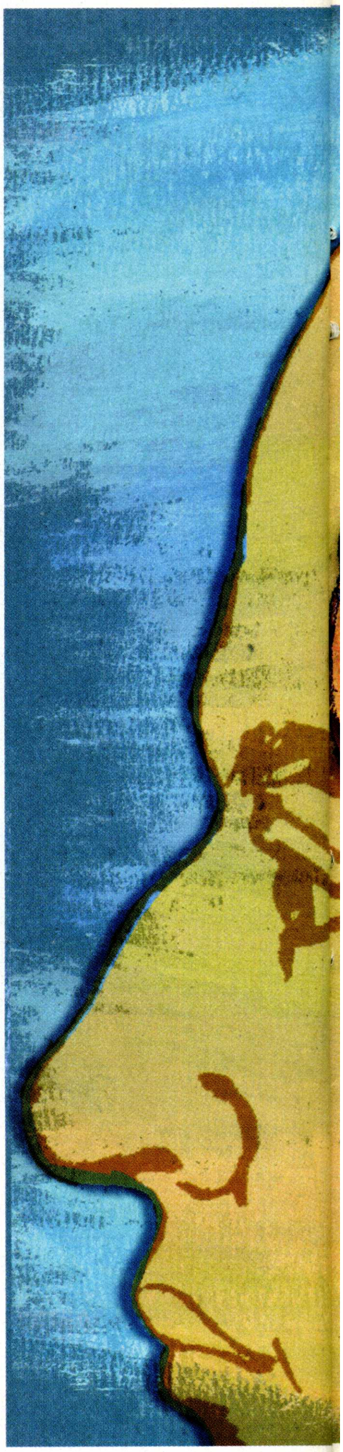
outsmarting Alzheimer's

Rutgers-Newark neuroscientists have devised a way to predict who is most at risk for the disease—long before it strikes.

