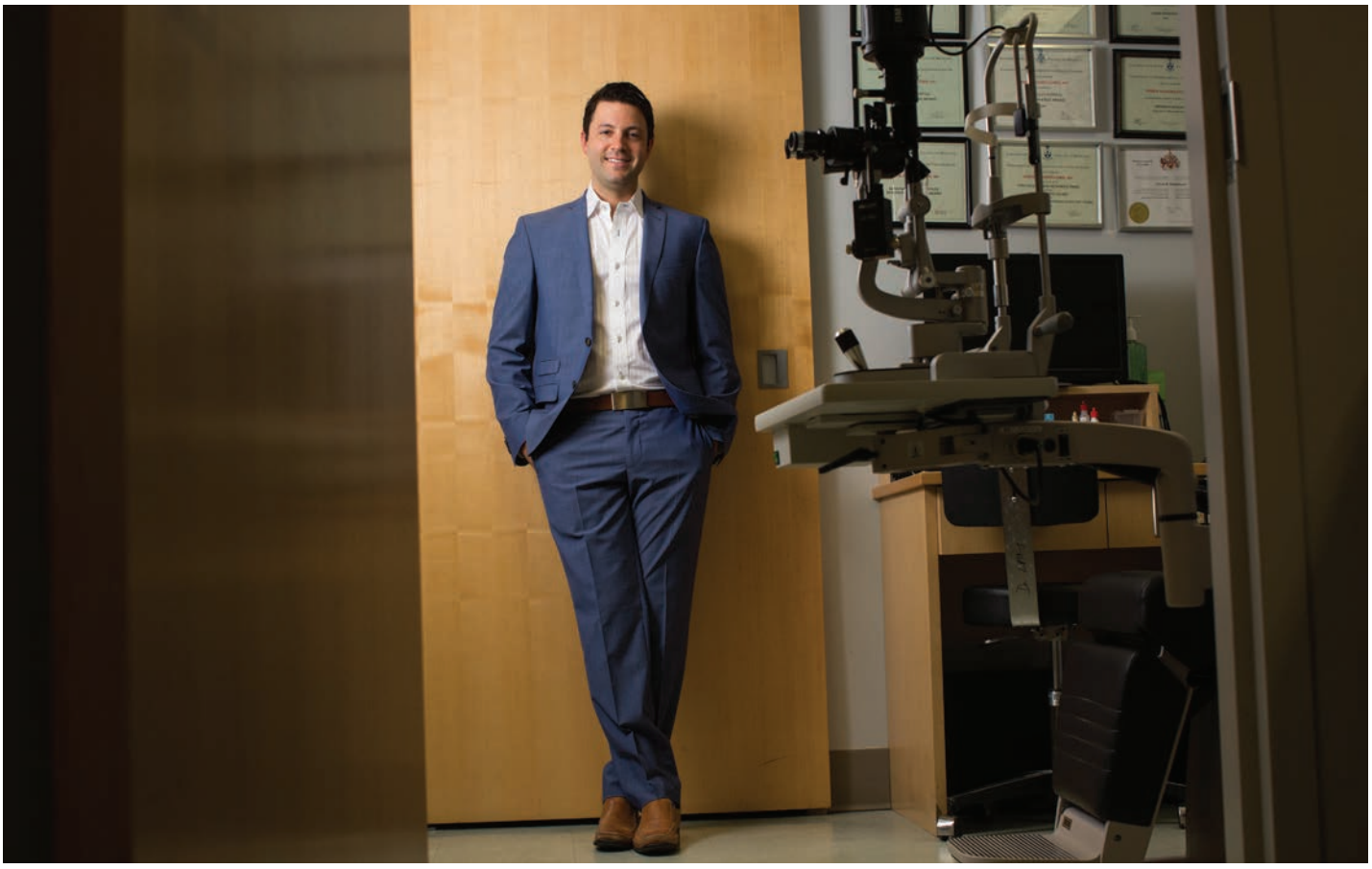


Are your eyes also the windows to your brain?

Dr. Efrem Mandelcorn is exploring whether a simple eye test could help detect Alzheimer's earlier

Shelley White

The test takes about a minute … two minutes, tops.

Perched on a stool, face supported on a chinrest, the patient looks into the optical coherence tomography (OCT) machine. A white cross on a black background is in her field of vision, with red lines that move up and down, back and forth. Dr. Efrem Mandelcorn, clinician investigator at the Krembil Research Institute and a retinal surgeon at the Donald K. Johnson Eye Institute's Retina Clinic, directs a laser into the patient's eye. He's using light waves to take cross-sectional pictures of the patient's retina and optic nerve. It's painless, it's simple and it's over very quickly.

