News in Review

A LOOK AT TODAY'S IDEAS AND TRENDS

Devices Trump Docs in Glaucoma Diagnosis

DIAGNOSTIC FACE-OFF. In a European study that pitted general ophthalmologists armed with stereo optic disc photos against GDx-VCC and HRT imaging, the devices showed greater sensitivity and specificity in glaucoma diagnosis. The doctors did better at identifying normal optic discs (1) than smaller-than-normal discs (2).

In the competition between human and machine, the machines won, at least this round. That is, scanning laser polarimetry and confocal scanning laser ophthalmoscopy did better at distinguishing glaucomatous eyes from healthy ones than most of the European general ophthalmologists who evaluated stereo optic disc photographs of the same eyes ($p < 0.0005$). And in the case of a few clinicians, the difference in accuracy was quite large, the European Optic Disc Assessment Trial found.[1]

"If you want to improve your diagnostic accuracy, it is important to use these types of imaging techniques," said Nicolaas J. Reus, MD, PhD, an ophthalmologist at Rotterdam Eye Hospital, The Netherlands, who coauthored the report. "We know that clinicians are missing the diagnosis of glaucoma. And this might be a way to make that number smaller."

The European Optic Disc trial analyzed the performance of 243 general ophthalmologists in 11 European countries. The clinicians were asked to evaluate stereo optic nerve photos from 88 eyes: 48 with varying stages of glaucoma, and 40 of them healthy.

The researchers also imaged the eyes with the GDx with variable corneal compensation (Carl Zeiss Meditec) and the Heidelberg Retina Tomograph I (Heidelberg Engineering). Machine classifier systems were used to evaluate the images for glaucoma.

Overall, the study found, the physicians correctly identified a mean of 80.5 percent of the stereo optic disc photos (range 61.4 to 94.3 percent). Their mean sensitivity—i.e., correct identification of glaucomatous discs—was 74.7 ± 10.6 percent. But the ophthalmologists' range on this measure varied by nearly 60 percentage points (43.8 to 100 percent). There also were statistically significant differences between countries. And accuracy declined for the older physicians compared with the younger ($p < 0.001$).

The ophthalmologists did better overall at identifying normal discs, with a mean specificity of 87.4 ± 11 percent. However, individual doctors correctly identified as few as 25 percent and as many as 100 percent of the healthy eyes.

The GDx-VCC nerve fiber indicator classification system yielded the correct results for 93.2 percent of the eyes (sensitivity, 91.7 percent; specificity, 95.0 percent). The HRT's best classifier diagnosed 89.8 percent of the eyes correctly (sensitivity, 85.4 percent;

specificity, 95.0 percent).

The results suggest that general ophthalmologists could reduce diagnostic errors by using GDx-VCC, HRT or a tool that has similar accuracy,[2] such as the optical coherence tomograph, Dr. Reus said.

"In one large study in Greece[3] more than half of the glaucoma cases they detected were undiagnosed, even though a large proportion of the subjects had been examined within the previous year by an ophthalmologist or optometrist," Dr. Reus said. In addition, the correlation between the number of years since an ophthalmologist's residency and inaccurate results indicates a need for refresher courses every few years in optic nerve head evaluation, he said.

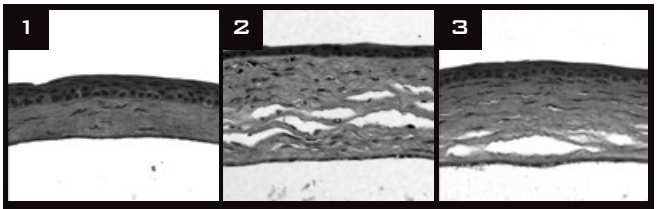
"We sometimes forget to update the knowledge that we once had," he said. "Our ideas about what a normal optic nerve disc should look like might drift or distort over time." —*Linda Roach*

1 Reus, N. J. et al. *Ophthalmology* 2010;117(4):717–723.
2 Medeiros, F. A. et al. *Arch Ophthalmol* 2004;122(6):827–837.
3 Topouzis, F. et al. *Am J Ophthalmol* 2008;145(2):327–335.