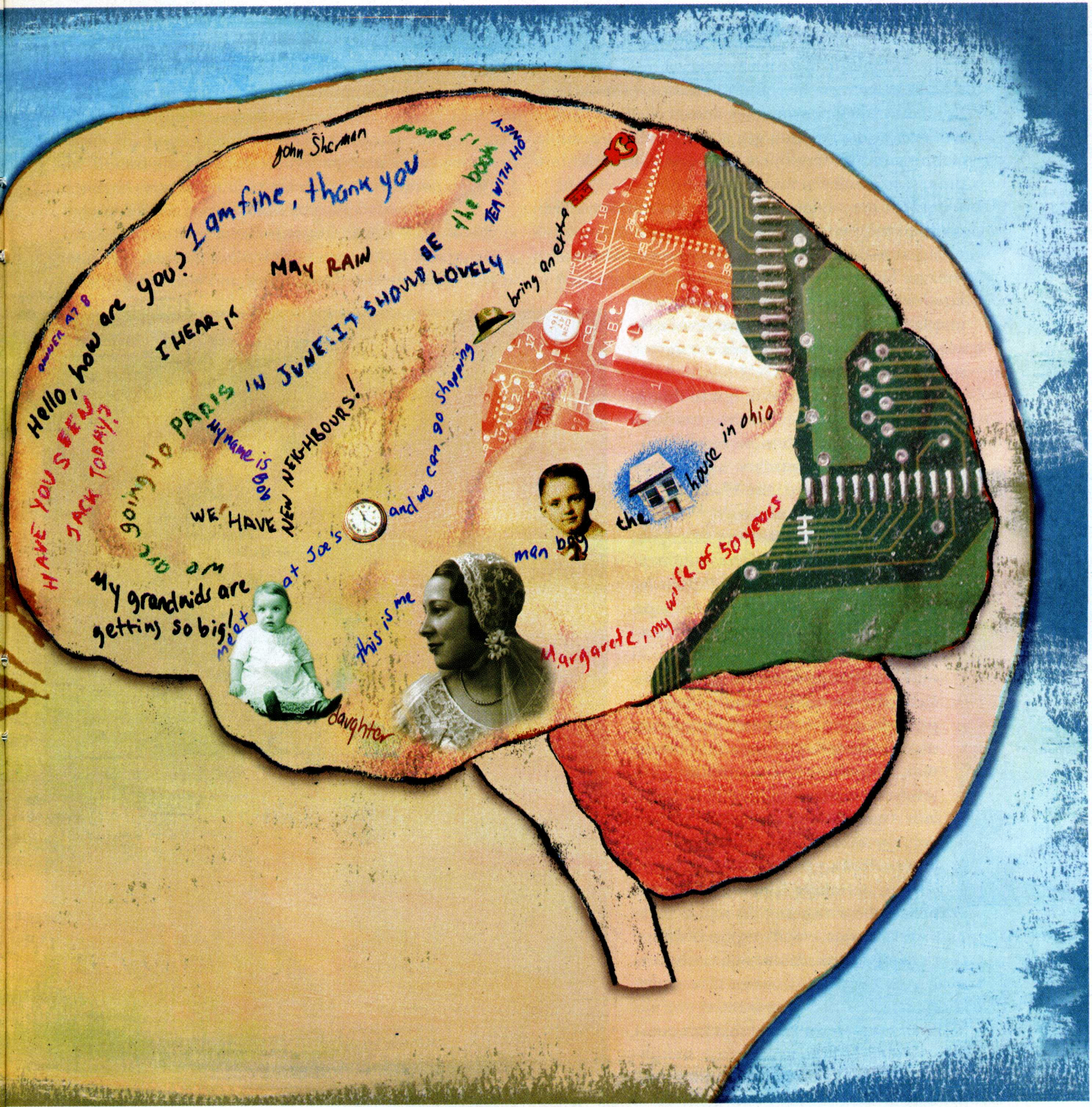
By Tom Ewing

Alzheimer's disease is a thief. It steals lives from those who fall victim to it, as well from those closest to them. Nor is it selective; those who have lived a life of the mind are far from immune. In the 1999 memoir, *Elegy for Iris,* John Bayley lovingly recounts the life he shared with his wife, Iris Murdoch, the highly esteemed British novelist who taught philosophy at Oxford. Alzheimer's, Bayley writes, erased her entire past. "She does not know she has written 26 remarkable novels, as well as her books on philosophy; received honorary doctorates from major universities; become a Dame of the British Empire."



You have to
that
for the patient

Illustration by Ellen Weinstein



be aware that these are *real human* beings—and you've *discovered* something that is going to have implications and family for the *rest of his or her life.*

By the time memory loss is noticeable, Alzheimer's is already well entrenched. Short of a cure, scientists hope to identify—before symptoms appear—who is most at risk so that intervention can start as soon as possible. Cognitive tests developed at Rutgers–Newark show promise in doing just that.

Still in the experimental stage, the tests have been given to some 100 subjects at New York University's Aging and Dementia Research Center in Greenwich Village. Many who come to be tested simply want to know whether an increasing tendency to misplace eyeglasses or forget names of new acquaintances at dinner parties is a sign of something more serious.

The testing goes something like this. A subject—let's call her Sarah—comes to the center for an interview with a neuropsychology researcher, a grad student, affiliated with the Memory Disorders Project at Rutgers–Newark. Sarah then takes a battery of cognitive tests to evaluate her memory, intelligence, and attention span. As the testing proceeds, she finds some of the tasks to be almost embarrassingly juvenile.

> ALZHEIMER'S IS A PROGRESSIVE DEMENTIA, IN WHICH PATIENTS LOSE ALL HIGHER COGNITIVE FUNCTIONS, INCLUDING MEMORY, LANGUAGE, AND PERCEPTION.

In a "paragraph-recall" test, for example, the student reads a lengthy passage of prose to Sarah, pauses for several minutes, and then asks her to recite what she heard. Another test involves a computer image of a mouse in a maze. If Sarah presses the correct key, the mouse skitters through the labyrinth and discovers a piece of cheese, squeaking happily. When she presses the wrong key, the mouse finds only a black square and responds with a discouraged squeak. Sarah, who catches on quickly and is able to connect mouse and cheese repeatedly, aces the tests.

Sarah's test scores reveal that her occasional bouts of forgetfulness are merely the consequence of age-associated memory impairment (AAMI), informally known as "senior moments." For most people, the ability to learn new information and recall it at will declines naturally and very gradually with age. Forgetfulness is only a cause for concern when the severity of it—as measured by the paragraph-recall exercise and several other standard memory tests—exceeds that which has been established as normal.

Her test scores give her another piece of valuable information: That she is able to absorb new information and apply it to a changing situation. This ability strongly indicates that the hippocampal region of her brain is blissfully intact.

Sarah's cognitive tests were designed by researchers working with Rutgers' Memory Disorders Project, established in 1998 as part of the university's Center for Molecular and Behavioral Neuroscience (CMBN) in Newark. The project is run by Drs. Mark Gluck and Catherine Myers,

who are optimistic that these tests and other related work will grow to play a significant role in diagnosing early-stage Alzheimer's disease, a form of dementia that now afflicts an estimated four million Americans.

