wild-type TIMP3, reports Dr. Anand-Apte.

Experiments are also under way to investigate whether TIMP3 could be used therapeutically to prevent CNV.

“Knowing that TIMP3 inhibits VEGF, we are interested in determining if it has efficacy in regulating VEGF-mediated pathological angiogenesis,” Dr. Anand-Apte says.

Initial studies are being performed with intravitreal delivery of TIMP-3, but in the future, other modes of administration will be examined, including subcutaneous and scleral injections as well as intravitreal delivery using a controlled-release system.

For more information, contact Bela Anand-Apte, M.B.B.S., Ph.D., at anandab@ccf.org.
Biomarker Discovery Research Aims to Develop Tools for Predicting AMD Susceptibility, Therapeutic Monitoring

Age-related macular degeneration (AMD) continues to be the leading cause of blindness among older people in Western countries. Current estimates indicate that more than 9 million people in the United States are affected by some form of AMD, with about one out of every five of those patients having advanced AMD and being legally blind.

At the Cole Eye Institute, John W. Crabb, Ph.D., and colleagues have been working to identify biomarkers that could be used to predict who is at risk for AMD prior to the appearance of clinically evident disease. Such biomarkers could also be useful for monitoring therapeutic efficacy in early intervention or prophylaxis. They are hoping that measurement of disease-related peptides in plasma might provide useful tools for predicting AMD susceptibility.

“Plasma contains about 5,000 peptides that are derived as proteolytic degradation products from tissues throughout the body. We are using mass spectrometry and peptidomic profiling in my laboratory to sort through these plasma peptides as an approach to monitoring the health of the retina,” Dr. Crabb explains.

Based on findings from a series of previous studies, the research for defining AMD biomarkers has focused on oxidative protein modifications known as carboxyethylpyrrole (CEP) adducts. Originally, Dr. Crabb and colleagues discovered CEP adducts in drusen and found elevated levels in other ocular tissues such as Bruch's membrane from patients with AMD compared with normal controls. They then found that patients with AMD (AREDS categories 2, 3 and 4) also had higher plasma levels of CEP adducts and CEP autoantibodies relative to age-matched normal subjects.

CEP protein adducts are uniquely derived from oxidative fragmentation of docosahexaenoate-containing lipids, which are abundant in the retina. Animal studies in rats and mice have shown that intense light induces CEP adducts in retina and that CEP adducts can stimulate new blood vessel growth. This suggests that CEP adducts may play a role in choroidal neovascularization in advanced AMD.

Other collaborative studies have shown that CEP proangiogenic activity can be inhibited with monoclonal antibody to CEP, raising the possibility that CEP antibodies may offer another avenue to AMD therapeutics. Several laboratories elsewhere have recently shown an association between genetic variants of complement components and susceptibility to AMD, implicating inflammatory processes in AMD pathogenesis. Dr. Crabb thinks CEP adducts and autoantibodies may play a role in the inflammatory processes relevant to AMD.

“Taken together, these findings led us to hypothesize that the CEP adducts serve as a primary catalyst in AMD pathology and are causally involved in drusen formation, Bruch’s membrane thickening, choroidal neovascularization and activation of the immune response,” Dr. Crabb says.

As a proteomic approach to AMD biomarker discovery, the researchers used anti-CEP monoclonal antibodies attached to magnetic beads to fractionate plasma for recovery of CEP adducted peptides. The recovered peptides were analyzed by MALDI TOF mass spectrometry followed by bioinformatic methods to determine which peptides were statistically significantly different between patients with AMD and controls. These peptides were then grouped together in patterns or clusters based on the mass analyses. Remarkably, the resulting patterns also reflected with significant accuracy whether the plasma was from a patient with AMD or a normal control donor. For example, from 170 plasma samples, including 90 from AMD donors (AREDS categories 2, 3 and 4) and 80 from unaffected control donors, correct identification as either AMD or normal was obtained for 94% of the 170 plasma samples based on the mass analysis.

Current work is focused on characterizing the structure of key peptides in the patterns that distinguish AMD from normal plasma. Such sequence information is expected to provide the identity of (1) peptide antigens for producing new antibodies that could be
useful prognostic tools and (2) the parent protein, which could lead to new insights into mechanisms of AMD pathology.

Immunological measurement of plasma CEP adducts and CEP autoantibody titer may also offer a method for therapeutic monitoring. For example, in a preclinical study evaluating an experimental drug that protects rats from retinal light damage, CEP parameters in plasma were measured by ELISA and found to be decreased relative to those in control animals without drug treatment.

“We believe that a combination of these techniques may eventually provide methods for early identification of AMD-susceptible individuals and for monitoring the efficacy of AMD therapeutics. However, clinical validation of these methods requires more time and research,” Dr. Crabb concludes.
Elucidation of the molecular genetics underlying inherited diseases holds promise for a number of important clinical applications relating to screening, diagnosis, counseling and treatment. In her research laboratory at the Cole Eye Institute, geneticist Stephanie A. Hagstrom, Ph.D., has been focusing on using a candidate gene approach to screen for mutations associated with inherited retinal degenerations, including retinitis pigmentosa, Leber congenital amaurosis and juvenile and age-related forms of macular degeneration.

In addition, she has been collaborating with colleague John W. Crabb, Ph.D., in performing genomics studies that are directed by findings in Dr. Crabb’s proteomics research to identify biomarkers for age-related macular degeneration (AMD) and glaucoma.

“Our hope is that the combined efforts of genomics and proteomics will yield biomarkers that can be detected in those at risk for these diseases prior to vision loss,” says Dr. Hagstrom.

All of the physicians on staff at the Cole Eye Institute alert the coordinator of the Center for Genetic Eye Diseases if they see a patient with a known inherited ocular disorder or who has a disease that is thought may have a genetic component, such as a child with syndromic congenital malformations including eye-related findings. The coordinator tries to recruit those patients into the genetic screening program, and after obtaining consent, performs a complete medical history and blood draw.

In Dr. Hagstrom’s lab, the DNA from the specimens is submitted to direct sequence analysis using high-throughput, semi-automated screening to identify the presence of any differences compared with a control sample.

“Our lab is equipped with cutting-edge molecular biology technology that allows us to screen specimens from hundreds of patients each day and puts us on par with much larger laboratories in the country,” she says.

The screening efforts may be focused on particular candidate genes based on existing reports of genetic associations. However, Dr. Hagstrom is also taking a more targeted approach to the mutation screening guided by the findings of Dr. Crabb’s proteomics research.

For example, based on Dr. Crabb’s studies characterizing the proteins in drusen and the findings of peptidomic profiling of plasma in patients with AMD, mutation screening has been undertaken focusing on pathways of genes that are involved in the regulation of oxidative damage and immune-mediated processes that have been implicated in AMD pathogenesis. In addition, proteomics studies conducted by Dr. Crabb revealing the presence of Cochlin (COCH) deposits in the trabecular meshwork of both patients with open-angle glaucoma and glaucomatous DBA/2J mice have focused mutational screening on the COCH gene, as well as other genes, in patients with glaucoma.

Those studies are still in progress, but have led to the identification of several genetic sequence changes in both patients with AMD and glaucoma that are being studied further to identify their functional consequences and determine whether they represent a pathogenic link.

“We believe this joint approach involving our two laboratories is somewhat unique in the genetic research field, and we believe it offers a synergy that will enable the discovery of underlying genetic causes of these common sight-threatening diseases,” Dr. Hagstrom says.
Studies on Redox-Sensitive Retinal Proteins Aim to Provide Clues for Strategies to Counter Oxidative Stress

Although the pathophysiology of age-related macular degeneration (AMD) remains unclear, available evidence points to a role of oxidative stress. Consistent with that concept, results from the Age-Related Eye Disease Study (AREDS) indicated a positive effect of antioxidant therapy with high doses of vitamins and minerals for reducing disease progression in patients with advanced AMD.

Research being conducted by George Hoppe, M.D., Ph.D., and Jonathan Sears, M.D., at the Cole Eye Institute is aiming to gain insight into the endogenous antioxidant protective mechanisms in the retina with the hope that information may ultimately be used to design more effective antioxidant interventions.

“Understanding of the molecular basis for the antioxidant mechanisms in the retina could allow us to develop more targeted therapies that could induce or facilitate their function. In current clinical use, antioxidant treatment involves administration of high doses and yields only a modest benefit. We believe that therapeutic efficiency could be enhanced by more precise elucidation of the molecular basis for antioxidant mechanisms,” says Dr. Hoppe.

His research is focusing on characterizing redox-sensitive proteins and the changes they undergo in response to oxidative stress, and in particular determining proteins that undergo redox-dependent interactions with glutathione, a ubiquitous peptide anti-oxidant.

“Oxidative modifications of cysteine residues on proteins is a potent way of regulating protein function, and when there is a redox shift toward oxidative potential, glutathione tends to bond covalently with the sulfhydryl moieties on proteins and this in turn results in changes in protein conformation and activity,” he explains.

So far, Drs. Hoppe and Sears have identified two proteins that appear to mediate retinal adaptation to a high oxidative environment. The chaperone heat shock cognate protein 70 (Hsc70) is one of those proteins, and their studies show that as a result of interactions with glutathione during oxidation, Hsc70 increases its chaperone activity and becomes more protective.

"Another interesting finding is that this increase in Hsc70 chaperone activity occurs as an ATP-independent process. That suggests this protein can adapt to conditions of high oxidative stress where ATP concentration is reduced by forming disulfide bonds with glutathione," Dr. Sears says.

The nuclear transcription factor high mobility group protein B1 (HmgB1) is a second protein that they have identified as being redox-sensitive. HmgB1, which also has DNA chaperone-like properties, has been shown to be modified by glutathione with resultant changes in its chaperone activity. Most

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recently, in a rodent study, Drs. Hoppe and Sears found that the expression of HmgB1 in retinal photoreceptor cells is under circadian regulation.

“Our studies show that the expression of this protein peaks during the middle of the day and is lowest at night, even in animals that are kept in the dark. HmgB1 is also found in other cells, but its expression and activity in those cells is constant rather than cyclical,” Dr. Hoppe says.

Based on those findings, Drs. Hoppe and Sears are postulating that HmgB1 is essential for transcription activity in the photoreceptors during daylight hours and that it regulates or facilitates expression of genes that are important for photoreceptor function during the light phase.

Other studies with HmgB1 have led to the identification of the function of each of its three cysteine residues. Two have been found to participate in the formation of the intermolecular disulfide bridge that results in altered molecular conformation and the third is involved in mediating HmgB1 transfer in and out of the nucleus. Upon obliteration of that third cysteine, nucleocytoplasmic shuttling of HmgB1 no longer occurs.

“Understanding of the regulation of transcription in retinal photoreceptors is of interest as it may suggest strategies for regenerating photoreceptors that are being lost as a result of age or disease. Our finding that the expression of HmgB1 is under circadian control may suggest new concepts on its function,” Dr. Sears says.

References


Diverse Spectrum of New and Investigational AMD Therapies Target VEGF

Identification of the activity of vascular endothelial growth factor (VEGF) as a regulator of angiogenesis and vascular permeability and evidence of its role in the pathogenesis of exudative age-related macular degeneration (AMD) has led to the development of a number of pharmacologic approaches targeting VEGF as a new strategy to treat AMD.

In December 2004, pegaptanib sodium (Macugen) became the first anti-VEGF agent approved by the FDA for the treatment of wet AMD. An aptamer that acts to bind and inactivate VEGF, pegaptanib sodium was an exciting new modality because it received an indication for use in eyes with any subfoveal choroidal neovascular lesion, regardless of size, location or composition. Research with that compound is continuing, and an ongoing study is evaluating its role in combination therapy with verteporfin photodynamic therapy (PDT).

Now, FDA approval of a second anti-VEGF agent, ranibizumab (Lucentis), is here. Ranibizumab is an antibody fragment that binds VEGF, and in Phase III trials of patients with exudative AMD, it demonstrated impressive potential to improve vision rather than simply slowing its progressive loss.

Meanwhile, a host of other pharmacologic agents that act through diverse mechanisms of action to inhibit the activity of VEGF are in various stages of clinical investigation for the treatment of AMD-related choroidal neovascularization.

“There has been little to offer in the way of therapeutic intervention for patients who are losing their sight from AMD, and so it is very exhilarating to see this proliferation of clinical research focusing on AMD treatment. Considering the number of compounds now in clinical trials, their innovative mechanisms, their favorable safety profiles even with repeated treatments and the exciting responses that have been achieved with ranibizumab, this is certainly a hopeful and exciting time for patients affected with AMD and the physicians who treat them,” said Peter K. Kaiser, M.D., of Cleveland Clinic Cole Eye Institute.

In January 2006, Dr. Kaiser had the honor of being the first to present publicly the results from the Phase III Anti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in AMD (ANCHOR) study that demonstrated ranibizumab had activity for improving vision. After 1 year in that study, about 95% of patients treated with ranibizumab 0.3 mg or 0.5 mg had stable or improved vision (lost less than 15 ETDRS letters), and similar results were achieved after 1 year in the Phase III Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular AMD (MARINA) study. In ANCHOR, patients in the ranibizumab 0.3 mg and 0.5 mg groups had average vision gains of 8.5 letters and 11 letters, respectively, and almost 40% had a clinically significant improvement in vision (gain of 15 letters or more). Controls in ANCHOR received PDT. They experienced an average vision loss and only about 6% had a clinically significant improvement.

“The benefits achieved in this study using ranibizumab also occurred regardless of lesion subtype and translate into important effects on patient function and quality of life,” Dr. Kaiser says.

The Cole Eye Institute is also distinguished as the site of the first human treatment using a novel anti-VEGF approach based on synthetic small interfering RNA (siRNA) therapeutics. The compound being studied, SIRNA-027 (SIRNA), prevents expression of VEGF receptor-1 (VEGFR-1) by silencing the gene coding for that protein.

“The VEGFR-1 is stimulated by both VEGF and placental growth factor (PLGF), which may also play a role in angiogenesis and potentiate the activity of VEGF. By interfering with the action of all agonists for VEGFR-1, SIRNA-027 may offer a more powerful treatment modality than those approaches targeting only VEGF,” notes Dr. Kaiser.

Another siRNA (Cand5, Acuity Pharmaceuticals) is also under investigation at other centers. That agent blocks the formation of VEGF altogether, rather than acting to inhibit the activity of protein that has

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already been produced, and is showing promise in initial trials, Dr. Kaiser says. The Digital OCT Reading Center of the Cole Eye Institute serves as the reading center for the Candi5 clinical studies.