Financial disclosure: The European Optic Disc Assessment Trial was financed by an unrestricted grant from Pfizer. Dr. Reus has no other financial relationship with the company.

Cornea Report

Insight Into the Mechanisms of Pink Eye



SIMILAR REACTIONS. The first of these mouse corneas was injected with virus-free buffer **(1).** The second was exposed to the intact adenovirus that causes pink eye **(2).** The last was injected with the virus' empty capsid **(3).** The study found that the virus' coat caused corneal inflammation similar to that of the full virus.

A recent paper has shed new light on the biological mechanisms that result in corneal inflammation in epidemic keratoconjunctivitis (EKC).[1] While the adenovirus associated with EKC may cause disease by replicating, the scientists found that its physical components—particularly the viral protein coat or capsid—were instrumental in producing an inflammatory response in the corneal stroma. "We found that the most inflammatory part of the virus was actually its coat, and that it interacts with surface receptors on corneal stromal cells that initiate inflammation," said senior author James Chodosh, MD, MPH, physician-scientist at the Massachusetts Eye and Ear Infirmary.

"For the first time, we're beginning to understand the actual molecular mechanisms by which the EKC viruses cause disease, and to realize that it's not just viral growth and replication that contributes to the associated corneal inflammation," he said. This realization could eventually have important implications for treatment, Dr. Chodosh noted. Because the physical components of the virus are instrumental in causing the severe inflammation that accompanies the infection, antivirals that stop growth and replication might have limited use in reducing inflammation. Yet peptides that could block the interaction between the viral capsid and corneal cells might be a possible avenue for successful treatment.

In the study, scientists separated out the physical components of the EKC-causing adenovirus and studied their effects on the corneas of mice. They found that neither viral DNA nor viral gene expression was necessary for inflammation. But the viral capsid induced corneal inflammation similar to the intact virus. And virus-associated inflammation in the mouse cornea could be successfully blocked with a peptide containing components of the viral capsid—a treatment that could prevent the essential interaction between the protein capsid and cornea, Dr. Chodosh said.

In the study, the scientists also provided new details about the role of the toll-like receptor 9 (Tlr9) molecule in initiating immune responses in the cornea after adenovirus infection. Mice without the Tlr9 molecule developed clinical inflammation after adenovirus infection similar to wild type mice, but interleukin-6 expression and inflammatory monocytes were reduced in the Tlr9 knockout mice. "These data suggest that viral genomic DNA may differentially simulate cytokine expression and play a role in mononuclear cell infiltration but is not essential to the development of keratitis," the scientists write.

The next step in understanding how EKC occurs is to decipher which cell types in the cornea—such as keratocytes and bone marrow–derived cells—are responsible for specific responses to adenovirus components, Dr. Chodosh said.

"We are beginning to understand that the cornea plays an active role in inflammation—that cells in the cornea can actually generate inflammation. To get to the next level of therapies for corneal inflammation, we will need to understand that role very specifically," he said.

—*Barbara Boughton*

1 Chintakuntlawar, A. V. et al. *PLoS Pathog* 2010;6(4):1–13.

CHINTAKUNTLAWAR, A. V. ET AL. (2010) PLOS PATHOG 2010;6(4):1-13.