Gluck, an irrepressibly energetic 40-year-old man who backpacks, kayaks, or skis when not in the lab, grew up in Princeton. After studying computer science and psychology at Harvard, he pursued a doctorate at Stanford University, where he was drawn to neuroscience. "At Stanford," he says, "I became interested in how learning and memory in humans are similar to

Photograph by Dennis Connors

those functions in animals." For his thesis, Gluck began developing computer models that simulate the neural networks involved in animal learning. Says Gluck: "That was really the beginning of what was to become the core part of all of the work we're now doing—the development of computer models that reveal links and similarities between human and animal learning."

After receiving his doctorate in 1987 and working at Stanford as a postdoctoral researcher, Gluck was recruited to Rutgers in 1991 by Drs. Paula Tallal, a behavioral neuroscientist, and Ian Creese, a molecular neuroscientist, who jointly administer CMBN's research activities. "We saw him as an innovative and productive researcher," recalls Creese, "and he's fulfilled his promise, particularly by expanding his research into the clinical realm."

Since then, Gluck has been widely recognized for advances that he's made in his field, most notably by the National Science Foundation (NSF). In 1996, he won NSF's Presidential Early Career Award for Scientists and Engineers, an honor that cited his accomplishments as both researcher and educator. The award, presented at a White House ceremony by President Clinton, included a grant of $100,000 per year for five years—an amount that, according to Gluck, "has been the core funding backbone of our lab at CMBN."

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>
> —*Mark Gluck*

The project's codirector, Catherine Myers, an engagingly friendly 35-year-old, exudes an infectious enthusiasm even when discussing the serious implications of her research. After receiving her bachelor's degree in cognitive science and computer science from the University of Delaware, Myers, who grew up in Nutley, did graduate work in neural networks at the University of London, where she earned her Ph.D. in 1990.

Shortly following his appointment at Rutgers, Gluck invited Myers to join his lab. And over the course of the decade, they have become close collaborators. Gluck, now an associate professor of neuroscience, and Myers, an assistant professor, are the coauthors of *Gateway to Memory: An Introduction to Neural Network Modeling of the Hippocampus and Learning* (MIT, 2000), a book praised for being "exciting" and "authoritative" by Daniel Schacter, chair of Harvard's psychology department.

> ALZHEIMER'S AFFECTS MORE THAN 10 PERCENT OF AMERICAN MEN AND WOMEN OVER THE AGE OF 65 AND ALMOST HALF OF ALL PEOPLE OVER THE AGE OF 85.

The Memory Disorders Project involves the work of 22 men and women—most of whom are grad students, the rest postdocs—working under Gluck's and Myers's supervision. The project is underwritten not only by the NSF, but also by the Office of Naval Research, the National Institutes of Health, and the Alzheimer's Association. Last year, another group—The Healthcare Foundation of New Jersey—agreed to fund the project's quarterly newsletter, *Memory Loss & the Brain*, which reports on memory impairments caused by disease, injury, and aging. The project also has a Web site (www.memory.rutgers.edu) supported by Johnson & Johnson.

For the last decade, Gluck and Myers have directed the project to broaden and deepen the understanding of the human mind. Their research largely focuses on the hippocampus, the area of the brain that is responsible for learning and memory. Their hope is to identify the changes in the hippocampus—whether caused by injury or disease—that are linked to significant memory loss or difficulty in acquiring new information. Over the years, collaborative neuroscience research at Rutgers, NYU, and other institutions has shown that the most subtle decline in these areas—accompanied by the loss of cell mass in the hippocampus—is believed to be a very early predictor of Alzheimer's disease.

From outward appearances, the hippocampus is unprepossessing. All mammals have two of them buried deeply within their brains, one on each side. The word hippocampus comes from the Latin word for seahorse, which it resembles when viewed in cross-section. Each human hippocampus is but a few inches long—about the size and shape of, as Myers puts it, "a crooked pinky finger." Despite its modest appearance, the hippocampus has considerable impact on human behavior. "We view the hippocampal region," Gluck explains, "as an information gateway during the learning process, determining what information about the world is to be sent to memory and how this information is to be encoded and stored by other regions of the brain."

MEMORY LOSS IS THE BEST KNOWN SYMPTOM. OCCASIONALLY FORGETTING WHERE YOU PARKED YOUR CAR OR MISPLACING KEYS ISN'T A PROBLEM—UNLESS THESE MISTAKES START TO PILE UP.

But how does the hippocampus actually work? "That has been the big question in memory research for the last 20 years," says Gluck. "There are different theories; everyone know it's important, but nobody knows exactly what it does. Our approach to finding the answer came right out of computer science."

