By Tamar Nordenberg

Photoillustration by Ralph Mercer

Revealing Alzheimer's

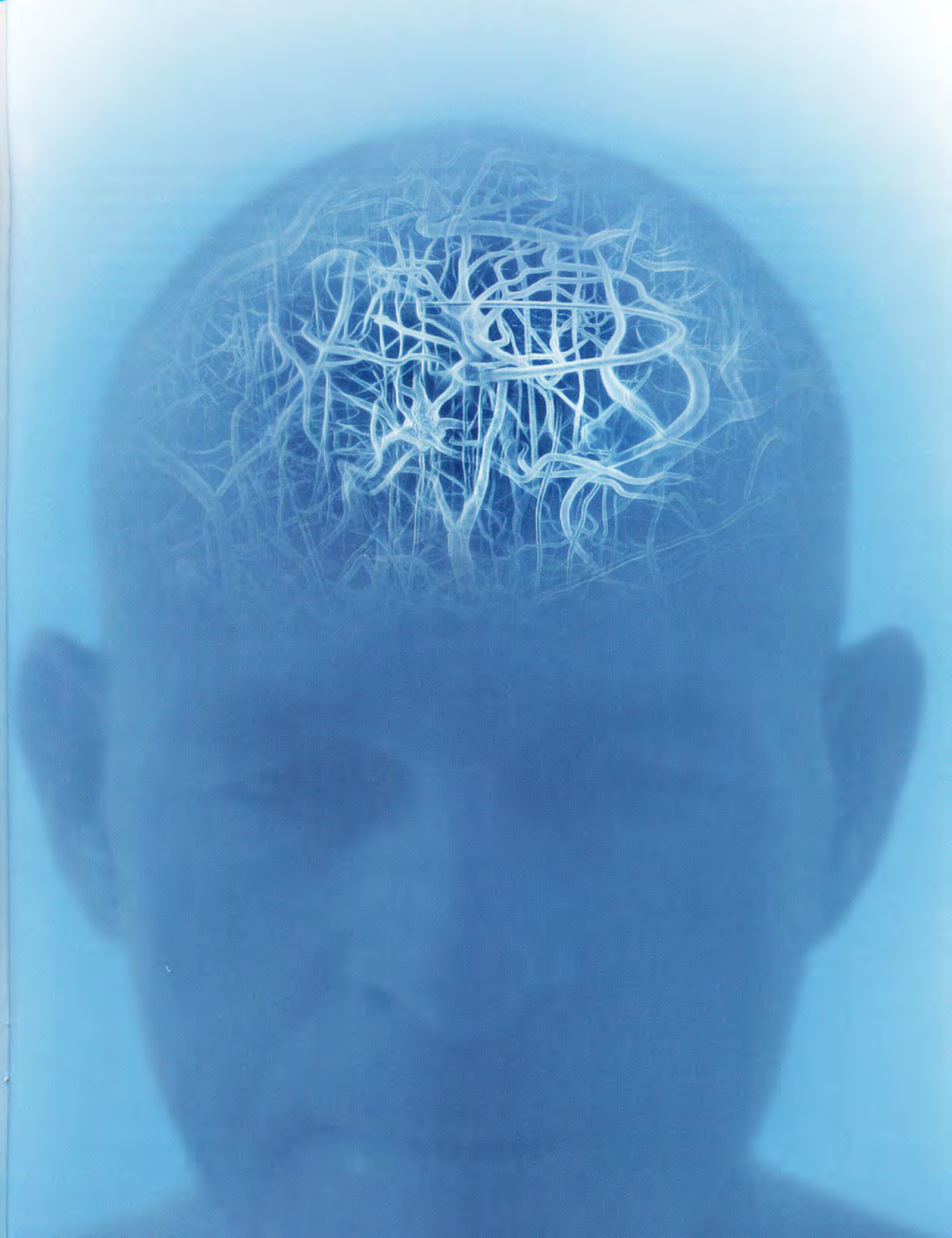
Forces I never knew existed have taken over places in my body. Alzheimer's works silently but its evil is steady, drilling through my brain until I no longer trust myself.

