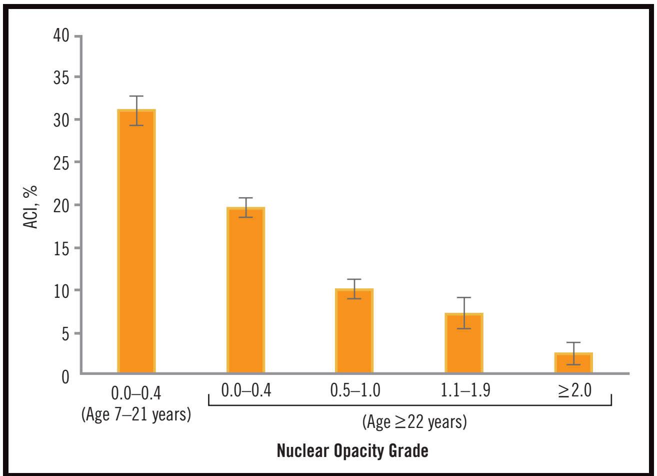
High-Tech Detection of Cataract Risk

A joint effort by scientists at NASA and the National Eye Institute has produced a noninvasive device that, by tracking the levels of alpha-crystallin in the human lens, can identify the patients who have clear lenses today but might be at the greatest risk for developing cataracts in the near future.

Originally developed by NASA biophotonics expert and senior scientist Rafat R. Ansari, PhD, to study protein crystallization in space, the device uses a laser-light technique called dynamic light scattering (DLS) to take a "molecular snapshot" of the amount of alpha-crystallin available to prevent damaged proteins from clouding the lens.

"The DLS alpha-crystallin measurements can be used to track early lens changes similar to the way creatinine clearance is used to track kidney functional reserve," said Manuel B. Datiles III, MD, lead author of a report on the device in the *Archives of Ophthalmology*.[1] Dr. Datiles is a medical officer and a senior clinical investigator at the NEI.

The DLS system uses a small fiberoptic probe to aim a low-energy beam of near-infrared laser light (80 to 100 µW, 670 nm) into the lens for five seconds, and analyzes the resulting electric field patterns ("light scatter"). A computer decodes the data to determine the types, sizes and relative numbers of protein molecules in the target tissue, with a standard error of 3 percent.



INVERSE CORRELATION. A new device can detect alpha-crystallin in the lens. This measurement can be used to predict a patient's risk for developing cataract, as there appears to be a strong inverse correlation between alpha-crystallin levels and nuclear opacity.

The DLS probe is mounted inside a keratoscope, but it can be easily adapted to another ophthalmic device, such as a slit lamp, Dr. Datiles said.

He and his colleagues studied lens protein levels in 380 eyes of 235 patients, 7 to 86 years old. In the youngest group (7 to 21 years old), 31 percent of the light scattering was from alpha-crystallin, a "chaperone molecule" that mitigates oxidative damage in the lens. It binds to damaged proteins and prevents them from aggregating to form a cataract.

The mean levels of alpha-crystallin declined steadily after age 21. In addition, the

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study showed:

- There was an inverse correlation between the level of alpha-crystallin and the grade of nuclear lens opacity on the AREDS scale ($p < 0.001$).
- This association held with increasing age, even in eyes that remained clinically clear (graded 0–1) at the slit lamp ($p < 0.001$).
- In subjects with a lens opacity grade of ≤ 1.0, alpha-crystallin reserves in those aged 60 was half that of the youngest group, and in those 76 years or older, the average level was about one-sixth as high as in the youngest patients.

DLS also illuminated several mysteries. In middle-aged subjects with 20/20 acuity who complained of distorted vision, testing detected clinically invisible clumps of oxidized, damaged proteins on the visual axis. In a 42-year-old man, Dr. Datiles was able to observe a sudden plummeting of alpha-crystallin levels that correlated with rapid development of an early presenile nuclear cataract. And in another subject who was older than 60, 26.5 percent of the lens light scatter was from alpha-crystallin—equivalent to the level in an average 26- to 35-year-old.

DLS offers the possibility of speeding up the search for new antioxidants to protect the aging lens, Dr. Datiles said. "And, even if there's no drug for prevention, you could warn your patients with low levels of alpha-crystallin that their lifestyle choices or environment are harming their eyes."

Widespread use of DLS in the lab or office is not imminent, however. Currently, there is only one ophthalmic prototype of Dr. Ansari's DLS detection system.

—*Linda Roach*

1 *Arch Ophthalmol* 2008;126(12):1687–1693.

Dr. Ansari is the coholder of a patent on the device. Dr. Datiles has no financial interest.

Comparative Ophthalmology

Ocular Evolution in the Deep-Sea Spookfish

SEEING DOUBLE. The deep-sea spookfish's unique ocular construction allows it to see, in focus, both above and below it. **(1)** A dorsal view shows upward-pointing tubular eyes, and the black surfaces next to the light-colored eyes are the upper surfaces of the diverticula. **(2)** A ventral view of the diverticula showing reddish eye shine.

While fishing over the Kermadec Trench near New Zealand—the second deepest spot on Earth—an international team of scientists brought up a live deep-sea spookfish in the ship's nets from a depth of about 800 m. It was quite the catch. Upon further study, the researchers found that part of the *Dolichopteryx longipes* eye uses a mirror to make a focused image, the only known adaptation of its kind in all vertebrates.[1]

So it can maximize the dim downwelling sunlight and see silhouettes of animals above it, the spookfish—like many other fish at these depths—has developed upward-pointing tubular eyes, which use lenses to focus the light. But these kinds of eyes, with their restricted visual field, have a downside. They miss a lot of the bioluminescence all around them. This is light emitted by about 85 percent of all animals in the deep sea and is used to communicate, startle predators and camouflage, said Ron Douglas, PhD, marine biologist and professor of optometry and visual science at City University, London.