To track activity in the hippocampus, Gluck and Myers use computer models designed to represent brain function, in a process that's much like an engineer designing a model plane. An engineer, for instance, might try one tail shape and then another to see how each one affects the plane's performance. Using neural network models, Gluck and Myers can disrupt—or even disconnect—an on-screen "hippocampus" and see how each change alters learning and memory.

By the mid-1990s, they were well on their way to proving their assumptions. Trouble in the hippocampus, their research showed, did indeed adversely affect learning and memory. They also determined that their animal research was likely to be relevant to the study of the human hippocampus.

Gluck was thrilled, not only because the ideas that he and Myers had worked on were showing promise, but because they realized that their theoretical work "might have some clinical value," he says. "It moved us into a whole new domain of applicability—into work that might lead to identifying people at high risk for Alzheimer's."

The opportunity to move science from the lab into practical use jelled in 1995 when Gluck's research team began to collaborate with scientists at NYU who had clinically established the link between Alzheimer's and atrophy of the hippocampal region. Individuals with Alzheimer's were shown, through magnetic resonance imaging (MRI), to have experienced shrinkage of the hippocampus. Conversely, people who had not shown early signs of Alzheimer's, but whose MRIs revealed hippocampal shrinkage, were far more likely than others to develop the disease.

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> —Catherine Myers

Of course, as Myers points out, an MRI scan will quickly detect hippocampal shrinkage. "But," she says, "given the nation's health-care system, you can't round up every person over 65 and give them an MRI. It would cost $1,000 a pop, and each one needs a highly trained technician to interpret it. The HMOs simply won't pay for that kind of broad screening."

The challenge then for Gluck's team was to devise simple behavioral tests that would serve as "early predictors" of Alzheimer's. "At present," says Gluck, "there is no known cure for the disease, and few researchers expect that we will ever be able to substantially reverse the cognitive deficits that have already occurred in a patient who's stricken with it. So the only realistic hope for preventing cognitive losses is through the application of drugs that retard this process," he says. With Alzheimer's, timing is everything. To head off such cognitive losses, Gluck explains, it's crucial that patients begin taking drugs in the earliest stages of the disease.

Gluck, Myers, and colleagues at the Memory Disorders Project and NYU started recruiting healthy seniors to take their cognitive tests. "We knew from our animal work and computer modeling," says Myers, "that there are very specific kinds of learning for which you need your hippocampus. When the hippocampus shrinks, there are certain types of learning that go first—long before everyday, normal behavior begins to suffer." One subtle loss is the ability to make generalizations. If a person is shown a red square and a yellow square and then rewarded for choosing the red square, the person should be able to repeat the behavior when presented with a red circle and a yellow circle. If not, there's a problem, says Myers. "The tests we created look for that specific kind of learning deficit," says Myers. "If we see that, a person can then go to their HMO and say, 'Look, I have probable cause to have an MRI test.' In that case, the HMO is more likely to pay for it."

Thus far, the tests have proved to be remarkably accurate at predicting hippocampal shrinkage—that is, subjects who do poorly on them and subsequently undergo MRI examination show a comparatively high incidence of hippocampal shrinkage, explains Gluck. Based on the earlier NYU findings, this puts these people at high risk for developing serious Alzheimer's symptoms within the next several years.

BIZARRE AND SUDDEN MOOD CHANGES ARE ANOTHER SYMPTOM, ESPECIALLY THOSE THAT MANIFEST THEMSELVES IN DEPRESSION, IRRITABILITY, AND PARANOIA.

For Myers, the project's success in accurately identifying a likely Alzheimer's victim is, of course, affirming. "But it's a very mixed feeling," she notes. "From a research point of view, it's wonderful when it all comes together—when this little idea that you had in your office one night pays off. On the other hand, you have to be aware that these are real human beings—and that you've discovered something that is going to have implications for the patient and family for the rest of his or her life."

Gluck says that the Memory Disorders Project has a full agenda for years to come. "We are going to be pursuing what's really working in Alzheimer's treatment, and we'll steadily keep trying to refine our diagnostic tests," he says. "We also think that our research may someday have application in the study and treatment of Huntington's chorea, Parkinson's disease, and schizophrenia. So we'll be using our computer models to pursue those research areas as well."

In a rare moment of lucidity after being diagnosed with Alzheimer's, Iris Murdoch said that she felt as though she were "sailing into darkness." While it's too late for Murdoch, who died in 1999, the research that Gluck and Myers are doing holds out hope that countless others will be able to stave off such a frightening end. ❑

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Photograph by Dennis Connors