— *Thomas DeBaggio, in his 2003 memoir,* When It Gets Dark

By the year Thomas DeBaggio, a gardener and journalist living in Arlington, Va., wrote of his bleak showdown with Alzheimer's disease, scientists had accumulated some structural understanding of what must have been happening within the author's self-described "brain turned wild, drunk with death and destruction."

Clumps of a protein called amyloid beta, or Aß, were probably building up into large plaques outside his brain's nerve cells. Inside the same nerve cells, or neurons, twisted protein fibers called neurofibrillary tangles were doubtless taking root.

Plaques and tangles have long been the hallmarks of Alzheimer's, but scientists are murky on the role of these formations in the disease. Are they to blame for mercilessly snatching a patient's ability to think and remember?



Before treatments can effectively target the disease, scientists need to know more. "We want to know which brain changes *cause* Alzheimer's disease," says Sanjay W. Pimplikar, Ph.D., an Alzheimer's researcher in the Department of Neurosciences at Cleveland Clinic Lerner Research Institute. "We want to know how the offending changes can be stopped cold."

Today's medical therapies do little to challenge Alzheimer's disease. Though they provide patients a short-lived boost by regulating two brain chemicals called acetylcholine and glutamine, current drugs hardly stop the disease from progressing and fail entirely to reverse its tragic consequences.

Dr. Pimplikar and his colleagues at Cleveland Clinic, Riqiang Yan, Ph.D., and Bruce Lamb, Ph.D., are doing cutting-edge research that could lead to profoundly better options for treating or preventing Alzheimer's. "We're working on a way to really treat the patient, and not just alleviate the symptoms like drugs approved so far," says Dr. Yan, a leader in Alzheimer's research.

And there's no time to lose. More than 5 million Americans — most of them 65 and older — live with the disease, according to the Alzheimer's Association. With the so-called "graying of America," the association predicts that nearly 8 million in the United States could have Alzheimer's by 2025 unless treatment or prevention improves.

As Alzheimer's disease descends on the brain, the result is a steady deterioration in intellectual capabilities — starting with memory and judgment deficiencies during the disease's mild to moderate stages, progressing to trouble speaking and understanding speech, and finally advancing to a stage in which people cannot care for themselves or recognize even those closest to them.

For people watching a loved one with Alzheimer's, "the nightmarish part is the emotional disconnect," says Dr. Pimplikar, whose close family friend confided to him the

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— Richard Lederman, M.D.

heartache of watching Alzheimer's take over her father's world. "Her dad doesn't know her anymore. The person who held her when she was a kid and stayed awake all night long when she had a fever — now Alzheimer's has stolen his personality. What's left behind is just a body."

By this advanced stage, rampant nerve cell death has caused the brain to shrink dramatically. A microscopic view of brain tissue reveals additional differences between a brain affected by Alzheimer's and a healthy one. For example, Alzheimer's-affected tissue has far fewer neurons, the cells that connect with each other and send signals that support memories, thoughts and feelings. Between the remaining neurons in an Alzheimer's-affected brain are plaques built up from the sticky Aß proteins that have clumped together.

Scientists have long viewed plaques as the primary culprits that shut down the brain. The "amyloid hypothesis" that fingers Aß and related plaques as the chief nerve cell killers in Alzheimer's remains a favored theory to explain the disease. Aß and built-up plaques rank as top targets for drug and vaccine developers.

HOPES FOR A VACCINE

Many scientists are pinning their near-term hopes on a vaccine against Alzheimer's plaques.

In one set of immunization studies, mice injected with Aß to mobilize their immune systems experienced complete elimination of plaques from their brains. "The results were stunning," says Dr. Lamb, who is studying Alzheimer's disease in mice in Cleveland Clinic's Department of Neurosciences. "The field was in complete shock, left with the million-dollar question, 'How exactly did it work?'"

