

Holding  
on  
to

# Memory

Strategies from vaccines to genetic manipulation may one day halt the ravages of Alzheimer's disease and other dementias

BY NANCY ROSS-FLANIGAN



Of all the marvelous organs we humans possess, the brain, with its capacity for self-awareness, reasoning, learning, creativity and emotion, most defines us. It endows us with remarkable abilities — to compose symphonies, write novels, solve scientific conundrums, ponder ethical dilemmas, fall in love and remember past loves — and its failure threatens more than physical health; it challenges our very sense of ourselves. No wonder Alzheimer’s disease and other dementias, which assault the brain and rob us of our most cherished abilities, both terrify us and impel us to search for cures and preventive therapies.

That search is becoming even more urgent today, as aging baby boomers expand the ranks of the elderly. Already dementias, more common in older people, affect one in seven Americans over age 70, and the prevalence is increasing. According to the Alzheimer’s Association, someone in America develops Alzheimer’s disease — the most common cause of dementia — every 71 seconds. By mid-century, the rate will be one every 33 seconds.

“It’s an avalanche, an epidemic,” says Sid Gilman, M.D., director of the Michigan Alzheimer’s Disease Research Center. “And not just in the U.S. The same thing is happening in Western Europe, Japan and other parts of the world.”

Thanks to advances made over the past couple of decades, medical scientists know a lot about the workings of the healthy brain and the malfunctions underlying Alzheimer’s disease and other dementias. “The harder part is figuring out how we can intervene in the disease process in a safe and effective manner,” says geriatric neurology specialist Judith Heidebrink, M.D. A number of approaches, informed by basic research on the biology of dementias, are being explored at the U-M and elsewhere, and although no definitive cure has yet been found, early results are promising.

## BROKEN CIRCUITS

In simplest terms, dementias occur when nerve cells (neurons) deteriorate and die, wreaking havoc on the brain’s circuitry. A healthy adult brain is a vast and highly interconnected switchboard with some 100 billion neurons connecting to one another at 100 trillion points known as synapses. Each synapse is an information channel across which signals, in the form of chemical pulses, pass from neuron to neuron. Those pulses are the cellular underpinnings of thought, learning and memory.

In Alzheimer’s, the lines of communication break down.

Synapses fail, triggering a cascade of events that ultimately destroys neurons. As neurons die and debris accumulates, the brain shrinks and becomes more compromised.

What kicks off the devastating process? Scientists are still exploring and debating answers to this question, but the prime suspect implicated in one leading theory is a snippet of protein known as beta-amyloid. According to the “amyloid hypothesis,” things start going awry when beta-amyloid accumulates, either because the brain produces too much or because mechanisms for disposing of it fail. The buildup creates roadblocks at synapses — obstructing information flow and triggering the damage that leads to neuron death.

Clumps, or plaques, of beta-amyloid are one telltale sign of Alzheimer’s disease; another is tangles of a protein called tau. In addition, brains of people with Alzheimer’s disease show signs of inflammation and oxidative damage. There’s no doubt these abnormalities occur in Alzheimer’s disease, but is any one of them the root cause?

The evidence is conflicting, explains Gilman. “In tissue culture, beta-amyloid is toxic to cells,” he says, and excess beta-amyloid is found both in individuals with garden-variety Alzheimer’s disease and those with the less-common, early-onset form that strikes people in their 30s and 40s. However, even people whose brains work perfectly well may have significant beta-amyloid deposits, autopsy studies suggest. “Only when they acquire tau abnormalities do they develop dementia,” Gilman notes. Also, the severity of dementia seems to be related more to the density of tau tangles than to the amount of beta-amyloid deposited.

So some researchers consider tau tangles the real villains and beta-amyloid an innocent bystander, while others still suspect amyloid involvement. “It could be that both pathologies are important,” says Gilman. “It doesn’t have to be either-or.”