Cole Eye Institute is also participating in a Phase II study of intravitreal VEGF Trap (Regeneron) therapy. VEGF Trap is a fusion protein of key domains of VEGFR-1 and VEGFR-2 that acts as a receptor decoy for VEGF, “trapping” it with extremely high affinity to prevent its binding to the endogenous VEGF receptor.

“The mechanism of the VEGF Trap is somewhat analogous to ranibizumab, but the VEGF Trap may have the benefit of a longer duration of action due to its higher binding affinity. That potential is being tested in the ongoing trial,” Dr. Kaiser says.

Several companies are also developing small-molecule receptor tyrosine kinase inhibitors targeting VEGF receptors as a new approach to the treatment of exudative AMD.

Although no formal studies are under way, Dr. Kaiser and colleagues at the Cole Eye Institute are evaluating their experience with bevacizumab (Avastin) as a last-resort treatment for patients whose exudative AMD is refractory to other interventions. Currently available on the market as an intravenously administered agent with approval for the treatment of metastatic colorectal cancer, bevacizumab is being used in off-label fashion as an intravitreal injection in the treatment of exudative AMD.

For more information, contact Peter K. Kaiser, M.D., at kaiserp@ccf.org.
CSNB Mouse Models Provide Valuable Tool for Understanding Disease Pathophysiology, Developing Therapeutic Approaches

Congenital stationary night blindness (CSNB) is a rare heritable disease that manifests in various phenotypes, but all forms are characterized by a profound loss of vision in darkness. At Cleveland Clinic’s Cole Eye Institute, Neal S. Peachey, Ph.D., and coworkers have made significant advances in CSNB research based on their identification and characterization of naturally occurring mouse models for two forms of the human disease.

“As these animals provide accurate models of clinical CSNB, we believe that the anatomical, biochemical and functional observations made with them will have direct relevance to humans and that they will provide a valuable platform for future research aiming to develop targeted gene therapy,” Dr. Peachey says.

The first murine model of CSNB was discovered serendipitously in animals being used in an unrelated research project. Results of electoretinography (ERG) studies revealed the mouse had a normal a-wave but an absent b-wave, and thus it was named the nob (no b-wave) mouse.

“The ERG pattern in this animal is analogous to what is seen in patients with complete CSNB (CSNB1) and it indicates there is normal rod phototransduction function but a communication defect such that the photoreceptor cells are failing to activate the depolarizing bipolar cells,” Dr. Peachey explains.

Other studies identified that these animals were affected by the same X-linked inheritance pattern seen in humans with CSNB1, and work conducted in collaboration with researchers from the University of Louisville led to the determination that they also had a mutation in the nyx gene encoding for the protein nyctalopin.

Extensive histological studies have also been conducted using general light and electron microscopy to evaluate structures from the photoreceptors to the bipolar cells, but have found no morphological defects in the retina.

Current research is focusing on identifying the function of nyctalopin in the normal retina and in developing gene therapy approaches. Encouraging success has been achieved in rescuing the ERG defect in the nob mice by introducing a correct copy of the nyx gene. Those studies involved crossing nob mice with transgenically engineered mice expressing and transmitting nyctalopin.

“Our ability to achieve bipolar cell expression of nyctalopin in offspring of nob mice and rescue their ERG function has huge implications for human therapy. As we expect that the retina in patients with CSNB1 will be normal and that they too will have null mutations, they are likely to be very good candidates for gene therapy. In theory, therefore, if we can insert a normal copy of the protein into the retina, we should be able to restore night vision in these individuals,” Dr. Peachey says.

He acknowledges that the research in the mouse model has centered on turning the gene on during development. Ongoing studies are investigating whether it can be turned on after birth and at different stages of life.

The second mouse model of CSNB, known as the nob2 mouse, has abnormal light- and dark-adapted b-waves on ERG and so is similar to patients with incomplete CSNB (CSNB2). Genetic studies in those animals identified they had a CNS-specific deletion of the gene encoding for a subunit of the L-type...
钙通道，正常情况下调节视锥细胞末梢的谷氨酸释放。

形态学研究由Dr. Peachey和同事进行，他们发现外层突触层和外层环层的解剖异常，功能研究显示ON-中心细胞的动态范围减少，而不影响OFF-中心细胞的响应。进一步的研究集中在定义L型钙通道在斑片突触形成中的作用。

因为CSNB非常罕见，只有大约50万人才有1人，而且可能被误诊，所以关于受影响患者解剖缺陷的信息不足。迄今为止，只有从一个尸体样本中得出的发现，但这些观察的意义尚不确定，因为患者可能有未定义的CSNB形式和并发性青光眼，Dr. Peachey指出。

“我们希望现在使用高分辨率OCT进行患者这两类CSNB的详细解剖检查，看看这些解剖发现是否与我们在动物模型中做出的观察相符，”他总结道。

For more information, contact Neal S. Peachey, Ph.D., at peachen@ccf.org.
Despite advances in laser technology, clinically significant haze still develops in 2% to 4% of eyes undergoing PRK for the correction of higher levels of myopia. Various hypotheses have been put forth regarding the pathogenesis for haze formation, but no studies have produced definitive evidence to support any one theory.

Now, however, results of a study undertaken by Steven E. Wilson, M.D., and colleagues at the Cole Eye Institute are providing new understanding about the basic mechanisms for the development of haze after PRK.

In an elegantly designed experiment using a rabbit model, the researchers demonstrated conclusively that haze development after PRK was related to levels of stromal surface irregularity and anterior stromal myofibroblast generation. In addition, they showed haze formation could be mitigated by performing phototherapeutic keratectomy (PTK) smoothing after PRK and provided evidence that defective basement membrane regeneration in eyes with surface irregularity likely plays a role in the development of haze.

“It has always been suspected that haze develops after PRK because of the rough stromal surface that remains after the ablation, and there has been some indirect evidence to support that concept. The results of our study demonstrate unequivocally that it is critical to leave a smooth surface at the end of any surface ablation procedure, and they also support the use of PTK-smoothing to achieve that goal. Based on another study we will be reporting that investigated the long-term effects of mitomycin-C on stromal cells, PTK-smoothing is certainly an option to adjunctive mitomycin-C from a safety standpoint as a method for minimizing haze when performing PRK for higher corrections,” says Dr. Wilson.

The study divided rabbits into eight groups to receive no treatment, −4.5 D PRK, −4.5 D PRK with a fine mesh screen positioned in the path of the laser to create surface irregularity by blocking 10%, 30% or 50% of the terminal pulses, −4.5 D PRK with 50% irregularity followed by PTK smoothing, −9.0 D PRK or −9.0 D PRK with PTK smoothing. Haze was graded at the slit lamp after 4 weeks using a scale of 0 to 4.

Consistent with previous studies, the results of those evaluations showed haze was trace or absent in the eyes treated with the −4.5 D ablation whereas severe haze developed after the −9.0 D PRK. In the groups where the −4.5 D PRK was performed with the mesh screen in place for part of the procedure, the amount of haze present increased proportionally as the percentage of surface irregularity increased.

The effect of surface irregularity on haze development was also demonstrated by the findings in eyes that underwent PTK smoothing. In eyes that had a −4.5 D ablation with 50% irregularity, use of the PTK smoothing technique essentially mitigated haze development.
while PTK smoothing after the −9.0 D PRK treatment significantly reduced haze development, but did not eliminate it.

“The failure of PTK smoothing to prevent haze after the higher correction indicates that there must be additional factors besides stromal irregularity that contribute to haze development,” Dr. Wilson notes.

The rabbit study also confirmed that myofibroblast density was a key factor in producing corneal haze. Use of alpha-smooth muscle actin staining to identify myofibroblasts showed the density of those cells in the anterior stroma corresponded to the severity of haze.

“The relationship between haze severity and myofibroblast density makes sense since myofibroblasts are less transparent than keratocytes and also produce collagen and other stromal matrix components that are disorganized compared with components in normal stroma,” Dr. Wilson says.

Using high-power confocal microscopy and immunohistochemical staining techniques to examine the corneas in vitro at 4 weeks after PRK when the epithelium had healed, the researchers also identified residual ultrastructural defects in the basement membrane in eyes with surface irregularity and grade 1 or greater haze, along with localization of the myofibroblasts beneath those breaks in the basement membrane.

“The finding of imperfect regeneration of the basement membrane is perhaps the most important finding of this study because it can be used to explain why higher PRK corrections are associated with more haze. Our study suggests that phenomenon occurs because the higher correction produces more surface irregularity that translates into structural and/or functional basement membrane anomalies and greater potential for transforming growth factor-beta, and perhaps other cytokines, to penetrate into the stroma from the overlying epithelium to stimulate myofibroblast generation from stromal fibroblasts,” Dr. Wilson says.

The study also provided evidence that late apoptosis of the myofibroblast cells may be a key mechanism for the disappearance of post-PRK haze over time.
Corneal Biomechanical Clues Studied to Optimize Results of Intrastromal Ring Segment Surgery

A number of studies demonstrate that insertion of intrastromal ring segments (Intacs, Addition Technology) can be a useful procedure to reduce corneal irregularity, improve vision and delay or avoid the need for corneal transplantation in eyes with keratoconus and other ectatic disorders. However, the mechanisms mediating the effect of the intrastromal ring segments on corneal curvature are not fully understood, and topographic and visual outcomes can be less predictable than desired. Therefore, identification of prognostic factors for determining the treatment response would be a welcome advance for optimizing surgical decision-making.

Since placement of the ring segments presumably works via a biomechanical effect, William J. Dupps, Jr, M.D., Ph.D., and Bennie H. Jeng, M.D., at Cleveland Clinic’s Cole Eye Institute are studying whether there is any correlation between preoperative corneal biomechanical properties and surgical outcome. Based on the hypothesis that stiffness of the cornea may be an important variable affecting the response to segment placement, they are using non-invasive ultrasound elastometry (Sonic Eye, Priavision) to measure stiffness in various locations across the cornea in normal donor eyes prior to and after Intacs placement surgery.

“We believe patients with keratoconus represent a very heterogeneous group both biologically and biomechanically. As a result, it is difficult to predict with high confidence the response any given patient will have topographically to segment insertion,” says Dr. Dupps.

“Identifying features that predict the flattening response to intrastromal segments could help surgeons to select candidates most likely to benefit from the procedure and also provide a guide for surgical dosing, which is a function of ring diameter, channel diameter, segment thickness and channel depth,” he continues.

The prototype elastometer they are using to investigate corneal stiffness consists of a handheld probe with a resonant element and receiver spaced 4.5 mm apart. It measures the “time-of-flight” in velocity units (meters per second) for propagation of a low-frequency ultrasonic stimulus. Wave velocity is a marker for corneal stiffness because the speed of a sound wave increases with increasing rigidity of the medium. Dr. Dupps and co-investigators at the Cole Eye Institute have a scientific manuscript in press describing the technique and illustrating its potential utility in a variety of clinically important situations.

“This technology is noninvasive and has the advantage of being able to measure regional and directional differences in stiffness,” says Dr. Dupps.

Using a template Dr. Dupps devised in early studies with the device, measurements are acquired along 10 corneal vectors, including the horizontal and vertical vectors at the center of the cornea, radial vectors in all four peripheral quadrants and circumferential vectors just anterior to the limbus of the same quadrants. Average velocities were calculated for the central, radial and circumferential regions and analyzed for correlations to the surgical curvature change measured from intraoperative topography maps.

So far, an analysis of one ring segment size has been performed in a small subset of three human globes maintained at a physiological IOP of 15 mm Hg and with corneas that were restored to normal thickness with hyperosmotic solution. Measures of corneal stiffness (surface wave velocity) and corneal curvature (Keratron Scout topography) were obtained prior to surgery and after placement of two 0.45-mm segments through a superior incision at 12 o’clock. Both the incision and channels were created using the standard Intacs surgical kit.

The results showed a correlation between the surgical change in simulated keratometry values and the preoperative stiffness in the radial mid-peripheral vectors such that the flattening effect was greater when preoperative stiffness was higher. No relationships were found between central and circumferential

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stiffness measurements and curvature response to intrastromal segment implantation.

“It is logical that the region of the cornea that was found to be predictive of response directly straddles the site of channel insertion. In other words, the mechanical properties of the tissue closest to the inserts seem to be most important in predicting surgical response. These findings are very preliminary; they are based on a small number of non-keratoconic donor eyes and account only for the acute biomechanical changes associated with surgery. But continued experimentation in this vein may provide us with predictive information for planning surgery that we simply didn’t have before,” Dr. Dupps says.

As a caveat, Dr. Dupps also notes that previous research with the elastometer indicates that posterior corneal properties may be relatively underrepresented in the measurements it produces. Furthermore, clinical measurement of corneal stiffness by this technique involves additional challenges, including a tendency toward much lower wave velocities in the presence of a normal tear film.

“We are actively investigating technique and instrument modifications to overcome these issues and are fortunate to have the support of both Addition Technology and PriaVision in this venture,” says Dr. Dupps.
Autologous Serum Eyedrops May Offer Effective Therapy for Patients with Intractable Ocular Surface Disorders

Treatment of severe ocular surface disorders remains a challenge, and in some patients, the disorder is refractory to conventional interventions. For them, Cole Eye Institute ophthalmologist Bennie H. Jeng, M.D., has found that the topical use of autologous serum is a safe and often highly effective modality for affording symptomatic relief and/or promoting ocular surface healing.

Relative to tears, autologous serum contains a similar spectrum of growth factors, vitamins and immunoglobulins that have positive epitheliotropic activity, and the concentrations of some of those components in autologous serum exceeds that found in tears. Over the past 2 years, Dr. Jeng has used autologous serum eyedrops to treat approximately 25 patients with a variety of ocular surface conditions that were intractable to more conventional therapies. The diagnoses in those patients included persistent epithelial defects secondary to a variety of etiologies as well as severe, chronic dry eye, often associated with chronic graft-versus-host disease. Some patients with recurrent erosion syndrome are also candidates for treatment with autologous serum eyedrops.

Follow-up in those cases showed that improvement, measured as a reduction in symptoms and/or as epithelial repair, occurred fairly rapidly, within the first few weeks of treatment, while complete healing of epithelial defects was observed most of the time within 4 weeks. Overall, the efficacy rate for autologous tears has been 80% to 90%, reports Dr. Jeng.

“While that still leaves us with a 10% to 20% failure rate, considering that these are intractable cases of eyes that have otherwise reached the end of the therapeutic line, the outcomes achieved with autologous tears are really quite impressive,” he says.