A subsequent study of the same type of Aß immunization in people was stopped in 2002 because some participants developed encephalitis, a viral infection of the brain. Some people in the study, however, experienced small improvements in functions of daily living. There are now studies of modified vaccines that, at least preliminarily, seem to avoid the negative effects, says Richard Lederman, M.D., a neurologist at Cleveland Clinic's Neurological Institute who treats patients with Alzheimer's. "In these early studies the vaccine not only prevented the development of plaques, it could even erase some signs of amyloid buildup in the brain," he explains. "The possibility of stabilizing and preventing progression would be a huge step."

Meanwhile, new theories are evolving that consider other culprits. Dr. Pimplikar and others are coming to believe that Aß is not solely accountable for the assault on the brain. "If you look at all aspects of Alzheimer's disease and ask the question, 'Can every single facet of the disease be explained by Aß?' the answer is becoming a clear 'no,'" Dr. Pimplikar says. "Aß is definitely a prominent factor, but there is a lot more to the disease than this agent alone."

ON THE HUNT FOR OTHER CAUSES

Scientists are probing parts of the neuron that have barely been explored to find out what else might be behind the disease. For his part, Dr. Yan has improved the understanding of dystrophic neurites — nerve cell extensions that have become swollen and unable to carry messages between neurons as they are normally counted on to do. He wanted to know about these abnormal nerve cell extensions that are found surrounding the Aß deposits in plaques: Do they cause Alzheimer's disease? Or are dystrophic neurites merely a byproduct — a sign, but not a precursor — of Alzheimer's?

AN ALZHEIMER'S GLOSSARY

Amyloid beta (Aß): A protein found in clumps of tissue (called plaques) that appear in the brains of Alzheimer's patients.

Amyloid plaques: Unusual clumps of material found in the tissue between nerve cells. Amyloid plaques, which consist of a protein called amyloid beta along with degenerating bits of neurons and other cells, are a hallmark of Alzheimer's disease.

Amyloid precursor protein (APP): A normal brain protein that, in Alzheimer's, breaks down into three fragments, including amyloid beta.

APP intracellular domain (AICD): A second fragment of APP, which seems to prompt chemical changes that convert proteins, called tau, into the tangles.

BACE1: An enzyme involved in the creation of the plaques found in Alzheimer's patients.

Dystrophic neurites: Nerve cell extensions that become swollen and unable to carry messages between neurons.

Neurofibrillary tangles: Bundles of twisted filaments found within neurons that are found in the brains of Alzheimer's patients. These tangles are largely made up of a protein called *tau*.

RTN3: A protein involved in formation of dystrophic neurites.

Tau: A protein that is part of the cell's structural support and helps to deliver substances throughout the cell. In Alzheimer's disease, tau is changed in a way that causes it to twist into filaments that collect into tangles.

Source: National Institute of Neurological Disorders and Stroke, National Institutes of Health

Can You Reduce the Risk?

As with many degenerative diseases, prevention is likely the best medicine. While studies in mice have raised hopes that memories lost to Alzheimer's disease might be recaptured through exercises or drugs that help rewire the brain, some lost memories are likely gone forever.

Prevention may be as simple as eating right and exercising the body and mind.

The Mediterranean diet — lots of fruits, vegetables, legumes and cereals, plus good amounts of fish and little dairy and meat — is winning praise in Alzheimer's research circles. Recent studies show a reduced risk of Alzheimer's, even a reduced risk of death, in people who adhered to such a diet. "I tend to be a skeptic, but these studies are strong," says Cleveland Clinic neurologist Richard Lederman, M.D.

Several studies have suggested that physical activity and exercise — as little as 1.5 hours of walking each week — may protect the health of the brain, though researchers aren't sure how.

