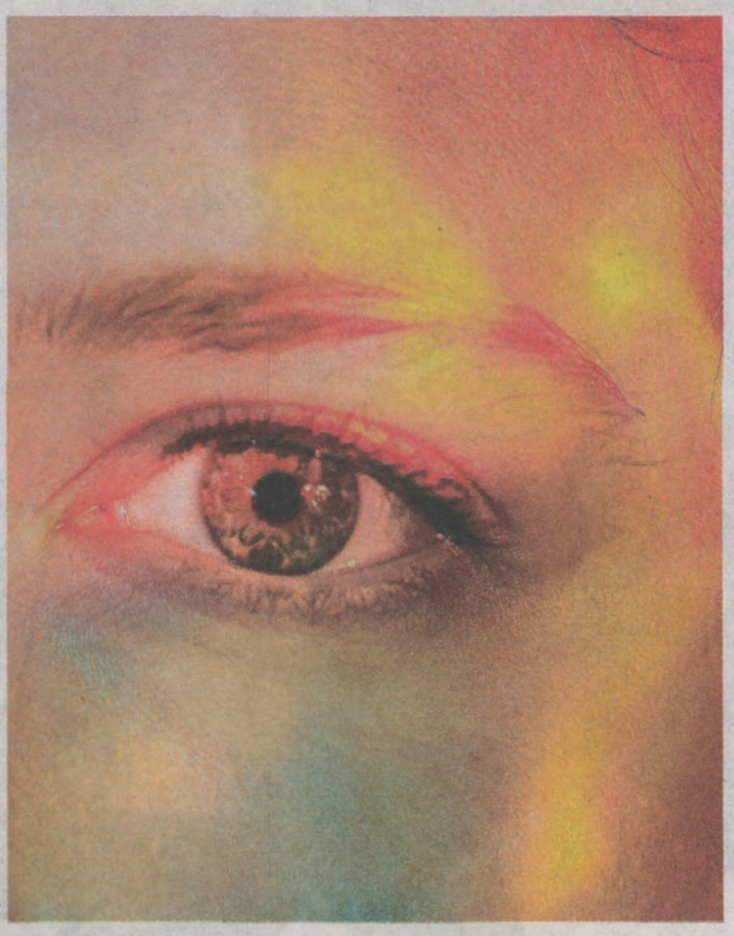
Anne Hanneken, associate professor of molecular medicine at Scripps Research Institute, is co-leader of the effort to bring eyes from organ donors back to life.

A SPARK OF LIFE AFTER DEATH IN SIGHT RESEARCH

Scientists are restoring function to the eyes of organ donors, providing a new path for studying diseases like macular degeneration **By Ron Winslow**



Researchers have discovered a way to revive eyes from organ donors after death, an advance that opens doors to progress against age-related macular degeneration, glaucoma and other major causes of blindness.

The accomplishment, which many experts hadn't thought possible, gives scientists the ability for the first time to conduct experiments on a functioning human retina, potentially unlocking a treasure trove of new information about the chemistry of vision and what goes wrong in the intricate network of retinal cells when people start losing their sight.

"If you don't understand what the fundamental basis of these abnormalities is, you won't be able to identify drugs or other treatments that could treat these conditions," said Anne Hanneken, associate professor of molecular medicine at Scripps Research Institute, La Jolla, Calif., and co-leader of the effort.

The achievement also may help advance prospects for eye transplants, though Dr. Hanneken cautioned that such potential treatments are many years away. Doctors for decades have been able to transplant corneas from donor eyes, but that outer layer of the eye that helps with focus doesn't have a blood supply and isn't directly connected to retinal neurons that send sight signals to the brain. Getting transplanted eyes or retinal tissue to communicate with the brain is a daunting challenge.

Ambitious research is under way across the field of ophthalmology to find new ways to prevent, slow or treat vision loss. Strategies range from developing drugs that protect people with vision loss against further damage to restoring vision with cell and gene therapies that would replace, regenerate or repair retinal neurons that no longer work. The first approval for any gene therapy came in 2018 for a mutation that causes blindness.

More than 7 million Americans of all ages are living with loss of visual acuity, according to a study published last year in JAMA Ophthalmology, of whom more than 1 million are blind. The toll is growing, partly reflecting an aging population and a high prevalence of diabetes, a precursor to such diseases as glaucoma and diabetic retinopathy. Worldwide, more than 250 million people have vision loss while a further 43 million are blind.