Candidates for this experimental therapy are screened to exclude people with hepatitis or HIV infection. Eligible patients have their blood drawn at Cleveland Clinic. The sample is then spun down, and the separated serum is shipped to a pharmacy in California for further processing and purification. The prepared autologous serum eyedrops are shipped to the patients’ homes packaged in small containers that are kept frozen until time for use.

In recent years, there has been an increase in reports in the literature describing autologous serum eyedrops as a treatment for ocular surface disorders. The majority of those investigators have used autologous serum that has been diluted to 20% with the addition of normal saline. However, Dr. Jeng has the pharmacy prepare a 50% autologous serum formulation for his patients.

“Not only does this provide a higher concentration of the epitheliotropic factors, but it is also more viscous, and that thicker consistency offers an additional soothing effect when instilled into the eye,” he says.

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Patients are usually instructed to begin treatment with instillation every 2 hours, and then the frequency of administration is titrated to response. Once there is some onset of effect, dosing is reduced to four times a day and it can be further reduced as healing occurs. In patients who were being treated for persistent epithelial defects, no recurrences have been observed during follow-up of 6 to 12 months after treatment discontinuation. Patients using the autologous serum for dry eye relief continue maintenance therapy indefinitely.

Treatment with the autologous serum eyedrops has had an excellent safety profile. The drops are well tolerated, and so far there have been no cases of secondary infectious keratitis or any other adverse events.
Accurate IOL power prediction for eyes undergoing a triple procedure with penetrating keratoplasty (PK), cataract extraction and IOL implantation presents a challenge because the preoperatively measured biometric data used for power calculation can be significantly altered by the surgery. Nevertheless, the predictability of refractive outcomes can be improved if surgeons analyze their outcomes to determine average postkeratoplasty keratometry values and personalized A-constants for use in IOL power calculations.

Following that approach, Cole Eye Institute surgeon Roger H. S. Langston, M.D., was able to achieve good refractive results when performing a triple procedure with lens removal by extracapsular cataract extraction (ECCE). However, when he switched to phacoemulsification, he encountered some surprises in postoperative K values that were associated with a poor refractive result.

Now, Dr. Langston is further investigating his outcomes after combined PK/phaco/IOL implantation to try to identify factors and techniques that could improve the accuracy of IOL power calculation. However, his experience provides a cautionary note to colleagues who may also be switching from ECCE to phacoemulsification.

“Surgeons need to be aware that despite its advantages, changing from ECCE to small-incision cataract surgery can alter the average corneal power after a triple procedure. It is important to analyze one’s outcomes carefully,” says Dr. Langston.

Weighing the risk of inaccurate IOL power calculation, he suggests that it may also be worthwhile to consider consecutive rather than simultaneous surgery, allowing the cornea to heal after PK before going back to do the cataract procedure and IOL implantation.

“Of course, the liability of the staged approach is that it exposes the patient to the risks of a second procedure and significantly delays visual rehabilitation since one must wait until after the graft sutures are removed to assure corneal curvature stability. However, the pros and cons of both simultaneous and staged surgery should probably be discussed with patients, who can then make their own informed decision,” Dr. Langston says.

He compared his outcomes of triple procedures performed with ECCE or phacoemulsification in a retrospective study including eyes that underwent corneal transplantation for Fuchs’ dystrophy. There were 22 cases performed with ECCE and 16 performed with phacoemulsification. In the ECCE eyes, the postoperative K value averaged 47 D and ranged from 44.75 to 50.0 D. Mean astigmatism was 5 D with a range from 0 to 12 D.

In the phacoemulsification group, mean astigmatism was 3.7 D with a range of 0 to 7.5 D. However, in analyzing the K values, Dr. Langston found the corneas were flatter overall (range 39.25 to 48.5 D) and on average (mean K 45.4 D), and two eyes in particular had a corneal power much lower than anticipated.

As a result, the refractive predictability was worse in the eyes that underwent phacoemulsification. While 19 of the 22 eyes (86%) that had the triple procedure with ECCE were within 2 D of their intended SE target, only 9 of the 16 eyes (56%) undergoing phacoemulsification had an achieved SE within that range.

There are a number of factors that can influence the corneal curvature outcome after a triple procedure. However, recognizing that IOP affects tissue response during trephination, Dr. Langston has hypothesized that his experience may be explained by increased IOP variability after phacoemulsification compared with ECCE.

“Based on that concept, I started to measure IOP after completing the phaco procedure and confirmed there was significant variation,” Dr. Langston says.

Currently, he is applying a Honan balloon as he would in eyes undergoing ECCE in an effort to control IOP, and will be analyzing his outcomes to see if that technique is beneficial for limiting variation in corneal curvature outcomes and improving refractive results.
Artificial Cornea Provides Hope for Sight in Patients with No Alternatives

With advances in device design, surgical technique and postoperative management, keratoprosthesis implantation has become a viable approach for attempting to restore vision in eyes that are at high risk for corneal transplantation.

Of the several types of keratoprostheses that are commercially available, the Boston keratoprosthesis developed by Claes Dohlman, M.D., Ph.D., professor emeritus of ophthalmology, Harvard Medical School, is the most widely used in the United States. Cole Eye Institute corneal surgeon Victor L. Perez, M.D., completed his fellowship training with Dr. Dohlman and has been performing implantation of both the type I and type II Boston keratoprostheses at Cole for 3 years. To date, he has treated six eyes, and the results have been encouraging with respect to both safety and visual rehabilitation.

“As my experience with these procedures increases, so too has my level of comfort for using this approach in appropriate candidates. Now, the keratoprosthesis has become an important part of my armamentarium for trying to provide a clear window for vision in patients with a history of multiple graft failures,” Dr. Perez says.

One of the most satisfying cases undertaken so far involved a Russian radiologist who, while living in that country, suffered corneal burns in both eyes as a result of having lye thrown at his face. The patient developed severe corneal melts and was treated by a Russian ophthalmologist with permanent tarsorrhaphy.

He presented to Dr. Perez several years later, after moving to the United States. An ultrasound study revealed that the eyes were present in the orbit and that the retinas were attached. Therefore, Dr. Perez proceeded to open the tarsorrhaphy in the right eye for further evaluation, but was unable to find the anterior segment.

“It was clear to me that the only intervention that might help this man was to implant the type II Boston keratoprosthesis and attempt to provide a tunnel for vision through the lid,” he says.

Due to the excessive scar tissue present, the implantation surgery was lengthy and challenging. However, Dr. Perez was successful in implanting the type II keratoprosthesis and placed a glaucoma shunt as well. He reports that the patient has done well postoperatively and now has vision of 20/100.

“For the first time, this gentleman has been able to see his grandchildren who were born after his accident, and he is able to read again. So far so good as far as safety is concerned as well, but we are proceeding with very cautious optimism because these are such complicated cases,” Dr. Perez says.

Most of the Boston keratoprosthesis procedures performed by Dr. Perez involved the type I device. In that series of eyes, he has not encountered any significant complications, such as corneal melt, device extrusion or endophthalmitis. Visual outcomes have been limited by macular potential.

“These patients tend to have multiple ocular abnormalities that limit their visual potential. At least, however, the keratoprosthetic surgery provides an opportunity to restore some functional vision,” Dr. Perez says.

Since retinal conditions are often present in patients who come for keratoprosthesis surgery, a team approach with an experienced retinal surgeon is also important to optimize outcomes.

“We want to try to offer these patients the best possible vision, and we are fortunate at the Cole Eye Institute to have talented retinal surgeons who can collaborate in these procedures,” Dr. Perez says.

Historically, success with keratoprosthetic surgery has presented a difficult challenge. Biocompatibility between the prosthetic device and the corneal tissue and avoidance of device extrusion and corneal melts have presented a major obstacle. However, Dr. Dohlman made a significant contribution to addressing those problems with his design of the two-plate keratoprosthetic device that allows nutrients from the anterior chamber to interface with the cornea. Recognizing that it was also important to maintain a moist surface, Dr. Dohlman introduced the idea of covering the eye with a bandage contact
lens. That technique has also been important in reducing postoperative degradation of the cornea and the prosthesis.

Based on Dr. Dohlman’s suggested postoperative management scheme, patients who undergo keratoprosthesis implantation at Cole Eye Institute are treated with routine topical antibiotics to prevent infection.

“This strategy is somewhat controversial, but with its use, the risk of endophthalmitis has been markedly diminished,” Dr. Perez says.

Comanagement of glaucoma is another important consideration in these eyes. Many patients have glaucoma already or are at risk for developing it because keratoprosthesis implantation changes the anatomy of the angle. For that reason, an aggressive approach to IOP control is taken with implantation of glaucoma devices at the time of the keratoprosthesis procedure in eyes with advanced existing glaucoma or those considered to be at high risk.
Simultaneous Penetrating Keratoplasty/Pars Plana Vitrectomy/Glaucoma Implant Surgery Yielding Encouraging Outcomes

Uncontrolled glaucoma is an occasional comorbid finding in patients with corneal disease who are candidates for penetrating keratoplasty. Placement of a glaucoma drainage implant has become a valuable option for maintaining IOP in these challenging cases. However, the presence of a glaucoma implant tube in the anterior chamber has also been associated with an increased risk for graft failure.

At the Cole Eye Institute, glaucoma specialist Edward J. Rockwood, M.D., has been collaborating with corneal transplant surgeon David M. Meisler, M.D., and vitreoretinal specialists Jonathan E. Sears, M.D., and Peter K. Kaiser, M.D., to perform a simultaneous procedure combining penetrating keratoplasty, pars plana vitrectomy and placement of the glaucoma implant tube through a pars plana sclerotomy. They have accumulated eight eyes in their combined procedure series so far with follow-up ranging from a few months to up to 3 years.

“It is critical to achieve and maintain good IOP control in eyes undergoing penetrating keratoplasty because both elevated IOP and any need for additional glaucoma surgery increase the risk of graft failure. For some patients, a glaucoma implant has been the best choice for achieving that goal, and our outcomes with posterior implant tube placement in this small series of cases have been very encouraging in terms of successful IOP control with reduced need for glaucoma medications and maintenance of graft clarity,” says Dr. Rockwood.

In the combined procedure, Dr. Rockwood first places the glaucoma implant but without inserting the tube in the vitreous. Then the retina specialist performs the vitrectomy with scleral depression to remove as much of the vitreous base as possible in the planned quadrant of the implant tube insertion, usually supero-temporal. Next, the cornea surgeon takes over to perform the transplant, and finally Dr. Rockwood steps in again to insert the glaucoma implant tube, place a preserved pericardial graft over the tube and close the conjunctiva. The glaucoma implant tube is passed through a 23-gauge needle tract at a location about 3.5 mm posterior to the limbus.

“In some patients with significant corneal edema that precludes good surgical visualization, a keratoprosthesis will be placed temporarily after insertion of the glaucoma implant to enable vitrectomy. Once that portion of the operation is completed, the cornea surgeon removes the keratoprosthesis and places the corneal graft tissue,” Dr. Rockwood says.

Since undertaking the triple procedure a few years ago and based on additional experience with combined glaucoma implant surgery and pars plana vitrectomy in other eyes, the surgeons have introduced a number of modifications to their technique that have proven useful for minimizing complications postoperatively, and particularly serious posterior segment events. For example, in order to lessen the risk of hypotony and the associated potential in these vitrectomized eyes for choroidal effusion and suprachoroidal hemorrhage, Dr. Rockwood now uses only a valve-style glaucoma implant in the combined procedures.

The vitrectomy technique has also been refined to ensure adequate removal of the vitreous near the planned site of tube insertion to reduce the risk of vitreous incarceration and tube obstruction. In addition, it has been found best to leave the tube long (at least 3-4 mm) in the vitreous. While too long a tube in the anterior chamber can cause problems, it has not been a problem in the vitreous and may reduce the risk of vitreous obstructing the tube, notes Dr. Rockwood.

“By reducing complications, these refinements have also been important for eliminating the need for further surgical intervention and its related morbidity,” he adds.

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NEI-Sponsored Study Evaluating Role of Primary IOL Implantation in Infants with Unilateral Congenital Cataract

Primary IOL implantation has become generally accepted as the standard of care for achieving visual rehabilitation after cataract surgery in older children. In infants, however, although use of primary IOL implantation has been increasing at some centers, the procedure remains controversial, particularly because of the paucity of data on long-term risks. As such, contact lenses are still considered the gold standard for visual rehabilitation after cataract surgery in children less than 1 year of age.

However, contact lens wear has its own limitations. According to some available data, when it is used in infants after removal of a unilateral congenital cataract, a significant proportion of children remain legally blind in their aphakic eye as a result of competition from the sound eye and contact lens compliance issues.

Now, in order to define better the benefits and risks of primary IOL implantation in infants with unilateral congenital cataracts, the National Eye Institute of the National Institutes of Health is sponsoring the Infant Aphakia Treatment Study (IATS), a multicenter, randomized clinical trial comparing primary IOL implantation with contact lens wear. Cleveland Clinic’s Cole Eye Institute is one of only 12 sites nationwide participating in that study. Pediatric ophthalmologist Elias I. Traboulsi, M.D., is the principal investigator at Cole.

“IOL implantation is doable in these very small eyes, but technically challenging, and a pilot study found that secondary surgery was often needed to remove proliferating lens material. However, by providing immediate visual rehabilitation with an implant and eliminating potential problems with contact lens use, it is hoped primary IOL implantation can provide better visual outcomes and reduce caregiver stress. We are looking forward to the results of this trial that will show us whether there are advantages that offset the limitations,” Dr. Traboulsi says.

Enrollment in the study began in early 2005 and is planned to occur over a 4-year period. To be eligible, infants must be 28 to 210 days of age with a visually significant, monocular, congenital cataract. The surgery in all patients involves lensectomy, posterior capsulotomy and anterior vitrectomy. For children in the implant group, the IOL will be placed in the capsular bag and spectacles prescribed to correct residual refractive error. Protocols for patching and follow-up after surgery are identical for the two study groups, and all functional assessments and safety evaluations are being performed by a traveling vision examiner.

So far, the Cole Eye Institute has been one of the more active IATS sites, enrolling five patients as of May 2006. Recruitment, however, is difficult because unilateral congenital cataract is a relatively rare condition, notes Dr. Traboulsi.

“Since these patients are uncommonly encountered, we are very dependent on referrals to enroll participants in this trial. We are very grateful to the physicians who have referred patients to us so far, and we strongly encourage others to contact us if they are caring for or aware of a child who might be a candidate for this study,” he says.

Dr. Traboulsi has been performing primary IOL implantation after cataract surgery in infants for several years. A few years ago at an annual meeting of the Association for Research in Vision and Ophthalmology, he reviewed that experience in a series of 34 eyes of 23 patients who underwent lens extraction prior to 2 years of age for unilateral or bilateral cataracts. Twenty-five (78%) of the procedures were performed when the child was younger than 20 weeks. Eighteen (56%) of the eyes received an in-the-bag IOL at the time of cataract extraction.