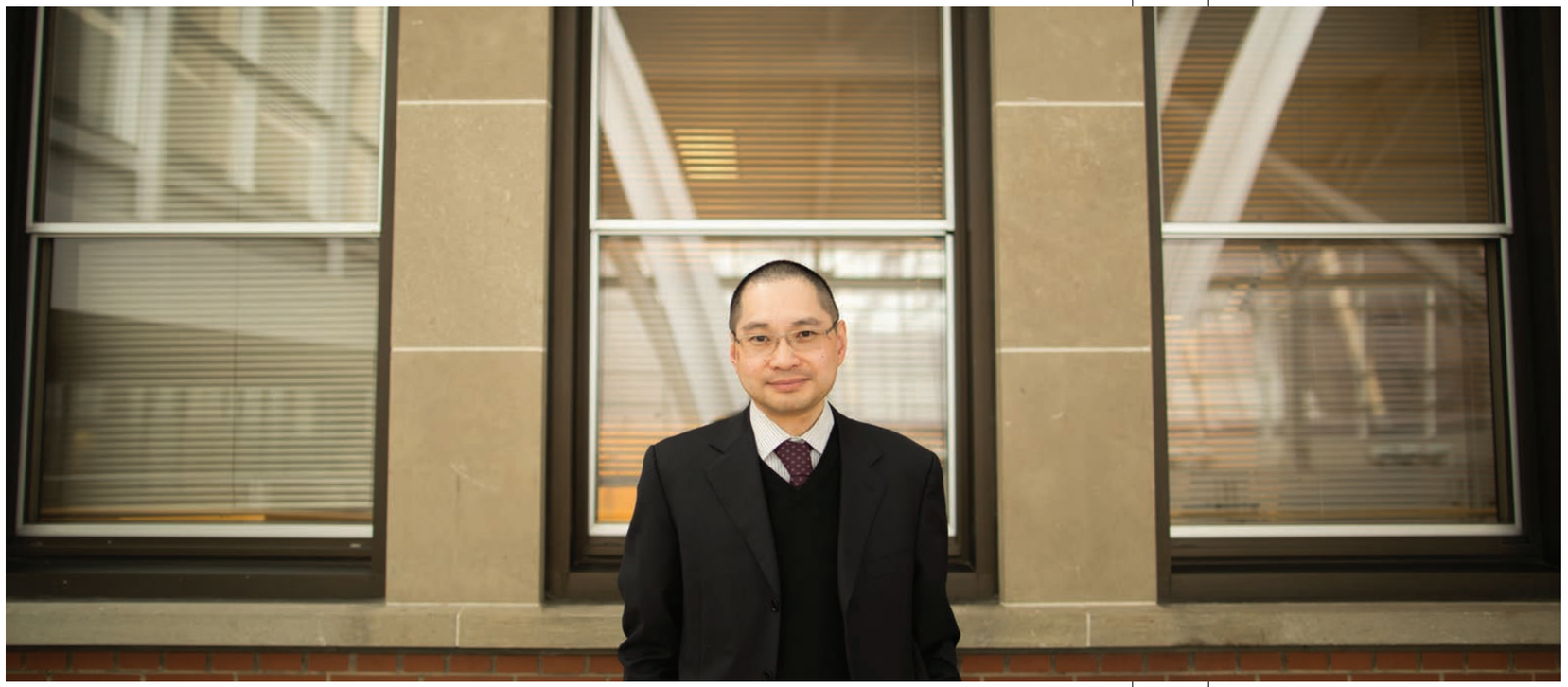
OCT has been used in optometrist's and ophthalmologist's offices to diagnose eye diseases like glaucoma for years. But researchers like Dr. Mandelcorn are hoping this simple test could be used someday to help doctors diagnose neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS), even before patients show symptoms.

"We have very good technology to look at the eye," explains Dr. Mandelcorn. "You can look at what's called the retinal nerve fibre layer, which goes right to the optic nerve. It is a direct connection from the eye to the brain – a window to the brain."

Dr. Mandelcorn says that some smaller studies showed that when looking at images of the optic nerve head, the upper or "superior" portion of the nerve is thinner in late Alzheimer's, more so than in a control group of subjects the same age.

If this nerve fibre layer loss could be proven to be a biomarker – an accurate early indicator of Alzheimer's – then a simple eye test could become a valuable diagnostic tool for neurologists.

"The idea is that if you can find a pattern of nerve fibre layer loss on an OCT scan, which is exquisitely detailed, you



can then maybe say this person is at risk [for Alzheimer's]," says Dr. Mandelcorn.

The prospect of an eye test to predict the onset of Alzheimer's is, so far, still a theory, but it's one of the exciting avenues being explored by the Ontario Neurodegenerative Disease Research Initiative (ONDRI). ONDRI is an Ontario-wide, large-scale, collaborative study that could lead to major breakthroughs when it comes to the diagnosis and treatment of neurodegenerative diseases.

As our population ages, dementia is becoming the single greatest cause of disability in Canada's senior population. More than 500,000 Canadians have dementia, and more than 100,000 will develop dementia in the coming year.

By investigating early predictors of dementia in many forms, the study endeavours to identify tools to diagnose and treat these diseases to soften the impact on patients and their families.