The spookfish has solved this problem with a unique mirror. Connected to its tubular eyes, on either side of its head are lensless ocular diverticula, which look downward and detect bioluminescence using thousands of reflective crystals derived from a retinal tapetum. Many nocturnal animals have reflective tapeta behind their retinas, which maximize absorption of light by photoreceptors, said Prof. Douglas. But the spookfish diverticulum focuses light using a mirror in front of the retina.

"When we first caught the fish, we photographed it from above and observed an eye shine reflex," said Prof. Douglas, coauthor of the spookfish report. "Then we photographed it from underneath, also detecting eye shine—the first indication that the animal was seeing from both above and below."

The next step involved sectioning the eye and working out its detailed anatomy under the microscope. Serial sectioning and reconstruction revealed that the retinas of the two parts of the eye—tubular and diverticular—were continuous, although they initially appeared to be separate. But most exciting was the discovery of the varying orientation and arrangement of reflective plates within the ocular diverticulum, allowing formation of bright, high-contrast images. Computer modeling helped prove that the mirror could actually produce a focused image.

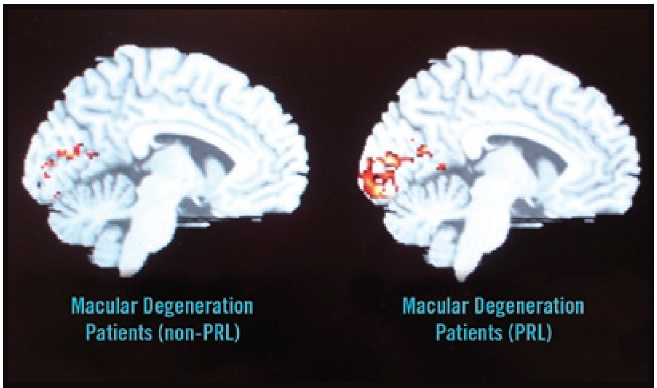
"I think this was a simple matter of evolution," said Prof. Douglas. "It's difficult to evolve a second lens, but it's a relatively smaller number of mutations for a reflective tapetum to become a mirror." —*Annie Stuart*

1 Wagner, H. et al. *Current Biology* 2009;19;108–114.

Current Biology/Elsevier

Vision and the Brain

Visual Cortex Responds to Eccentric Viewing



STIMULATING SIGHT. When patients with central vision loss from age-related macular degeneration used preferred retinal location (PRL) viewing, the MRI showed increased activity in the same parts of the visual cortex that are normally activated when healthy patients focus on objects with their central visual field.

Scientists have long known that when macular degeneration patients lose the spatial resolution of the fovea, they begin to rely on a preferred retinal location (PRL), or eccentric viewing, to continue performing necessary activities such as reading and recognizing facial expressions. Now scientists from Georgia Tech and Emory University have shown that this adaptation results in the reorganization of neural connections in the visual cortex.[1]

In the study, the scientists presented 13 volunteers—six with macular degeneration and seven with normal vision—with a series of tests designed to visually stimulate their peripheral visual regions. Magnetic resonance imaging showed that the brain activity in macular degeneration patients increased when their PRLs were stimulated. MRIs also revealed that this adaptation increased brain activity in the same parts of the visual cortex that are normally activated when healthy patients focus on objects with their central visual field. In essence, the parts of the visual cortex that usually represent central vision were reprogrammed in those with macular degeneration to process information from other parts of the eye—namely each patient's PRL.

While other studies on the plasticity of the visual cortex have produced contradictory results, this study is the first to present evidence that not only can the brain reorganize itself in response to retinal disease but that also this reorganization is directly related to the patients' behavior of training themselves to use this new region of their visual field.

Although the brain seems to reorganize itself in response to idiosyncratic PRLs in macular degeneration patients, Dr. Schumacher and his fellow researchers would like to test whether the same process could be initiated by short-term low vision training. "We'd like to discover whether patients can activate a PRL region for central visual tasks in a relatively short period," he said.

—*Barbara Boughton*

1 Schumacher, E. H. et al. *Restor Neurol Neurosci* 2008;26:391–402.

Retina Report

Bevacizumab May Raise Blood Pressure

Should ophthalmologists discuss with their patients the potential effects that intravitreal injections of bevacizumab (Avastin) may have on blood pressure? Researchers in Istanbul say, yes. Furthermore, patients who take antihypertensive drugs should receive a cardiology consultation, they say.

In the Turkish study, patients with subfoveal choroidal neovascularization caused by AMD experienced elevations in systemic blood pressure that were measurable three to six weeks after an intravitreal injection with bevacizumab.[1] "We observed this effect in hypertensive patients who were taking antihypertensive drugs as well as in patients with normal blood pressure," said Rifat Rasier, MD, lead study investigator and professor of ophthalmology at Istanbul Bilim University.

In their paper, the researchers note that several studies have shown that the inhibition of VEGF can cause, or increase, systemic hypertension in patients. With this in mind, they followed 82 patients, aged 53 to 81, for six weeks and compared those diagnosed with hypertension and taking antihypertensive medication with patients who had normal blood pressure and were not taking antihypertensive drugs to determine the short-term effects on systemic blood pressure of intravitreal bevacizumab.

"Our results are statistically and clinically significant with regard to systolic and diastolic blood pressure," said Dr. Rasier. "They reveal that there is a risk of dysregulation in blood pressure or a persistence of hypertension in hypertensive patients taking antihypertensive drugs after receiving intravitreal bevacizumab injections."

—*Leslie Burling-Phillips*

1 Raiser, R. et al. *Eye.* Published online Dec. 12, 2008.