“There were no significant intraoperative complications whether or not an IOL was implanted primarily. Notably, however, there were no cases of glaucoma among the IOL recipients during follow-up extending to 4 years, whereas glaucoma developed in three eyes of two patients who did not have an IOL implanted.

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That latter observation is consistent with previous studies of infants who have undergone surgery for congenital cataracts without IOL implantation,” Dr. Traboulsi says. However, he notes the findings from his review must be considered against the limitations of the study, which was retrospective and not randomized.

“The safety and benefits of primary IOL implantation in infants need to be confirmed in the ongoing, prospective IATS study,” Dr. Traboulsi says.
Case Study: Five-Month-Old Boy Presents with Incomitant Esotropia

By Evelyn Fu, M.D., and Elias I. Traboulsi, M.D.

A 5-month-old boy with no significant ocular history presented to Cleveland Clinic Cole Eye Institute with esotropia of the right eye for 1 month. No other visual symptoms were noted. His medical history revealed a recent episode of otitis media treated with antibiotic eardrops. He was born at full term via vaginal delivery without perinatal complications. Review of systems is significant for episodic nonprojectile vomiting with increasing frequency that began one week prior to presentation. Family history is positive for hypertension and aortic dissection in paternal great-grandfather and grandfather.

On examination, the boy appears well nourished and developed. He fixes and follows well with both eyes. There is a moderate esotropia of the right eye in primary gaze that increases on right gaze and decreases on left gaze. The degree of esotropia is equal at distance and near. There is severe limitation in abduction of the right eye beyond midline. Globe retraction is not noted in adduction. The pupils are equal, round and reactive to light without an afferent defect. Slit-lamp examination and dilated ophthalmoscopy are normal in both eyes. The remaining medical and neurological examination is normal.

Differential Diagnosis
Incomitant esotropia describes an inward deviation of the eye that varies in different fields of gaze. It results from a variety of etiologies including sixth-nerve palsy, Type I Duane syndrome, divergence insufficiency and orbital blowout fracture with restriction of the lateral rectus muscle. Patients with Type I Duane syndrome have poor abduction with globe retraction in adduction. Divergence insufficiency is characterized by esotropia that is greater at distance than at near. Further, the deviation does not change with vertical or horizontal gaze. Our patient’s symptoms and signs are most consistent with an isolated sixth-nerve palsy.

Diagnosis
The most common causes of sixth-nerve palsy in children are trauma and intracranial lesions. In the absence of trauma, a full neurological evaluation including neuroimaging is recommended. On head CT, a 2.6-cm hyperdense mass was noted in the right middle fossa with remodeling of the adjacent sphenoid body and greater wing (Figure 1). CTA and MRI demonstrated characteristics of a giant thrombosed aneurysm of the cavernous internal carotid artery, without compression of the optic nerve or chiasm (Figure 2). The diagnosis was a giant intracavernous carotid artery aneurysm (ICCAA).

Discussion
ICCAAs are extremely rare in the pediatric population. Information regarding the natural history, pathogenesis, radiographic features, treatment and prognosis are derived from large case series of adult patients. Symptoms from ICCAA can be divided

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into two categories: vascular and compressive. Vascular symptoms include subarachnoid hemorrhage, carotid-cavernous fistula, epistaxis, subdural hematoma and embolic or ischemic events. Compressive symptoms are caused by pressure of the aneurysm wall on surrounding structures and depend on the initial location, size and direction of growth.

Ophthalmically anterior and lateral extensions may result in superior orbital fissure syndrome and cavernous sinus syndrome, respectively. Hahn et al. reported patients often complain of diplopia (89%), retro-orbital pain (61%), headache (19%), blurred vision (14%) and photophobia (4%).

Common presenting signs include partial ophthalmoplegia (77%), ptosis (51%), decreased visual acuity (12%), complete ophthalmoplegia (16%), proptosis (7%) and visual field defects (7%). Isolated cranial nerve palsies most frequently occur in the sixth nerve (39%) because it is anatomically closest to the artery, follow by the third nerve (11%). Fourth-nerve palsy has not been reported. The mechanisms of cranial nerve palsies are believed to result from direct compression or acute ischemia secondary to occlusion of the cavernous sinus arterial branches supplying the cranial nerves.

Spontaneous improvement and complete resolution are often noted. Nguyen et al. reported a case of 60-year-old woman with recurrent episodes of isolated sixth-nerve palsy as a result of ICCAA. Mortality of ICCAA is low and spontaneous rupture is rare. Surgical intervention is reserved for complications of vascular rupture, progressive ophthalmoplegia, visual loss and radiographic evidence of enlargement and extension into the subarachnoid space.

Our patient is being followed closely with frequent neuroimaging. His right eye is being patched 2 hours per day to avoid amblyopia.

References


Study Investigates Risk Factors for Choroidal Melanocytic Lesion Growth

Clinical distinction between a choroidal nevus and small choroidal melanoma may be difficult, and patients who are diagnosed as having a choroidal melanocytic lesion may become confused as they seek several opinions and get conflicting information about diagnosis and management.

The identification of parameters that could improve the diagnosis and management of choroidal melanocytic lesions represents a major research interest of Arun D. Singh, M.D., Director, Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic. In a recently published paper [Ophthalmology, June 2006], Dr. Singh reported the findings of a study he undertook to characterize baseline features of small choroidal melanocytic lesions that were predictive of growth.

The study had a retrospective observational case series design and included 240 patients, mean age 62 years, with a presumptive diagnosis of a small choroidal melanocytic lesion who underwent observational management. During a mean follow-up of 3.3 years, tumor growth occurred in 11 (4.6%) patients, and most of those events occurred within the first 33 months after initial recognition. Univariate analyses identified lesion thickness, location in relation to the foveola, gender and presence of symptoms and orange pigment as significant predictors of growth risk.

“The ability to differentiate choroidal nevi from small choroidal melanoma is an important clinical issue. Currently, tumor growth over a short period is used to make that distinction, and so frequent careful observation is recommended to document changes in lesion size. However, better information is needed about the risk of tumor growth and prognostic factors for that occurrence. Our study provides some insight as to features of small choroidal melanocytic lesions that are associated with a higher risk of growth. However, a large multicenter, prospective study is needed to provide definitive answers for improving risk stratification,” says Dr. Singh.

The patients included in the study had lesions measuring between 1.0 and 3.5 mm in height and/or between 1 and 15 mm in largest basal diameter without prior growth, chose observation for growth as their management, and were followed for at least 12 months. Tumor growth was defined as increase in size of 0.3 mm or greater in any dimension based on comparisons of fundus drawings, fundus photographs and ultrasound A and B scans.

Comparisons of the groups with and without tumor growth showed the factors associated with the greatest relative risk (RR) for growth were presence of orange pigment (RR = 9.6), tumor height ≥2 mm (RR = 8.2) and juxtapapillary location (<3 mm to the foveola; RR = 6.3). In addition, presence of symptoms was associated with a nearly fivefold increase in risk of growth, and males were about three times more likely to experience tumor growth compared with females. In a forthcoming companion paper, Dr. Singh also reports that findings of angiographic studies using indocyanine green may have relevance in predicting growth.

Dr. Singh acknowledges that this study has limitations because of its retrospective design and exclusion of patients who were seen during the study period but chose to undergo treatment rather than observation. In addition, only univariate analyses could be performed because the study sample included only a small number of tumors demonstrating growth. Furthermore, there may be some referral bias in this population of patients seen at a tertiary ophthalmic oncology clinic.

“Nevertheless, the findings in this study are consistent with previous investigations of risk factors for choroidal melanocytic lesion growth and provide some useful information to clinicians as they attempt to determine growth potential of a newly recognized tumor,” Dr. Singh says.

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Customized Re-treatment Can Provide a Solution When 20/20 Is Not Good Enough

The development of wavefront-guided custom corneal ablation has led to significant improvements in the efficacy and predictability of laser vision correction surgery. However, wavefront-guided treatment is also proving to be a feasible method for enhancement in select patients who achieve 20/20 uncorrected visual acuity (UCVA) after LASIK but are unhappy because of quality-of-vision issues, says Ronald R. Krueger, M.D., medical director of the Department of Refractive Surgery at Cleveland Clinic’s Cole Eye Institute.

“UCVA measured on a high-contrast Snellen acuity chart has been the standard measure for assessing outcomes after refractive surgery, but the advent of wavefront aberrometry has led us to appreciate that it is not always an accurate gauge of quality of vision. Using wavefront devices to measure the optical quality of the eye, we now understand that 20/20 or even 20/15 UCVA is sometimes not good enough because patients can be emmetropic and have excellent visual acuity but still suffer debilitating visual symptoms as a result of higher-order aberrations induced by their surgery,” Dr. Krueger explains.

“While historically we would avoid treating any eye that is 20/20, using a wavefront-guided retreatment, we can sometimes selectively address the higher-order aberrations underlying a patient’s complaints to provide those individuals with the quality of vision they desire,” he continues.

In a study undertaken a few years ago in which more than 100 post-LASIK eyes were evaluated with the LADARWave aberrometer (Alcon), Dr. Krueger and colleagues found statistically significant correlations between certain higher-order aberrations and particular visual symptoms. For example, patients who had high levels of horizontal coma suffered with double vision while spherical aberration was associated with complaints of halos, glare and starburst.

Subsequently, Dr. Krueger has used the CustomCornea system (Alcon) to perform an “upgrade treatment” in about 30 eyes that were 20/20 after LASIK but symptomatic. The primary treatment in most of those eyes was done with a conventional LASIK procedure, but there were some cases that had wavefront-guided ablations, primarily. For the vast majority of patients, the custom enhancement procedure has resulted in a very good outcome. The following is a description of an illustrative case.

A 37-year-old female pharmacist presented to the Cole Eye Institute with complaints of poor vision in dim light, with the right eye being worse than the left, along with bothersome glare and halos when driving at night. She originally had a spherical error of about −5.0 D in both eyes and had undergone LASIK 5 years earlier at another refractive surgery center followed by a bilateral enhancement about 1 year ago. At presentation, her right eye was −0.25+0.25 × 88° and 20/20+1 UCVA. Her left eye was plano with UCVA of 20/15–2. A few dry spots were noted on her cornea, but otherwise her ophthalmic exam was unremarkable and showed normal pupils and corneal thickness for post-LASIK eyes. Corneal topography revealed slight irregularity and asymmetry in the previously treated central area (Figure 1a), and wavefront aberrometry showed higher levels of coma and spherical aberration that were consistent with her vision complaints (Figure 1b).

After a thorough discussion of the potential risks of yet another re-treatment, the patient chose to undergo the custom upgrade procedure in the right eye. On the first postoperative day, the eye was 20/20 uncorrected and the patient was extremely happy with her vision. Aberrometry revealed her refraction was close to plano and showed significant improvement in the higher-order aberrations. At day 7 postop, the vision was −0.25 D by manifest refraction and 20/20. After dilation, the eye measured +0.50 D and 20/15–1. Coma and spherical aberration had both decreased by at least 50%. The exam findings at 1 month were similar, and the patient was still very pleased with her outcome.
However, a few months later she returned, complaining that she was still having difficulty with vision at night in her left eye. Dr. Krueger dissuaded the patient from having a custom upgrade in that eye with 20/15 UCVA, but she returned 2 months later determined to have surgery. Still reluctant, Dr. Krueger proceeded to do a preoperative work-up that revealed abnormally high levels of coma and spherical aberration. A carefully planned ablation was performed with a good result. At 1 week and 6 weeks, aberrometry showed a refraction of −0.25 D with the level of coma reduced by about one-third and spherical aberration reduced by about 50%. Complaints of starburst and glare at night were markedly improved, and the patient was very happy with her vision in both eyes.

**Note of caution**

Although the outcome in this case and others has been favorable, Dr. Krueger warns that in eyes in which there is minimal refractive error, the custom re-treatment needs to be carefully planned to avoid a spherical overcorrection that can leave the patient even more unhappy.

“When correcting higher amounts of higher-order aberrations, it is important to incorporate an offset into the ablation that will compensate for the relatively large amount of treatment that is delivered. Unfortunately, we have seen several patients treated elsewhere with a custom enhancement whose vision has been massively overcorrected,” Dr. Krueger says.

**WR: +0.38–0.57x09**

- Coma=0.76 µm
- Sph Ab=0.78 µm
- Other=0.26 µm
Corticosteroid treatment has long been a mainstay of therapy for uveitis, and until recently, most patients with vision-threatening posterior, intermediate and panuveitis were treated with systemic anti-inflammatory therapy using corticosteroids and/or steroid-sparing immunosuppressive medications.

Given the serious systemic side effects associated with those modalities, the approval of the intravitreal fluocinolone acetonide implant (Retisert, Bausch & Lomb) for the treatment of chronic, noninfectious posterior uveitis represented a significant advance because it afforded long-lasting, effective disease control without extraocular toxicity. Nevertheless, these benefits were not achieved without risks.

“In the premarketing clinical trials, nearly two-thirds of patients who received the implant required IOP-lowering treatment, about one-third had to undergo glaucoma surgery and nearly all phakic eyes developed cataracts that required removal,” explains Cole Eye Institute ophthalmologist Careen Y. Lowder, M.D., Ph.D.

Now, the Cole Eye Institute is one of the clinical sites participating in two recently launched multicenter studies that are evaluating the efficacy and safety of a dexamethasone posterior segment drug delivery system (Posurdex, Allergan) for the treatment of noninfectious anterior and intermediate uveitis. Dr. Lowder and other investigators in those trials are hopeful that this sustained-release corticosteroid will also prove effective for reducing inflammation while offering a better ocular safety profile than the fluocinolone acetonide implant.

Results of a Phase II trial investigating the dexamethasone posterior segment drug delivery system for the treatment of cystoid macular edema (CME) provide evidence of its potential efficacy in the treatment of uveitis, notes Dr. Lowder.

That study included 39 patients with CME associated with uveitis. Analyses of vision outcomes showed that at 2 months after randomization, approximately 60% of patients who received the 350 or 700 µg dexamethasone implant achieved a 10-letter-or-greater improvement in best corrected visual acuity (BCVA) compared with only about 21% of those in the observation control arm. By 6 months after implantation, 42% of patients in the 350-µg implant group and 46% of those in the 700-µg group maintained a 10-letter-or-greater improvement from baseline in BCVA compared with only 21% of patients in the observation group.