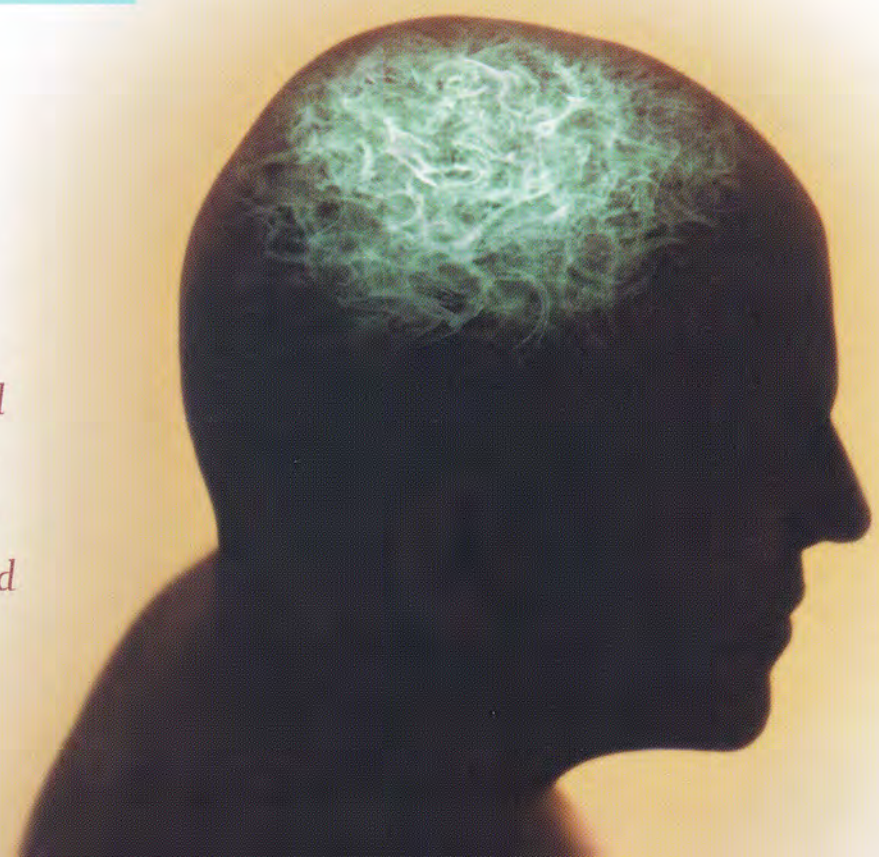
And mind-challenging hobbies, such as doing crossword puzzles, playing chess, playing an instrument or even listening to music, can help.

Dr. Yan's research team showed for the first time that dystrophic neurites can impair learning and memory — even in the absence of Aß deposits. In this study, published in the May 3, 2007, issue of *The EMBO Journal*, the researchers identified a promising target for new drugs: a protein called RTN3 that causes dystrophic neurites to form.

Dr. Yan's mouse study made an important connection between RTN3 and Aß production. Blocking the protein inhibited an enzyme called BACE1 that is necessary for creation of Alzheimer's plaques. "RTN3 may present a key to blocking plaques while at the same time blocking dystrophic neurite formation — that's our goal," Dr. Yan explains.

There's still more to learn, however. BACE1, which Dr. Yan co-discovered several years ago, is also critical to nervous system health. Blocking it could increase the risk for neurodegenerative diseases such as multiple sclerosis.

Another important clue being examined is the cause of the neurofibrillary tangles in the brain of Alzheimer's patients. The investigation starts with a large protein called amyloid precursor protein (APP), which helps neurons survive and grow. APP breaks down into three fragments in Alzheimer's patients, including the villainous Aß, but scientists remain baffled as to why this happens. After an unanticipated discovery in his lab several years ago, Dr. Pimplikar became intrigued by a second of APP's fragments, called APP intracellular domain (AICD). The surprising finding that revved his enthusiasm: AICD goes into a cell's nucleus and turns some genes on and others off.