Sight begins when light passes through the cornea and lens and hits neurons called photoreceptors that live in the retina in the back of the eye. It takes a seamless network of other retinal cells—each with distinct roles—to process the light signals and transmit them via the optic nerve to the brain, which converts the data into the clear, focused, color images we see.

Eye diseases such as glaucoma, age-related macular degeneration, and the inherited retinitis pigmentosa exact a toll on vision by damaging or killing various retinal cells. A class of drugs including Regeneron Inc.'s Eylea and Roche Holding AG's Lucentis can be injected into the eye to treat wet age-related macular degeneration—the most advanced and debilitating form of AMD and the leading cause of reading loss and irreversible blindness in the elderly.

The disease damages a layer of neurons called the retinal pigment epithelium, which is crucial to the survival of the photoreceptors. The injections stanch the growth of abnormal, leaky blood vessels that grow under the macula region of the retina, which is responsible for clear central vision.

But the drugs don't affect dry AMD, the more common and earlier stage of AMD, and may be less effective against a host of genetic alterations that each represent a different variant of the disease.

24
the number of hours that revived eyes have remained viable for research, according to Dr. Hanneken.

"We whack everything with the same hammer," said Julia Haller, ophthalmologist in chief at Wills Eye Hospital, Philadelphia. "A more sophisticated understanding that would potentially lead to more drug targets and more personal approaches would be fantastic."

So would, say, more insight into early stages of macular degeneration, where treatments are needed to protect against worsening disease. "You could imagine doing experiments in organ-donor tissue from people who had early macular degeneration," said Joan Miller, chief of ophthalmology at Harvard-affiliated Massachusetts Eye and Ear. "It might help you tease out what are some of the early steps" in the condition.

Researchers for decades have relied heavily on mouse studies to help understand the basis of human eye diseases. But mice don't see in color. "They don't even have a macula, and they don't get macular degeneration," said Dr. Hanneken, who is also a retinal surgeon at Scripps Memorial Hospital, La Jolla. "You want a model that mimics the human disease."

That was the motivation behind Dr. Hanneken's six-year quest to bring dead eyes back to life. It drew skeptics. Trying to revive dead nerve cells challenged a basic belief that the death of neurons is irreversible.

But her research with eyes obtained after autopsy convinced Dr. Hanneken that some metabolic activity persisted at least briefly after death. Experiments with both mice and human post-mortem eyes showed that loss of oxygen and changes in acidity were the main culprits in the rapid demise of retinal cells.

She began a collaboration with Frans Vinberg, a neuroscientist at University of Utah, who built a container akin to the coolers transplant surgeons use to transport organs recovered from donors. The container is equipped with tiny tanks (which the researchers usually fill at a scuba-dive shop) to provide oxygen to donor eyes. The eyes are also bathed in a cocktail of nutrients designed to normalize acidity and wake up the retinal cells and restore their function.

For some two years, the researchers obtained donated eyes from several sources and carried them in the container to their lab for testing. Apart from an occasional small electrical signal, they got nothing. The problem, they concluded: Too much time had elapsed between the death of the donor and the removal of the eyes.

Then an organ-donor organization agreed to allow Dr. Hanneken to recover eyes from patients who were declared brain dead, but who remained on life support to keep their heart and other organs viable for transplant.

"That changed everything," she said. In eyes recovered within 30 to 60 minutes after life support was removed, the researchers were able to detect the entire light-signaling cascade through the macula region of the retina—from the photoreceptors that first absorb the light to the neurons that send the signals to the brain. While doctors can measure such signals to diagnose sight loss in patients, the new research now enables experiments and drug tests on the donor eyes that wouldn't be possible on living people. Details of the effort were published in the journal Nature in May.

The researchers couldn't prove that the revived eyes could actually see. "The eyes can respond to light, [but] they can't read the headlines of The Wall Street Journal," Dr. Hanneken said. "They're not connected with a brain." So far, revived eyes have remained viable for research for up to 24 hours, she said.

Efforts to analyze the datastream from the light signals have already revealed promise for learning about molecular abnormalities associated with various retinal diseases and devising ways to treat them, she said.

Indeed, having access to revived human retinal tissue marks an advance that will "help us better understand how these cells work and influence that response with drugs or changes in gene expression to allow them to function better," said Akrit Sodhi, an ophthalmologist and researcher at Johns Hopkins Medicine, Baltimore, who wasn't involved in the research.

Dr. Hanneken believes the research has implications beyond ophthalmology: If retinal neurons can be brought back to life, what about central-nervous-system cells associated with other diseases? She has already begun discussions with scientists who are looking for ways to overcome damage to neurons associated with stroke and Parkinson's and Alzheimer's diseases.