“In contrast to the fluocinolone device that released corticosteroid for a period of almost 3 years, the biodegradable dexamethasone implant was formulated specifically for use in the eye and releases medication for only about 3 months. We hope that duration of treatment will be adequate to control the ocular inflammation but be short enough that it will be associated with lower risks of glaucoma and cataractogenesis compared with the longer-lasting fluocinolone implant,” Dr. Lowder says.

Both the anterior uveitis and intermediate uveitis studies are masked, have a planned 26-week duration and will randomly assign patients equally to three arms to receive one of two doses of the dexamethasone posterior segment drug delivery system (350 µg and 700 µg) or sham treatment with a needleless applicator system. The primary efficacy assessment will be performed after 6 weeks in the anterior uveitis study and after 8 weeks in the intermediate uveitis study, and will be based on anterior chamber cells (anterior uveitis) and vitreous haze (intermediate uveitis) using standardized grading scales.
Each trial will enroll 189 adult patients with a diagnosis of non-infectious uveitis in at least one eye based on criteria established in the Standardization of Uveitis Nomenclature Working Group classification report. To be eligible, patients with intermediate uveitis must have vitreous haze of at least +2 and a Snellen equivalent BCVA of 20/40 to 20/200 in the study eye. Patients with anterior uveitis must have persistent inflammation for more than 3 months and an anterior chamber cell score of at least +2.

Patients taking stable regimens of topical steroids, topical NSAIDs, systemic corticosteroids or systemic immunosuppressants are eligible. Patients with ocular hypertension, glaucoma or a history of an IOP-steroid response are excluded.

“We look forward to the results of the dexamethasone posterior segment drug delivery system trials. Treatment of chronic non-infectious posterior and diffuse uveitis continues to be a challenge because all currently available treatment modalities have significant side effects. We need to continue to search for better options,” Dr. Lowder concludes.
Müller’s muscle-conjunctiva resection ptosis repair is a highly effective technique for treating mild upper eyelid ptosis. However, sutures placed for wound closure can cause significant postoperative discomfort and result in complications that include keratopathy, granuloma formation and infection.

For the past several years, oculoplastic surgeon Julian D. Perry, M.D., and colleagues at Cleveland Clinic’s Cole Eye Institute have been using fibrin sealant (Tisseel, Baxter AG Industries) to perform sutureless ptosis surgery. Their review of outcomes in a consecutive series of 53 procedures performed in 33 patients over a 2-year period shows the sutureless approach is safe, predictably effective and reduces morbidity by both hastening postoperative healing and avoiding suture-related complications. As reported in a recently published paper [Ophthalm Plast Reconstr Surg 2006;22(3):184-7], symmetry results for the group were excellent and there were no significant complications attributable to the fibrin sealant.

“This tissue sealant has been used most widely as a topical hemostatic agent in general surgery, and several authors have described its use in various external ophthalmic or corneal procedures. However, we believe we are the first to report on sutureless ptosis surgery using fibrin sealant,” says Dr. Perry.

“This product is nontoxic to the ocular surface and mucous membranes, non-irritating to the cornea because it is soft, and our experience indicates it is a useful alternative to sutures for improving results and patient satisfaction with ptosis surgery.”

Dr. Perry added that the fibrin sealant does have some limitations to consider.

“It is more costly than suture material, and since it is derived from human donor sources, patients need to be informed there is a risk, albeit very low, of disease transmission,” he explains.

The sutureless ptosis surgery is performed with the same technique as is used when suture closure is done, using an approach from the posterior aspect of the eyelid and an algorithm published by Dr. Perry and colleagues in 2002 to determine the amount of tissue resection.
Briefly, after evertting the eyelid, the tissue is grasped within a Putterman ptosis clamp and two locking 0.5 forceps are placed beneath the clamp to maintain the relationship of the wound edges. Then, half of the tissue in the clamp is excised, cautery is used to achieve hemostasis, the wound edges are held in approximation and the tissue glue is placed onto the dry field. Then the same steps are repeated after the remaining half of the tissue is excised.

The glue sets within several minutes, and the eyelid retractor is removed after checking wound security. The site is dressed with antibiotic ointment. Total time for the procedure is about eight minutes per side, which represents a slight reduction in time compared with when the procedure is performed using suture closure.

“Average surgical time for the standard procedure is only about 11 minutes, and so increased efficiency is not a major advantage of the sutureless procedure,” notes Dr. Perry. Without question, however, there is less bleeding intraoperatively when the fibrin sealant is used, and as a result, ecchymoses and swelling are reduced postoperatively and resolve more quickly.

“When patients return for their postoperative visit after 1 week, most have minimal bruising and swelling. There is some evidence that the fibrin sealant may accelerate healing by promoting fibroblast proliferation and accumulation of vascular endothelial growth factor, and it is likely that when a suture is placed, fluid remains trapped in the eyelid until the suture is removed,” notes Dr. Perry.

Occasionally, patients who undergo sutureless ptosis surgery may experience a brief episode of conjunctival bleeding 4 to 5 days postoperatively. The event is painless and its onset appears consistent with the timing of degradation of the fibrin sealant.

The fibrin sealant is derived in part from a human plasma donor pool. Manufacturing protocols incorporate rigorous testing and vapor heat viral inactivation, and to date there are no known reported cases of viral or prion disease associated with use of the product since the manufacturer introduced PCR viral screening methodology. Nevertheless, a risk of infectious disease transmission cannot be excluded.

“This information is provided to patients and they are given the option of sutureless or standard surgery. However, because of its various benefits, we consider use of the fibrin sealant the method of choice in patients at increased risk for bleeding or suture morbidity as well as for patients undergoing cosmetic ptosis repair who would especially appreciate a faster and more comfortable course of healing,” Dr. Perry says.}

For more information, contact Julian D. Perry, M.D., at perryj1@ccf.org.
We push the boundaries at every step of the way, refusing to be saddled by conventional thinking or limitations.
Who We Are

Cleveland Clinic Cole Eye Institute is one of the few dedicated, comprehensive state-of-the-art eye institutes in the world. We are here to serve the needs of patients and referring physicians by providing early, accurate diagnosis and excellent, effective patient care. We strive daily to make this commitment to innovation a reality.

At the Cole Eye Institute, the lines between research and patient care blur. The belief that the two are interdependent and synergistic is the foundation for everything we do. We believe that this approach enhances diagnosis and advances treatment, to the benefit of our patients today and tomorrow.

Our program ranks high in the U.S. News & World Report annual survey, and is consistently the highest rated in Ohio. We have some of the highest patient volumes in the United States, handling more than 150,000 patient visits and more than 5,000 surgeries per year. We offer treatment of the full range of vision disorders and conditions, as well as offering routine eye care for all ages. Our internationally recognized staff of 26 ophthalmologists is composed almost entirely of subspecialists, and eight optometrists round out our comprehensive services.

Our state-of-the-art building demonstrates our dedication to patients and to the tradition established by the founders of Cleveland Clinic – a commitment to world-class care that always puts the patient first as well as providing further education for those who serve.

Our facilities are designed for maximum patient comfort, service and quality. We offer one-stop eye care, with our diagnostic services suite located just a quick elevator ride away from the clinical suites, and our state-of-the-art operating rooms also are on premises. All windows in the patient areas feature special light filters to minimize the discomfort of patients whose eyes are dilated or newly treated. Our waiting rooms are designed to be comfortable and include a special area for children to play while they wait. We also have a Pearle Vision on site and offer such amenities as valet parking and an easy drive-up area for pick-up of postoperative patients. Our regional eye care program provides services in five suburban locations throughout the Greater Cleveland area, including one ambulatory surgery center.

We are pioneering treatment protocols for complex vision-threatening disorders, including age-related macular degeneration and glaucoma, through our clinical trials program. Our aggressive research program bridges the gap between laboratory and patient care, and our team of dedicated researchers works in some of the most well-equipped labs anywhere.

Other unique programs housed at Cole Eye Institute:

- The Center for Genetic Eye Diseases: The Center for Genetic Eye Diseases provides clinical diagnostic and therapeutic services for patients with inherited eye conditions such as corneal and retinal dystrophies and microphthalmia. Patients with inherited disorders that involve the eye, such as neurofibromatosis, albinism, neurodegenerative disorders and Marfan syndrome, are referred to the Center by physicians from around the country. A monthly specialty clinic is dedicated to patients with retinal dystrophies and their families.

- A National Eye Donor Program: Cole Eye Institute houses The Foundation Fighting Blindness’ center for eyes donated by individuals across the United States for blindness research. The center shares tissue samples with researchers worldwide. Formally known as the Retinal Degeneration Pathophysiology Facility, the collection center accepts eye donations after death from any person of any age who has normal vision or any degree of vision loss resulting from a retinal-degenerative disease. Cole Eye Institute staff prepares a detailed medical report about each donated eye to help researchers track the effects of eye disease in different types of people and environments. Prior to moving to Cleveland Clinic, the center was located in Philadelphia.

For more information about our services or to refer a patient, please call 216.444.2020 or 800.223.2273 ext 42020 or visit clevelandclinic.org/eye.
Cole Eye Institute Vision First Program

HELPS KIDS IN CLEVELAND PUBLIC SCHOOLS

The Cleveland Clinic Cole Eye Institute reaches out to children in the Cleveland Municipal School District with free vision screenings on its Vision Bus.

The bus, operated by The Vision First project, began in the 2002-2003 school year and travels to all elementary schools in the district to test the vision of kindergarten and first-grade pupils, as well as pre-kindergarten pupils in schools that offer that program. The bus, the size of a recreational vehicle, is fully equipped to perform complete eye examinations.

In the 2004-2005 school year, more than 6,000 children were screened at 88 elementary schools. About 550 were found to need glasses and more than 200 had a vision problem that required further follow-up.

Elias I. Traboulsi, M.D., head of pediatric ophthalmology at the Cole Eye Institute, is the medical director for the program. Heather Cimino, O.D., and Rhonda Wilson, an ophthalmic technician, staff the bus. They assess the need for glasses as well as depth perception, ability to use both eyes fully, color perception and eye muscle strength on each child whose parents return a signed permission slip. Children in whom problems are identified are given a more comprehensive examination by Dr. Hasley that includes dilating their pupils. If glasses or further medical attention are warranted, the school nurse is given information to mail home to parents. Many families are eligible for no-cost follow-up care from pediatric ophthalmologists who accept Medicaid.

This program is so important because many childhood vision problems such as amblyopia are treatable if caught early enough, but can lead to permanent vision loss that hinders a child’s ability to learn if they are not. Also, the earlier students who need glasses get them, the sooner they can start doing better in school.

In a typical school year, more than 6,000 children are screened at 88 elementary schools.

Because the program is designed for such young children, the bus is equipped with a system that lets the staff use letters, numbers and even pictures in the exams. Video cartoons are sometimes used also, and plenty of stickers are handed out as rewards. School nurses play a vital role in making sure the students bring back their signed permission slips and working with families to be sure the children get any follow-up care they need.
Refraction Surgery
FREEING PATIENTS FROM GLASSES OR CONTACT LENSES

The Cleveland Clinic Cole Eye Institute Refractive Center is a national leader in laser vision correction, and our refractive surgeons are among the most experienced anywhere. The Cole Eye Institute laser vision correction team is internationally respected for providing world-class eye care and for playing a prominent role in many major ophthalmic clinical trials.

We utilize the most advanced techniques to offer the complete range of vision correction options. We recently were among the first in the nation to get the newest Alcon excimer laser, the LADARVision 6000. We also have added the newest version of the IntraLase device, the 60 KHz upgrade. Both lasers now deliver quicker, more accurate treatments with less irritation and faster recovery of excellent visual acuity. Treatments for myopia, hyperopia and astigmatism are offered. Also, monovision/blended vision treatments, in which one eye is corrected for near and the other for mid-range, are a popular choice for many of our patients over 40.

Our volumes have increased nearly 20 percent since 2002, and we have achieved that growth by always remembering that patients have a wide variety of choices available for laser vision correction today. Our team proudly differentiates itself by consistently putting patients first and delivering high quality results and sensitive, thorough care before, during and after each procedure. Patients include many members of the local business, cultural, law enforcement and athletic communities, and the highest compliment they pay us is referring a family member or friend.

Every aspect of our refractive unit adheres to the highest standards set by the Cole Eye Institute for all patients.

Our team proudly differentiates itself by consistently putting patients first.
Staff

Our world-renowned experts have extensive experience treating the full range of ophthalmic disorders with precision and compassion.
Cole Eye Institute Staff

Hilel Lewis, M.D.
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Director, Cole Eye Institute
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William J. Dupps Jr., M.D., Ph.D.

William J. Dupps Jr., M.D., Ph.D., a refractive surgeon and corneal specialist who also has a strong interest in ocular biomechanics, has joined the staff of Cleveland Clinic’s Cole Eye Institute.

Dr. Dupps earned his master’s and doctoral degrees in biomedical engineering at The Ohio State University in 1995 and 1998, respectively, followed by a medical degree in 2000 from the same institution. After an internship in transitional medicine at Indiana University, he completed a residency at the University of Iowa Department of Ophthalmology and Visual Sciences in 2004. He is the first fellow to complete a two-year Cornea, External Disease and Refractive Surgery Fellowship at the Cole Eye Institute, a program designed to emphasize training of clinician-scientists.

He also completed a fellowship in ocular gene therapy at the National Eye Institute in 1996 and studied under a Medical Scientist Training Program Fellowship as a Presidential Fellow at The Ohio State University from 1997 to 2000.

In addition to seeing patients in the refractive surgery and cornea clinics, Dr. Dupps, with the help of a National Institutes of Health career development grant, will conduct multi-disciplinary research emphasizing application of engineering tools to the diagnosis and management of biomechanical disorders such as keratoconus and glaucoma. His work also focuses on developing diagnostic tools for optimizing corneal and refractive surgery.

Nadia K. Waheed, M.D.

Nadia K. Waheed, M.D., a retina specialist, has joined Cleveland Clinic Cole Eye Institute’s staff.

Dr. Waheed is a graduate of Aga Khan Medical School in Karachi, Pakistan, and earned a masters degree in public health from the Harvard School of Public Health. She completed her residency and her fellowship training at the Massachusetts Eye and Ear Infirmary at Harvard Medical School.

She will specialize in treating medical and surgical diseases of the retina.

* Denotes joined the Cole Eye Institute in 2006
Leadership Roles

Our physicians are committed to being involved in the ophthalmic world and serve in leadership positions with numerous journals, organizations and conferences. Here are selected highlights of that service.