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— Stephen Rao, Ph.D.

Stop-Gap Therapies

Five Alzheimer's drugs are available by prescription, and all are considered to have modest benefits. All but one are cholinesterase inhibitors — they halt the unhealthy breakdown of the brain chemical acetylcholine, which supports memory and other mental processes. The other is thought to normalize the activity of glutamine, a chemical associated with learning and memory that can go amok in Alzheimer's disease.

Treatment...	Approved For...	Works On...
• Donepezil (Aricept)	• Mild, moderate or severe AD	• Acetylcholine
• ENA-713 (Exelon)	• Mild to moderate AD	• Acetylcholine
• Galantamine (Razadyne)	• Mild to moderate AD	• Acetylcholine
• Memantine (Namenda)	• Moderate to severe AD	• Glutamine
• Tacrine (Cognex)	• Mild to moderate AD	• Acetylcholine

Tests in mice by Cleveland Clinic's Dr. Pimplikar suggested that AICD is important to the hallmark tangles. AICD seems to prompt chemical changes that convert a brain cell protein called tau into the tangles. As they build up within the neuron, tangles wreck the system for transporting nutrients and other supplies that neurons need to survive.

Within five years, Dr. Pimplikar hopes to understand much more about the toxic effects of AICD. "Right now, AICD is just starting to creep onto the radar," he says. "But if AICD's contribution turns out to be very large, then the molecule may make for another valuable target for therapies."

IMPROVING DISEASE PREDICTION AND DIAGNOSIS

The early signs of the disease can be difficult to recognize, and current screening approaches for Alzheimer's rely heavily on psychological testing, which is slow to identify a cognitive deficit.

Disease prediction and early identification are major goals, and medical imaging may help. Researchers are developing imaging techniques using compounds that act as markers in the brain that "light up" on a diagnostic test called a positron emission tomography (PET) scan. "It allows scientists to see the abnormal amyloid plaques in the brain, which would allow a specific diagnosis of Alzheimer's — something we still can't do," explains Dr. Lederman. This technology may identify those at highest risk for developing Alzheimer's, which would be a big improvement, but this expensive technology is not likely to be used as a widespread screening tool.

Others are working with more accessible technology, such as MRI, to pinpoint areas of the brain that show early signs of atrophy, or cell death. Stephen Rao, Ph.D., Director of Cleveland Clinic's new Shey Center for Cognitive Neuroimaging, is using a specific type of MRI, called functional MRI, to reveal brain changes consistent with the disease, in at-risk patients who do not yet exhibit symptoms. As the patient performs a task such as remembering, the MRI produces a brain map, which appears to be sensitive enough to detect preclinical stages of Alzheimer's. Though this is less specific than showing the amyloid plaques, scans like these are still an earlier marker for Alzheimer's than behavioral or clinical signs.

Another fascinating approach to detection, according to Dr. Lederman, uses the eye as the window to the brain. Scientists are looking at changes in the lens of the eye, detectable by a brief laser pulse that might indicate the earliest stages of Aß buildup. A blood marker may soon help as well. In October, researchers at Stanford University announced they have had preliminary success with a blood test that indicates which individuals with mild memory loss are most likely to go on to develop Alzheimer's disease two to six years later.

"Most of the current focus is on treating the disease after a diagnosis is made, which as things stand is probably too late," says Dr. Rao. "It's possible that, used much earlier, current Alzheimer's drugs and those in the works could arrest the early biological changes that set the stage for the disease and delay its onset." Because the disease most often strikes the elderly, delaying the disease by even five years, Dr. Rao points out, could slash prevalence by half. And a 10-year delay could "virtually wipe out" the disease.

And that will mean fewer fathers vanishing into inanimate shells, fewer authors regressing until they struggle to string together rudimentary sentences.

Tamar Nordenberg is a freelance health writer whose work has appeared in FDA Consumer magazine and on the WebMD and Discovery Health Channel Web sites.