Dr. Barry Greenberg is the director of strategy for the Toronto Dementia Research Alliance and the director of neuroscience drug discovery and development at University Health Network (UHN). He's the ocular co-lead for ONDRI and says the overarching goal is to do "deep characterization" of the people who have the neurodegenerative diseases included in the study. ONDRI will study close to 600 participants enrolled for up to three years – people who have been clinically identified as having these diseases.

"It's to get an idea of the features, the phenotypes of these individuals and how they change from year to year [as the disease progresses]," says Dr. Greenberg.

In partnership with the Ontario Brain Institute, ONDRI will employ more than 50 investigators at 13 sites around the province to study five neurodegenerative diseases. These are some of the most pervasive and debilitating diseases that humans can face: Alzheimer's disease, Parkinson's disease, ALS, frontotemporal lobar degeneration (a group of neurodegenerative diseases that cause dementia) and vascular cognitive impairment (resulting from stroke). Each of these diseases has one symptom in common: dementia. (Although not everyone with Parkinson's or ALS gets dementia, it is associated with these diseases.)

As part of the study, researchers will do eight assessments with each participant. One is gait and balance; another is neuroimaging. Other tests include neuropsychology (measuring cognitive skills such as attention and memory) and genomics (blood samples taken to compare all participants genetically). There are two ocular tests. One involves eye tracking or measuring eye movements while people follow a light. Dr. Mandelcorn is an investigator for the other ocular test, the OCT imaging described earlier.

"If you really want to be sure about it, you have to wait until the patient dies and [then] look into an autopsy ... so if an eye test works, this is great."

– Dr. David Tang-Wai

He likens ONDRI to a Rubik's Cube – each row of colours represents a different assessment or a different disease or a different period of time in the study. As you move the squares and mix up the colours, it's like the researchers detecting patterns in how the factors intersect and interact.

"Each investigator has his/her own platform," he explains. "If you get all this rich data from all these different platforms, you can then tease out what happens over time, what happens between diseases, what happens within the same disease."

But the question could be asked: "If a doctor were able to predict if someone was going to develop Alzheimer's, ALS or Parkinson's before it happens, how could that help someone?" After all, there are no cures for any of these diseases as of yet.

"From a basic science perspective, you want to catch something early while the brain is still normal," says Dr. Mandelcorn. "If you catch it late, then those brain cells are gone. Theoretically, if you catch something early, then you can preserve cells. And what that means for patients is, instead of getting dementia or Alzheimer's now, they get it five or 10 years later. For them, for their families and for the health system, it could be very significant."

Dr. David Tang-Wai is a neurologist, co-director at the UHN Memory Clinic, clinician investigator at Krembil Research Institute and one of the recruiting physicians with the study. His job is to recruit patients with early Alzheimer's disease or mild cognitive impairment to participate in the study. He says that finding a cheaper, faster way to diagnose Alzheimer's would be a boon to both patients and researchers. The currently methodology used to diagnose the disease (physical examinations, MRI or positron emission tomography (PET) scans) is not always accurate.

"If you really want to be sure about it, you have to wait until the patient dies and [then] look into an autopsy," he says. "We can do a spinal fluid exam and measure Alzheimer's proteins in the spinal fluid, but it's a needle in the back, and not too many people enjoy that particular test. So, if an eye test works, this is great. If it complements what we do now and improves our accuracy, that will just be a step forward."

An ocular test could also be a way to detect whether a trial Alzheimer's medication is working to prevent, or slow, the disease. Normally, doctors need to take a "wait-and-see" approach when testing an Alzheimer's drug, employing cognitive tests over years to measure impairment. Having a method that could accurately measure the progression of Alzheimer's would be a major step forward when it comes to drug research, says Dr. Mandelcorn.

"We use OCT scanning in ophthalmology all the time in the case of glaucoma to see how people respond to medication when they're asymptomatic, and if that worked in other types of diseases, it would be very interesting," he says.

Another intriguing avenue the study is pursuing is the connection between vascular disease (an abnormal condition of the blood vessels) and dementia. Dr. Greenberg says that studies in the United States and Europe are showing that vascular abnormalities may be part of the very early stages of neurodegenerative disease.

If scientists are able to prove that the same lifestyle changes that can ward off vascular disease (like diet, exercise and quitting smoking) could also prevent Alzheimer's, it would be a major breakthrough.

"Studies have shown that good cardiovascular health on a population statistic level depresses the prevalence of dementia at any given age," Dr. Greenberg notes. "Cardiovascular health, lifestyle, diet, intellectual engagement – all these things contribute to activity in the brain, to oxygenation to the brain. So it makes a great deal of sense."

As the investigators continue their research, there are already plans in place to extend the study.

"Unfortunately, Alzheimer's and Parkinson's are not diseases that last one or two years," says Dr. Tang-Wai. "The longer we can study people, the better we get at it, and the better we can answer questions." ■