Roles in Publishing

**American Journal of Ophthalmology**
- Executive Editor
  Elias I. Traboulsi, M.D.
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  Hilel Lewis, M.D.
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  Neal S. Peachey, Ph.D.
  Julian D. Perry, M.D.
  Steven E. Wilson, M.D.

**Archives of Facial Plastic Surgery**
- Reviewer/Referee
  Julian D. Perry, M.D.

**Archives of Ophthalmology**
- Reviewers/Referees
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  Hilel Lewis, M.D.
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  Andrew P. Schachat, M.D.

**Biomed Central (BMC) Ophthalmology**
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**British Journal of Ophthalmology**
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**Clinical Ophthalmic Oncology**
- Section Editor
  Julian D. Perry, M.D.

**Comprehensive Ophthalmology Update**
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**Contemporary Ophthalmology**
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**Cornea**
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**Current Eye Research**
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**Documenta Ophthalmologica**
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**Experimental Eye Research**
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**Eye**
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**EyeNet**
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**Genome Biology**
- Reviewer/Referee
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**German Journal of Ophthalmology**
- Reviewer/Referee
  Hilel Lewis, M.D.

**Graefe's Archive for Clinical and Experimental Ophthalmology**
- Reviewer/Referee
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International Ophthalmology
Reviewer/Referee
Hilel Lewis, M.D.

Investigative Ophthalmology and Visual Science
Reviewer/Referees
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Journal of Biological Chemistry
Reviewer/Referee
John W. Crabb, Ph.D.

Journal of Biomedical Optics
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Journal of Cataract and Refractive Surgery
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Journal of Neuro-Ophthalmology
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Journal of Refractive Surgery
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Molecular & Cellular Proteomics
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Molecular Vision
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John W. Crabb, Ph.D.

Ocular Infection and Immunity
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Pediatric Perspectives
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Proceedings of the National Academy of Sciences
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Argentina Ophthalmological Society
Invited Lecture
Andrew P. Schachat, M.D.

Association for Research in Vision and Ophthalmology
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Neal S. Peachey, Ph.D.
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David M. Meisler, M.D
Victor L. Perez, M.D.

Chinese Retina and Vitreous Society
Invited Lecture
Peter K. Kaiser, M.D.

Cleveland Ophthalmological Society
Invited Lecture
Michael Millstein, M.D.

European Society of Cataract and Refractive Surgeons
Invited Lecture
Ronald R. Krueger, M.D.

International Congress of EpilASIK LASEK and Advanced Surface Ablation
Planner
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International Congress of Eye Research
Session Chair
Steven E. Wilson, M.D.

International Congress on Wavefront Sensing
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Ronald R. Krueger, M.D.

Israeli Corneal Society Annual Meeting
Invited Lecture
Ronald R. Krueger, M.D.

Joint Commission for Allied Health Personnel in Ophthalmology
Invited Lecture
Elias I. Traboulsi, M.D.

Pan-American Congress of Ophthalmology
Invited Lecture
Peter K. Kaiser, M.D.
Careen Y. Lowder, M.D., Ph.D.

Refractive on-line
Invited Lecture
Steven E. Wilson, M.D.

Royal Hawaiian Eye Meeting
Invited Lectures
Peter K. Kaiser, M.D.
Ronald R. Krueger, M.D.
Andrew P. Schachat, M.D.

Sociedad Panamericana de Enfermedades Inflamatorias Oculares
Invited Lecture
Careen Y. Lowder, M.D., Ph.D.

Sociedad Puertorriqueña de Oftalmología
Invited Lecture
Peter K. Kaiser, M.D.

Wilmer Eye Institute Current Concepts in Ophthalmology
Invited Lecture
Ronald R. Krueger, M.D.

World Ophthalmology Congress
Coordinator
David M. Meisler, M.D.
Session Chair
Careen Y. Lowder, M.D., Ph.D.
Plenary Lecturer
Steven E. Wilson, M.D.
Invited Lecture
Ronald R. Krueger, M.D.

Roles in Professional Societies

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Gaining A New Sight for Unsighted In China (GANSU, Inc.)
President, Board of Directors
Ronald R. Krueger, M.D.
Heed Ophthalmic Foundation
Executive Secretary
Froncie A. Gutman, M.D.

International Society for Genetic Eye Disease and Retinoblastoma
Secretary/Treasurer
Elias I. Traboulsi, M.D.

International Society of Refractive Surgery
Education Committee Chair
Ronald R. Krueger, M.D.

Joint Commission on Allied Health Personnel in Ophthalmology
Annual Continuing Education Program
Elias I. Traboulsi, M.D.

Molecular Pathogenesis of Infectious and Inflammatory Eye Research
Scientific Advisory Board
Victor L. Perez, M.D.

Panamerican Association of Ophthalmology
President
Careen Y. Lowder, M.D., Ph.D.

Society of Heed Fellows
Trustee
Froncie A. Gutman, M.D.

The Diabetes Association of Greater Cleveland
Chairman
Philip N. Goldberg, M.D.

Recognition

American Academy of Ophthalmology
Lans Distinguished Lecturer Award
Steven E. Wilson, M.D.

Senior Achievement Award
Careen Y. Lowder, M.D., Ph.D.

Senior Honor Award
Elias I. Traboulsi, M.D.

American Society for Clinical Investigation
Travel Award
Victor L. Perez, M.D.

American Society of Cataract and Refractive Surgery
Best Paper of Session Award
William J. Dupps, M.D., Ph.D.

Appointment to U.S. Physician’s Advisory Board
Ronald R. Krueger, M.D.

Best Doctors in America
Careen Y. Lowder, M.D., Ph.D.
David M. Meisler, M.D.
Julian D. Perry, M.D.

Brazilian Ophthalmological Society
Visiting Professor
Steven E. Wilson, M.D.

Castle Connolly America’s Top Doctors
Ronald R. Krueger, M.D.

Cleveland Browns, National Football League
Team Ophthalmologist
Peter K. Kaiser, M.D.

Cleveland Cavaliers, National Basketball Association
Team Ophthalmologist
Peter K. Kaiser, M.D.

Cleveland Clinic
Innovator Award
William J. Dupps, M.D., Ph.D.
Gregory S. Kosmorsky, D.O.

Cleveland Clinic IRB member
Bennie H. Jeng, M.D.

Columbia University College of Physicians & Surgeons
Annual Ulrich Ollendorff Lecturer
Hilel Lewis, M.D.

Henry Ford Hospital
Visiting Professor
Ronald R. Krueger, M.D.

International Biographical Centre
Top 100 Health Professionals
Julian D. Perry, M.D.

Marquis’ Who's Who in Medicine & Healthcare
William J. Dupps, M.D., Ph.D.

National Leadership Award
Recipient
Ronald R. Krueger, M.D.

Singapore Eye Research Institute
Visiting Professor
Steven E. Wilson, M.D.

Strathmore’s Who’s Who of Professionals
Ronald R. Krueger, M.D.

The Edward S. Harkness Eye Institute
Ollendorff Lectureship
Elias I. Traboulsi, M.D.

Top Fifty Opinion Leaders (by readers of Cataract & Refractive Surgery Today)
Ronald R. Krueger, M.D.

University of Rochester Eye Institute
50th Annual Ophthalmology Conference
Snell Memorial Lecturer
Hilel Lewis, M.D.

Washington University in St. Louis
Visiting Professor
Victor L. Perez, M.D.
Education

Education is crucial to our mission, from residency and fellowship programs to continuing medical education, because we know it is the path to the future.
Training the Leaders of Tomorrow

The Cole Eye Institute is committed to offering one of the best residency and fellowship programs in the United States. These programs are highly competitive and produce superbly trained clinical and academic ophthalmologists.

**Residency Program**

The Cole Eye Institute Residency Training Program’s mission is to prepare participants to become leaders in patient care, teaching and vision research. The program meets all the requirements of the American Board of Ophthalmology and the Accreditation Council for Graduate Medical Education (ACGME). Four residents are accepted into the program each year.

Residents rotate among the Institute’s nine departments and a resident-run clinic at Metro-Health Medical Center, while completing their board requirements. They work under the direct supervision of the staff during each rotation. The departments are:

- Cornea and external disease
- Glaucoma
- Neuro-ophthalmology
- Ophthalmic pathology
- Ophthalmic plastic, reconstructive and orbital surgery
- Pediatric ophthalmology and adult strabismus
- Refractive surgery
- Retina and vitreous
- Uveitis, ocular inflammatory disease and immunology

This curriculum provides a balanced exposure to all subspecialty areas of ophthalmology, ensuring graduates the ability to perform general ophthalmology with skill, knowledge and confidence. Each resident works in a one-on-one relationship with a staff physician to provide the best opportunity to study disease processes and their medical and surgical management. This arrangement also provides excellent supervision and optimal continuity of patient care in the outpatient and hospital settings.

Residents are also expected to participate in clinical and basic research activities utilizing the staff’s expertise. Residents complete independent clinical research projects that involve reviewing the literature, developing a hypothesis and designing and executing the study. Research activities are carefully supervised by an experienced clinical investigator. Residents are expected to submit and present their research at national meetings and to write several papers for publication based on their research activities. Each June, ophthalmology residents, fellows and staff participate in the annual Research, Resident and Alumni Meeting, a scientific forum for the presentation of research projects.

**For more information** about the Cole Eye Institute Residency Training Program, contact Elias I. Traboulsi, M.D., at 216.444.4363.

**Fellowship Program**

Cleveland Clinic Cole Eye Institute also offers high-quality fellowship training opportunities in a variety of subspecialties. These fellowships train the next generation of academic leaders in the respective fields by combining an excellent academic environment with mentorship support in a state-of-the-art eye care facility.

Our fellowships include a two-year vitreoretinal program (3 slots), a two-year cornea, external disease and refractive surgery program (2 slots), a one-year glaucoma fellowship (1 slot) and a one- or two-year pediatric-ophthalmology fellowship (1 slot). In 2008, we will be adding a one-year oculoplastic surgery fellowship (1 slot).

**For more information** about Cole Eye Institute fellowship programs, contact Jane Sardelle at 216.444.2010.

Continued on page 48
Training the leaders of tomorrow
Continued from page 47

Our Recent Graduates
Here is where our recent residency and fellowship graduates have gone after completing their Cole Eye Institute training.

Residency Class of 2005
Susie Chang, M.D.
Vitreoretinal Fellow
Massachusetts Eye and Ear Infirmary
Harvard University
Boston, MA

Sai Chavala, M.D.
Vitreoretinal Research Fellow
Weill Medical School
Cornell University
New York, NY

Albert Dal Canto, M.D., Ph.D.
Oculoplastics Surgery Staff
West Virginia University Hospitals
Morgantown, WV

Alex Melamud, M.D., M.A. (Chief Resident 2005)
Vitreoretinal Fellowship
Duke University
Durham, NC

Residency Class of 2006
Pawan Bhatnagar, M.D.
Vitreoretinal Fellowship
Columbia University
New York, NY

Anat Galor, M.D. (Chief Resident 2006)
Uveitis Fellowship
Wilmer Institute
Johns Hopkins University
Baltimore, MD

Pankaj Gupta, M.D.
Cornea Fellowship
Massachusetts Eye & Ear
Harvard University
Boston, MA

Sunita Radhakrishnan, M.D.
Glaucoma Fellowship
Wilmer Institute
Johns Hopkins University
Baltimore, MD

Fellows Finishing in 2006
William J. Dupps, M.D., Ph.D. (was cornea, external disease & refractive surgery fellow)
Staff, Cole Eye Institute
Cleveland, OH

Rafael Ufret-Vincenty, M.D. (was vitreoretinal fellow)
Staff, Vitreo-Retinal Department
University of Texas Southwestern Medical Center
Dallas, TX
Physicians are invited to join their colleagues from around the country in attending 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 Eye Institute, except the Innovations in Ophthalmology course in March, which will be held in Los Cabos, Mexico.

For more information, contact Jane Sardelle, program coordinator, at 216.444.2010 or 800.223.2273, ext. 42010, or sardelj@ccf.org.

Innovations in Pediatric Ophthalmology and Strabismus

Strabismus Surgical Techniques, Instruments and Outcomes, Vision Screening and Telemedicine in Pediatric Ophthalmology

Saturday, September 16, 2006
8:00 a.m. to 2:00 p.m.

Course Directors:
Elias I. Traboulsi, M.D.
Head, Pediatric Ophthalmology and Adult Strabismus Department
Cleveland Clinic Cole Eye Institute

Andreas Marcotty, M.D.
Pediatric Ophthalmology and Adult Strabismus Department
Cleveland Clinic Cole Eye Institute

Guest Faculty:
David L. Guyton, M.D.
Chairman, Department of Ophthalmology
Director, Krieger Children’s Eye Center
Krieger Professor of Pediatric Ophthalmology
Wilmer Institute, Johns Hopkins Hospital
Baltimore, MD

David G. Hunter, M.D., Ph.D.
Ophthalmologist-in-Chief
Children’s Hospital of Boston
Associate Professor of Ophthalmology
Harvard Medical School
Children’s Hospital Boston
Boston, MA

M. Edward Wilson, Jr., M.D.
Director, Albert Florens Storm Eye Institute
Chairman, Department of Ophthalmology
The Medical University of South Carolina
Pierre Gautier Jenkins Endowed Chair
Charleston, SC

Description/Objectives: This course will focus on the mechanisms of amblyopia and eye movement disorders associated with infantile esotropia as well as on how insights into these mechanisms affect clinical management of patients with these conditions.

At the end of the symposium, participants should be able to:
1. Identify the cortical mechanisms that underlie amblyopia in humans.
2. List the types of conditions that lead to amblyopia and differentiate them from structural causes of reduced vision in infants and children.
3. Interpret the indications for different modalities of treatment of amblyopia.
4. Dissect the complex eye movement abnormalities in the infantile esotropia complex and understand their mechanisms.
5. Review information and decide on the timing of surgery for infantile esotropia.

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Innovations in Inflammatory Ocular Diseases
Saturday, October 14, 2006
7:30 a.m. to 4:00 p.m.

Course Director:
Careen Y. Lowder, M.D., Ph.D.
Uveitis Department
Cleveland Clinic Cole Eye Institute

Cole Eye Institute Faculty:
Peter K. Kaiser, M.D.
Vitreoretinal Surgery Department
Cleveland Clinic Cole Eye Institute
Victor L. Perez, M.D.
Cornea and Uveitis Departments
Cleveland Clinic Cole Eye Institute

Guest Faculty:
Glenn Jaffe, M.D.
Professor, Department of Ophthalmology
Duke University
Durham, NC
Eric Suhler, M.D.
Assistant Professor, Casey Eye Institute
Oregon Health & Science University
Eugene, OR
Howard Tessler, M.D.
Professor, Illinois Eye and Ear Infirmary
Chicago, IL
Scott Whitcup, M.D.
Vice President
Allergan
Irvine, CA

Description/Objectives: This course will review the latest treatment modalities in uveitis including the intravitreal delivery systems for long-acting and short-acting steroids and the various anti-tumor necrosis factor alpha. We will compare these new treatments to the currently accepted systemic immunosuppresion regimens with steroids and nonsteroidal immunosuppressive therapy. Cole Eye Institute experience will be discussed.