Cataract Update

Trypan Blue May Cause LEC Death

Trypan blue—often used in cataract surgery to facilitate capsulorhexis—may play a role in reducing the incidence of postsurgical posterior capsule opacification via its effects on lens epithelial cells (LECs). That's the suggestion raised by a prospective study conducted in São Paulo, Brazil.[1]

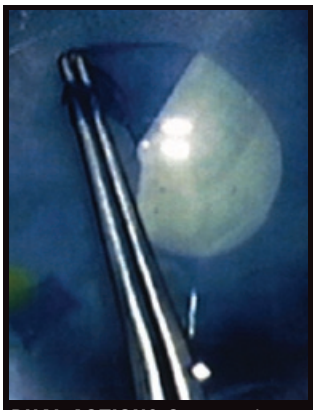
The researchers randomly assigned 30 patients—all of whom had early nuclear or posterior subcapsular cataracts—to either a treatment or a placebo group. Trypan blue staining was used in the treatment group only; in the placebo group, the capsulorhexis was created without the staining.

The lead surgeon performed a central capsulorhexis of approximately 5 mm, yielding a cell sample that was analyzed by several methods, including routine optical microscopy, transmission electron microscopy and an immunohistochemical test for beclin-1 expression (a marker of autophagy).

The results concur with previous studies showing that trypan blue–induced toxicity alters the density and viability of LECs. And this study is the first to find evidence of two pathways of cell death, apoptosis and autophagy. When taken together, the results suggest that the use of trypan blue may "help prevent proliferation of LECs after cataract surgery and thus reduce the incidence of posterior capsule opacification," the researchers write. They also caution that the "clear evidence of LEC death" suggests that cataract surgeons should take care when using trypan blue and that, especially, prolonged exposure or high concentrations should be avoided.

According to Steven I. Rosenfeld, MD, in private practice in Delray Beach, Fla., and a voluntary professor at the Bascom Palmer Eye Institute, the next step would be to demonstrate clinical relevance by comparing rates of posterior capsule opacification (PCO) in subsets of cataract patients with and without trypan blue exposure at the time of surgery. "If trypan blue truly does reduce the incidence of PCO, then it might be worth using it in all cataract patients," he said.

He cautioned, however, that "it's possible that the trypan blue wouldn't kill enough LECs—there might be some left in the far reaches of the capsular bag, such as the equator, that would then be able to proliferate and contribute to PCO. Still, given that PCO is such a clinically important problem, this is a provocative study." —*Jean Shaw*



DUAL ACTION? One study shows that in addition to staining the capsule, trypan blue may reduce the likelihood of posterior capsule opacification.

1 Portes, A. L. F. et al. *J Cataract Refract Surg* 2010;36:582–587.

Eye on Religion

Meals at Ramadan May Affect IOP, Tears

Ophthalmologists in Turkey found that increased intraocular pressure and reflex and basal tear secretion among a group of 31 healthy volunteers fasting in observance of Ramadan appear to be associated with fluid loading at the predawn meal.[1]

During Ramadan, most Muslims eat a high-carbohydrate predawn meal and drink nearly 50 percent more water than they consume in a normal diet in a 24-hour period, said Hürkan Kerimoğlu, MD, a coauthor of the study and assistant professor of ophthalmology at Selçuk University, Konya, Turkey.

While the exact amount of water taken at the predawn meal may be unknown, the authors cite evidence from an earlier study showing that drinking one liter of water significantly increases IOP for more than two hours.[2]

"Our results revealed that fluid loading at the predawn meal might increase the IOP (although within normal range) and tear secretion," said Dr. Kerimoğlu.

The authors took measurements at 8 a.m. and 4 p.m during Ramadan and again one month later at the same times. During Ramadan, mean IOP at 8 a.m. was 14.19 ± 3.53 mmHg, which was significantly higher than during the nonfasting period ($p = 0.005$), and at 4 p.m. IOP showed a decrease to 11.74 ± 2.39 mmHg, which was significantly lower ($p = 0.013$) than when patients weren't fasting. Reflex and basal tear secretions were significantly higher than normal at 8 a.m. during Ramadan ($p = 0.006$, and $p = 0.014$, respectively) but showed little difference from normal at 4 p.m.

—*Arthur Stone*

1 Kerimoğlu, H. et al. *Eye* 2010;23:97–100.
2 Buckingham, T. and R. Young. *Ophthalmic Physiol Opt* 1986; 6:95–99.