At the conclusion of this course, participants should be able to:
1. Describe the use of nonspecific drugs, including immunosuppressive therapy.
2. Describe current clinical trials in ocular inflammatory diseases.
3. Identify newer therapies for noninfectious posterior uveitis syndromes.
4. Evaluate and determine which patients will benefit from the various treatment modalities.

Innovations in Glaucoma
Saturday, December 9, 2006
7:30 a.m. to 4:00 p.m.

Course Directors:
Scott D. Smith, M.D., M.P.H.
Edward J. Rockwood, M.D.
Glaucoma Department
Cleveland Clinic Cole Eye Institute

Guest Faculty:
George Baerveldt, MBCHB
Chairman and Professor
Department of Ophthalmology
University of California Irvine Medical Center
Irvine, CA
Reay H. Brown, M.D.
Northside Hospital
Atlanta, GA

Description/Objectives: This is an update of diagnostic and surgical innovations and a new look at old techniques for the management of glaucoma. There will be didactic lectures, case presentations and question-and-answer sessions.

At the conclusion of this course, participants should be able to:
1. Identify the role of optic disc imaging in the management of ocular hypertension and glaucoma.
2. Review a comparison of ultrasound biomicroscopy and OCT anterior segment imaging for the diagnosis and management of narrow angles and angle-closure glaucoma.
3. Discuss surgical variations and why glaucoma surgery can be difficult to simplify and improve.
4. Evaluate outcomes analyses and how they can lead to improved surgical outcomes in glaucoma.
5. Identify the possible future role of the Eyepass glaucoma device.
6. Identify the role of cataract extraction in the management of angle-closure glaucoma.
7. Understand the role of the trabectome in the surgical management of glaucoma.
8. Identify the latest glaucoma implant innovations.
Innovations in Ophthalmology

Los Cabos, Mexico

Sunday-Friday, March 25-30, 2007
7:00 a.m.-1:00 p.m., except first day 1:00-6:00 p.m.

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

Cole Eye Institute Faculty:
William J. Dupps, M.D., Ph.D.
Cornea, External Disease and Refractive Surgery Department

Ronald R. Krueger, M.D.
Refractive Surgery Department

David M. Meisler, M.D.
Cornea and External Disease Department

Michael Milstein, M.D.
Comprehensive Ophthalmology Department

Victor L. Perez, M.D.
Cornea and External Disease Department

Julian D. Perry, M.D.
Oculoplastic and Orbital Surgery Department

Andrew P. Schachat, M.D.
Vice Chairman for Clinical Affairs

Scott D. Smith, M.D., M.P.H.
Glaucoma Department

Nadia K. Waheed, M.D.
Vitreoretinal Department

Steven E. Wilson, M.D.
Cornea and External Disease and Refractive Surgery Department

Guest Faculty:
Iqbal K. Ahmed, M.D.
Clinical Instructor
Department of Ophthalmology
University of Toronto
Toronto, Canada

Sterling S. Baker, M.D.
Assistant Clinical Professor
University of Oklahoma
Oklahoma City, OK

Perry S. Binder, M.D.
Preceptor
University of California, San Diego
San Diego, CA

Mark S. Blumenkranz, M.D.
Professor and Chairman
Stanford University School of Medicine
Stanford, CA

Robert J. Cionni, M.D.
Cincinnati Eye Institute
Cincinnati, OH

Roger A. Dailey, M.D.
Associate Professor of Ophthalmology
Lester T. Jones Chair, Ophthalmic Facial Plastic Surgery
Casey Eye Institute
Portland, OR

Thomas R. Friberg, M.D.
Professor, University of Pittsburgh
Pittsburgh Eye and Ear Institute
Pittsburgh, PA

Stephen D. Klyce, Ph.D.
Professor of Ophthalmology and Cell Biology/Anatomy
Adjunct Professor of Biomedical Engineering,
Tulane University
Louisiana State University Eye Center
New Orleans, LA

Stephen S. Lane, M.D.
Clinical Professor of Ophthalmology
University of Minnesota
Saint Paul, MN

Bradley N. Lemke, M.D.
Clinical Professor
University of Wisconsin-Madison School of Medicine
Lemke Facial Surgery
Madison, WI

Richard J. Mackool, M.D.
Assistant Clinical Professor
New York Medical College
New York Eye and Ear Infirmary
Astoria, NY

Continued on page 52
Continuing Medical Education
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Marguerite B. McDonald, M.D.
Clinical Professor of Ophthalmology
Tulane University School of Medicine
Southern Vision Institute
New Orleans, LA

Peter A. Netland, M.D., Ph.D.
Professor and Director of Glaucoma
University of Tennessee
Hamilton Eye Institute
Memphis, TN

Terrence P. O’Brien, M.D.
Professor of Ophthalmology
Bascom Palmer Eye Institute
University of Miami School of Medicine,
Miami, FL

Richard K. Parrish, M.D.
Professor
Associate Dean for Graduate Medical Education
Bascom Palmer Eye Institute
University of Miami School of Medicine
Miami, FL

Stephen C. Pflugfelder, M.D.
Professor, Department of Ophthalmology
Baylor College of Medicine
Houston, TX

Yaron S. Rabinowitz, M.D.
Director, Ophthalmology Research
Cedars Sinai Medical Center
Clinical Professor of Ophthalmology
UCLA School of Medicine
Los Angeles, CA

Description/Objectives: The course will provide a comprehensive review of new developments in clinical practice and will highlight state-of-the-art management, problem-solving, case presentations and evaluation of new innovations, interventions and technologies. There will be ample time for questions and answers and the course faculty will be available throughout the course for informal discussion and consultation.

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

1. Describe the pathogenesis of various ocular disorders.
2. Evaluate and utilize new diagnostic and surgical techniques.
3. Develop effective management strategies.

Innovations in Refractive Surgery & Cornea
Saturday, March 17, 2007
7:30 a.m. to 5:00 p.m.

Course Director:
Steven E. Wilson, M.D.
Director, Corneal Research
Cleveland Clinic Cole Eye Institute

Cole Eye Institute Faculty:
Ronald R. Krueger, M.D.
Refractive Surgery Department
David M. Meisler, M.D.
Cornea Department
Victor L. Perez, M.D.
Cornea and Uveitis Departments

Guest Faculty:
Perry S. Binder, M.D.
Associate Clinical Professor
University of California-San Diego
Co-Medical Director
IntraLase Corporation
San Diego, CA

Eric Donnenfeld, M.D.
Founding Partner
Ophthalmic Consultants of Long Island
Associate Professor of Ophthalmology
New York University
New York, NY

David T.C. Lin, M.D.
Medical Director
Pacific-Laser Eye Centre
Clinical Assistant Professor of Ophthalmology
The University of British Columbia
Vancouver, BC

Yaron S. Rabinowitz, M.D.
Director, Ophthalmology Research
Cedars-Sinai Medical Center
Clinical Professor of Ophthalmology
UCLA School of Medicine
Los Angeles, CA

George O. Waring, III, M.D., F.A.C.S., FRCOphth
Private Practice/Multispecialty
Professor, Emory University
Atlanta, GA
Description/Objectives: This course will highlight important information related to innovations that are critical to refractive surgeons, cornea specialists and comprehensive ophthalmologists regarding refractive surgery procedures, complications in refractive surgery and corneal diseases, such as chronic dry eye, keratoconus and corneal transplant rejection.

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

1. Identify factors predisposing eyes to corneal ectasia following refractive surgery.
2. Obtain a better understanding of procedures such as corneal endothelial replacement surgery, femtosecond laser procedures and the use of multifocal intraocular lenses.
3. Achieve a better understanding of the treatment of complications of refractive surgery.

6th Retina Summit: Innovations in Vitreoretinal Diseases and Surgery

Thursday and Friday, May 3-4, 2007
8:00 a.m. to 5:00 p.m.

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

Cole Eye Institute Faculty:
Bela Anand-Apte, M.B.B.S., Ph.D.
Ophthalmic Research Department

John W. Crabb, Ph.D.
Ophthalmic Research Department

Joe G. Hollyfield, Ph.D.
Ophthalmic Research Department

Peter K. Kaiser, M.D.
Vitreoretinal Department

Andrew P. Schachat, M.D.
Vice Chairman for Clinical Affairs

Jonathan E. Sears, M.D.
Vitreoretinal Department

Guest Faculty:
Mark Blumenkranz, M.D.
Stanford University School of Medicine
Department of Ophthalmology
Stanford, CA

Stanley Chang, M.D.
Professor & Chairman
Department of Ophthalmology
Edward Harkness Eye Institute
Columbia University
New York, NY

Eugene de Juan, Jr, M.D.
Assistant Clinical Professor
Department of Ophthalmology
Beckman Vision Center
University of California, San Francisco
San Francisco, CA

Martin Friedlander, M.D.
Professor, Department of Cell Biology
Scripps Research Institute
La Jolla, CA

José García-Arumi, M.D.
Professor of Ophthalmology
Universitat Autonoma de Barcelona
Institut de Microcirurgia Ocular
Barcelona, Spain

Mark S. Humayun, M.D., Ph.D.
Retina Institute
Doheny Eye Institute
Los Angeles, CA

Glenn J. Jaffe, M.D.
Professor of Ophthalmology
Vitreoretinal Diseases and Surgery
Duke University Eye Center
Durham, NC

Henry J. Kaplan, M.D.
Evans Professor of Ophthalmology
Chair, Department of Ophthalmology and Visual Sciences
Director, Kentucky Lions Eye Center
Louisville, KY

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Continuing Medical Education
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Philip J. Rosenfeld, M.D., Ph.D.
Associate Professor
Department of Ophthalmology
Bascom Palmer Eye Institute
Miami, FL

Yasuo Tano, M.D.
Professor and Chairman
Ophthalmology Department
Osaka University Medical School
Suita, Japan

Description/Objectives: This 6th Retina Summit is intended to provide ophthalmologists and vitreoretinal specialists with information about issues relating to diagnosing and treating patients with vitreoretinal diseases, utilizing the full spectrum of medical and surgical therapies currently available. Live surgery and live laser sessions are part of the summit format. We will examine interesting case presentations, in which experts will advise on specific treatments for patients with vitreoretinal diseases. This summit offers a great opportunity for audience participation.

At the conclusion of the summit, participants should be able to:
1. Discuss the pathophysiology and diagnosis of several vitreoretinal diseases.
2. Review a variety of new treatments for age-related macular degeneration, diabetic retinopathy, complicated retinal detachment and other macular and retinal diseases.
3. Examine new technology, including state-of-the-art and experimental imaging systems, drug-delivery systems and new instrumentation.
4. Analyze cost-effective therapeutic protocols.
5. Review publicized findings, ongoing clinical trials and the assessment of new data and discoveries.
7. Examine interesting case presentations.

Annual Research, Residents & Alumni Meeting

Thursday and Friday, June 21-22, 2007
5:00 p.m. to 7:30 p.m. (Thursday);
7:30 a.m. to 6:00 p.m. (Friday)

Course Directors:
Hilel Lewis, M.D.
Chairman, Division of Ophthalmology
Director, Cleveland Clinic Cole Eye Institute

Careen Y. Lowder, M.D., Ph.D.
Director, Uveitis Department
Cleveland Clinic Cole Eye Institute

Keynote Speaker:
Paul A. Sieving, M.D., Ph.D.
Director, National Eye Institute, National Institutes of Health
Bethesda, MD

Description/Objectives: This program provides a scientific forum to present original, thought-provoking clinical research papers and basic science research of the Cole Eye Institute residents, fellows, staff, alumni and invited ophthalmologists. In addition to the educational aspects of the program and learning about new and ongoing investigations, this event offers an excellent opportunity to meet current residents, fellows, new faculty and invited ophthalmologists, and to make and renew friendships.

At the conclusion of the meeting, participants should be able to:
1. Recognize the most up-to-date concepts and treatments in research and clinical ophthalmology.
2. Identify current basic science research in age-related macular degeneration.
3. Review the rationale and status of the most current treatments for uveitic and diabetic macular edema.
4. Discuss outcomes of complicated glaucoma and cataract surgery.
5. Describe the latest techniques in refractive surgery.
Spring Break in Los Cabos with the Brightest Minds in Ophthalmology

Innovations in Ophthalmology is a series of six half-day sessions designed to enhance your clinical and practice management skills. The Cole Eye Institute cordially invites you and your family to join us in beautiful and exotic Los Cabos. We promise an eye-opening experience:

- **New techniques, technologies and ideas** presented by leading ophthalmologists in the areas of cataract surgery, keratorefractive surgery, glaucoma, cornea, oculoplastic surgery and retina.

- **Special presentations** including surgical videos, case presentations, new technologies, practice management and revenue growth, and personal wealth management.

- **Bring your family!** Scheduled to coincide with most academic Spring Breaks, and the half-day sessions will allow plenty of time for having fun together. A world of activities is available for you and your family.

- **Los Cabos is the jewel of the Mexican Baja Peninsula.** Spectacular golfing at 6 world-renowned courses, including the Ocean Course by Jack Nicklaus; the miraculous Sea of Cortez with its diverse marine life and world-class sport fishing; the beautiful Sierra de la Laguna mountain range... and so much more.

- **Luxury accommodations at The Westin Resort & Spa, Los Cabos.** Dramatically nestled into the cliffs overlooking a long, white sand beachfront, this celebrated resort pampers and delights with world-class amenities — 7 swimming pools, lighted tennis courts, a kids activity program, baby-sitting services. This acclaimed resort redefines the idea of luxury for the entire family.

Register for this CME activity today.
www.clevelandclinic.org/eye/springbreak
or contact Jamie Belkin at 877.228.2132

This activity has been approved for AMA PRA Category 1 Credit™
Grand Rounds

Cole Eye Institute hosts Grand Rounds every Monday morning from 7 to 8 a.m. during the academic year (except holidays and major meeting times). For the academic year 2006–2007, they will begin Sept. 18, 2006, and run through late June. The meetings are designed for residents, fellows and staff physicians of the Cole Eye Institute, as well as other comprehensive and subspecialty ophthalmologists. We are pleased to offer Category 1 continuing education credits for each meeting. Evaluations are offered online following each meeting and attendance certificates can be printed or saved for your record-keeping purposes.

The Grand Rounds’ forum consists of two clinical cases presented by Cole Eye Institute residents, followed by extensive discussion. Cases selected for presentation represent outstanding teaching examples and are either difficult-to-manage cases, unusual presentations of common disorders, rare conditions or cases that highlight state-of-the-art diagnosis or management. In addition, approximately every six weeks, M&M cases are presented and discussed by third-year residents with follow-up discussion.

The meetings are held the James P. Storer Conference Room on the first floor of the Cole Eye Institute and registration is not required to attend. Park in the patient/visitor lot at E. 102nd Street (facing the front of the Cole Eye Institute), or the patient/visitors garage at E. 100th Street and Carnegie Avenue. Parking tickets will be validated.

For questions, please call Jane Sardelle at 216.444.2010 (sardelj@ccf.org) or see Careen Y. Lowder, M.D., Ph.D., at the meetings.
Distinguished Lecture Series

The Cole Eye Institute Distinguished Lecture Series provides a forum for renowned researchers in the visual sciences to present their latest findings. This series of lectures features advances in many areas of ophthalmic research presented by noted basic and clinical scientists from throughout the world. Ample opportunity for questions and answers is provided.

All lectures are held on Thursdays from 7 to 8 a.m. in the James P. Storer Conference Room on the first floor of The Cleveland Clinic Cole Eye Institute. Registration is not required. For questions, please call 216.444.5832.

Pathogenic Mechanisms in Uveoretinitis
September 14, 2006
John V. Forrester, M.D.
Cockburn Professor and Head
Department of Ophthalmology
University of Aberdeen
Institute of Medical Sciences
Forresthill
Aberdeen, Scotland

Circadian Clocks and Neuromodulators in the Retina
October 19, 2006
P. Michael Iuvone, Ph.D.
Professor
Department of Pharmacology
Emory University
Atlanta, GA

Making Sense of Neuronal Diversity: A Bottom-Up View of the Retina
November 16, 2006
Richard H. Masland, Ph.D.
Charles A. Pappas Professor of Neuroscience
Harvard Medical School
Investigator, Howard Hughes Medical Institute
Boston, MA

New Advances in Syndromic Retinal Degeneration
January 18, 2007
Elise Heon, M.D., F.R.C.S.C.
Ophthalmologist-in-Chief
Associate Surgeon-in-Chief for Research
Associate Scientist, Genetics and Genomic Biology
Research Institute, The Hospital for Sick Children
Professor of Ophthalmology
The University of Toronto
Toronto, Ontario

Using Experimental Genetics to Understand Mechanisms of Glaucoma
February 15, 2007
Simon W. M. John, Ph.D.
Associate Investigator
Howard Hughes Medical Institute
Jackson Laboratory
Bar Harbor, Maine

Continued on page 58
Distinguished Lecture Series
Continued from page 57

**Design of a Pediatric Clinical Trial for Treatment of Congenital Blindness**
March 15, 2007
Jean Bennett, M.D., Ph.D.
Professor
F.M. Kirby Center for Molecular Ophthalmology
Scheie Eye Institute
Institute of Neurological Sciences
University of Pennsylvania
Philadelphia, PA

**The Bizarro World of Angiogenesis**
April 19, 2007
Jayakrishna Ambati, M.D.
Department of Ophthalmology and Visual Sciences
University of Kentucky
Lexington, KY

**Defining a Retinal Stem Cell Niche**
May 17, 2007
Pamela Raymond, Ph.D.
Professor
Department of Molecular, Cellular and Developmental Biology
University of Michigan
Ann Arbor, MI

**RNA Tools for Retinal Diseases**
June 21, 2007
Alfred S. Lewin, Ph.D.
Shaler-Richardson Professor
Department of Molecular Genetics & Microbiology
University of Florida
Gainesville, FL

**Pathogenesis of Dry AMD: Role of Smoking and RPE Injury**
July 19, 2007
Scott W. Cousins, M.D.
Professor of Ophthalmology
Duke Center for Macular Disease
Duke University Eye Center
Durham, NC
Research

We will never stop pursuing answers to the most challenging problems in ophthalmology.
Cleveland Clinic Cole Eye Institute had an aggregate annual grant level of $19,965,008 in 2006*, with $13,305,405 coming from federal and state sources. Cole Eye Institute and its partners received $6 million for age-related macular degeneration (AMD) research under Ohio’s Biomedical Research and Technology Transfer (BRTT) Partnership Program, which supports biomedical and biotechnology research leading to commercialization and long-term improvements to the health of Ohio’s residents.

*Year-to-date through July 2006.

<table>
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<tr>
<th>Title</th>
<th>Source</th>
<th>Sponsor</th>
<th>ID#</th>
<th>Principal Investigator</th>
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<tr>
<td>A Multi-Center Study To Map Genes for Fuchs’ Dystrophy</td>
<td>Federal</td>
<td>NIH</td>
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<td>William J. Dupps, M.D., Ph.D.</td>
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<td>Advanced Imaging for Glaucoma</td>
<td>Federal</td>
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<td>Amblyopia Treatment Study: Pediatric</td>
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<td>Corneal Donor Study</td>
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<td>David M. Meisler, M.D.</td>
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<td>Corneal Epithelial Growth Factors and Receptors</td>
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<td>EY010056</td>
<td>Steven E. Wilson, M.D.</td>
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<td>Drusen and AMD: Sub-type Isolation and Characterization</td>
<td>Federal</td>
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<td>EY014240</td>
<td>Joe G. Hollyfield, Ph.D.</td>
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<td>Expression and Regulation of Retinal Angiotensin II</td>
<td>Federal</td>
<td>NIH</td>
<td>EY013752</td>
<td>Preenie deS Senanayake, Ph.D.</td>
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<td>Infant Aphakia Treatment Study</td>
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<td>Inhibition of VEGF Mediated Angiogenesis by TIMP-3</td>
<td>Federal</td>
<td>NIH</td>
<td>CA106415</td>
<td>Bela Anand-Apte, M.B.B.S., Ph.D.</td>
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<td>Mouse Models for Vision Research</td>
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<td>Proteomic Analyses of Human Trabecular Meshwork</td>
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<td>NIH</td>
<td>EY015266</td>
<td>Sanjoy Bhattacharya, Ph.D.</td>
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<td>Proteomic Studies of Age Related Macular Degeneration</td>
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<td>NIH</td>
<td>EY014239</td>
<td>John W. Crabb, Ph.D.</td>
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<td>Regulation of Corneal Inflammation by Fas Ligand</td>
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<td>NIH</td>
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<td>Victor L. Perez, M.D.</td>
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<td>Role of TIMP-3 in Ocular Neovascularization</td>
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<td>NIH</td>
<td>EY016490</td>
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<td>Role of TULP1 in Photoreceptor Cells</td>
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<td>Studies of Visual Cycle Proteins</td>
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<td>The dc-Electroretinogram</td>
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<td>The Intravitreal Corticosteroid for Macular Edema Study</td>
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<td>NIH</td>
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<td>Peter K. Kaiser, M.D.</td>
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<td>Vascular Remodeling and Effects of Angiogenic Inhibition</td>
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<td>EY017528</td>
<td>Peter K. Kaiser, M.D.</td>
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<td>Vision Research Infrastructure Development Grant</td>
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<td>NIH</td>
<td>EY015638</td>
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<td>Research into Age-related Macular Degeneration</td>
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<td>State of Ohio</td>
<td>BRTT 05-29</td>
<td>Hilel Lewis, M.D.</td>
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AMD Initiative for Prevention and Cure

The Cole Eye Institute AMD Initiative for Prevention and Cure was established through a grant from the State of Ohio, corporate sponsors, investors and leading academic institutions to develop and commercialize new comprehensive technologies for early diagnosis, prevention and treatment of age-related macular degeneration.

SPECIFIC INITIATIVES OF THE PROGRAM INCLUDE:

- The commercialization of a blood test for AMD based on biomarkers that can track therapeutic efficacy and identify high-risk patients prior to vision loss.

- The prevention of neovascular AMD-related blood vessel growth and leaking with novel cell-signaling inhibitors.

- Identification and analysis of therapeutic agents that prevent retinal protein oxidative damage and subsequent development of AMD.

- Characterization of oxidative changes in the retina associated with AMD that will aid in the identification of drug targets to prevent this disorder.

- Isolation of genetic factors involved in AMD and development of new animal models that will result in more efficient screening, faster optimization and better efficacy of new therapies for AMD.

- Characterization of inflammatory and immunological signals involved in the progression of disease that may lead to the development of an AMD vaccine.

- Investigation of retinal stem cell-mediated vision restoration in AMD.
Clinical Trials

The following studies are currently enrolling. All studies have been approved by the Institutional Review Board.

**RETINAL DISEASES**

**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 L. Schaaf, R.N., at 216.445.4086

**Protocol B7A-MC-MBCU The Effect of Ruboxistaurin on Clinically Significant Macular Edema in Patients with Diabetes Mellitus, as assessed by Optical Coherence Tomography**

**Objective:** The primary objective of this study is to test the hypothesis that oral administration of 32 mg per day of ruboxistaurin for 18 months will reduce the baseline to endpoint changes in central macular thickness, as measured by OCT in patients with CSME.

**Contact:** P. Kaiser, M.D., at 216.444.6702 or L. Schaaf, R.N., at 216.445.4086

**The Standard Care versus Corticosteroid for Retinal Vein Occlusion Study**

**Objective:** To evaluate the effectiveness of triamcinolone acetonide injections for treatment of macular edema versus standard treatment. Patients will have 11 to 13 visits over a period of up to three years.

**Contact:** P. Kaiser, M.D., at 216.444.6702 or L. Holody, C.O.A., at 216.445.3762

**A Six-Month Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System**

**Objective:** To evaluate the safety and efficacy of the 700 µg DEX PS DDS Applicator System and 350 µg DEX PS DDS Applicator System compared with a Sham DEX PS DDS Applicator System (needle-less applicator) for six months in patients with macular edema following branch retinal vein occlusion or central retinal vein occlusion. The safety of the 700 µg DEX PS DDS Applicator System will be assessed for an additional 6 months in patients who qualify for treatment in an open-label safety extension.

**Contact:** P. Kaiser, M.D., at 216.444.6702 or L. Schaaf, R.N., at 216.445.4086

**A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema**

**Objective:** To determine whether intravitreal triamcinolone acetonide injections at doses of 1 mg or 4 mg produce greater benefit, with an acceptable safety profile, than macular laser photocoagulation in the treatment of diabetic macular edema.

**Contact:** P. Kaiser, M.D., at 216.444.6702 or L. Holody, C.O.A., at 216.445.3762
A 3-Year, Phase 3, Multicenter, Masked, Randomized, sham-Controlled Trial to Assess the Safety and Efficacy of 700 μg and 350 μg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Diabetic Macular Edema

Objective: To evaluate the safety and efficacy of the 700 μg DEX PS DDS Applicator System and 350 μg DEX PS DDS Applicator System compared with a Sham DEX PS DDS Applicator System (needle-less applicator) in patients with diabetic macular edema.

Contact: P. Kaiser, M.D., at 216.444.6702 or L. Schaaf, R.N., at 216.445.4086

A Phase IIIb, Multicenter Study To Evaluate the Safety and Tolerability of Ranibizumab in Naïve and Previously Treated Subjects with Choroidal Neovascularization Secondary to Age-Related Macular Degeneration

Objective: To estimate the incidence of ocular and non-ocular serious adverse events in subjects treated for 12 months with 0.3 mg or 0.5 mg intravitreal ranibizumab.

Contact: P. Kaiser, M.D., at 216.444.6702 or L. Bartko, R.N., at 216.444.7137

GLAUCOMA

Advanced Imaging for Glaucoma

Objective: Advanced Imaging for Glaucoma (AIG) is a multi-center bioengineering partnership sponsored by the National Eye Institute to develop advanced imaging technologies to improve the detection and management of glaucoma. The advanced imaging technologies include optical coherence tomography, scanning laser polarimetry and scanning laser tomography. The technologies will be evaluated in a longitudinal five-year clinical trial composed of glaucoma suspects, glaucoma patients and normal subjects.

Contact: S. Smith, M.D., M.P.H., at 216.444.4821 or L. Holody, C.O.A., at 216.445.3762

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
Selected Recent Publications

**PEER-REVIEWED JOURNALS**

**Advances in Experimental Medicine and Biology**


**American Family Physician**

**American Journal of Medical Genetics. Part A**


**American Journal of Ophthalmology**


**Annals of Plastic Surgery**


**Archives of Ophthalmology**


**Arquivos Brasileiros de Oftalmologia**


**Biochemistry**


**British Journal of Ophthalmology**


**Cancer Research**


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Chemical Research in Toxicology

Cleveland Clinic Journal of Medicine

Cornea

Current Medical Research & Opinion

eMedicine Journal [electronic resource]

European Journal of Internal Medicine

Evidence-Based Ophthalmology

Experimental Eye Research


Experimental Neurology


Expert Opinion on Investigational Drugs


Eye


Eye & Contact Lens

Jeng BH, Millstein ME. Reduction of hyperopia and astigmatism after superficial keratectomy of peripheral hypertrophic subepithelial corneal degeneration. Eye & Contact Lens 2006 May;32(3):153-156.

FASEB Journal


Human Molecular Genetics


International Journal of Pediatric Otorhinolaryngology


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International Journal of STD and AIDS


International Ophthalmology Clinics


Investigative Ophthalmology & Visual Science


Journal of Biological Chemistry


Journal of Cataract and Refractive Surgery


Journal of General Physiology


Journal of Glaucoma


Journal of Medical Genetics


Journal of Neuroscience


Journal of Pediatric Ophthalmology and Strabismus

Journal of Refractive Surgery

Molecular and Cellular Neurosciences

Ocular Immunology and Inflammation

Ophthalmic Epidemiology

Ophthalmic Genetics


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Ophthalmic Plastic and Reconstructive Surgery

Ophthalmic Surgery, Lasers & Imaging

Ophthalmology


Schachat AP. **New treatments for age-related macular degeneration.** Ophthalmology 2005 Apr;112(4):531-532.


Ophthalmology Clinics of North America


Proceedings of the National Academy of Sciences of the United States of America


Progress in Retinal and Eye Research


Retina


Surgical Neurology


Survey of Ophthalmology


Transactions of the American Ophthalmological Society


Visual Neuroscience


BOOK CHAPTERS


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**BOOKS**


**SERIAL (BOOK, MONOGRAPH)**


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.

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 more than 1,000 available 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.

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