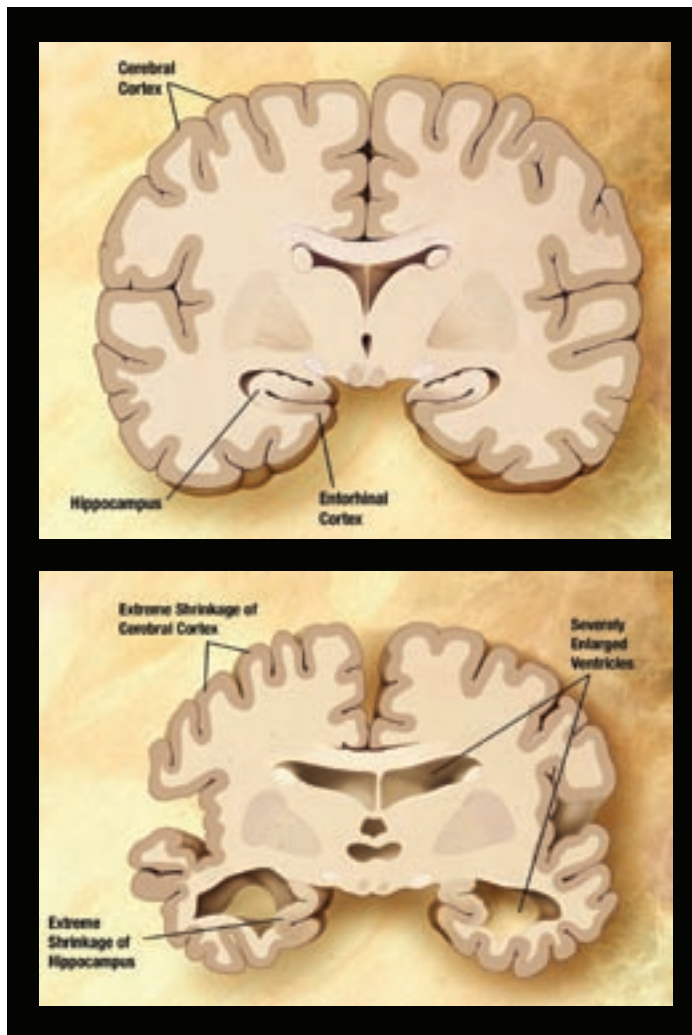
Even though the issue isn’t resolved, studies of beta-amyloid, tau, and normal brain function are pointing the way to

new treatments and prevention strategies. Current therapies are aimed at the end of the degenerative cascade, and thus can only ease symptoms, not alter the course of the disease, says Heidebrink. “What we really want to do is look at the front of the cascade and figure out how to stop the process altogether.”

It’s not a simple task. Many enzymes involved in the critical pathway have other functions that may be disrupted by attempts to alter their activity in Alzheimer’s. Still, progress has been made in identifying and manipulating potential targets. For example, in one project funded by the National Institutes of Health, U-M researchers led by Henry Paulson, M.D., Ph.D., are using a mouse model of Alzheimer’s disease to study a protein called X11 that slows production of beta-amyloid.

Another line of research builds on pioneering work by Dale Schenk of the pharmaceutical company Elan, who showed that mice engineered to develop Alzheimer’s could be immunized against the disease. If vaccinated early in life, Schenk and others demonstrated, the mice never developed beta-amyloid plaques or memory problems. Even when the mice received the immunization after beta-amyloid had accumulated, the treatment worked wonders, clearing away plaques and restoring the rodents’ memories.

More recently, human trials of a vaccine called bapineuzumab at the U-M and elsewhere had intriguing, if somewhat unexpected, results. Bapineuzumab targets beta-amyloid, and while it effectively cleared plaques



A healthy brain (top) compared with a brain affected by the onset of Alzheimer’s disease (bottom).

from vaccinated subjects, it showed no overall benefit in slowing disease progression. But when researchers studied the results more closely, they found something completely unexpected based on a genetic distinction.

About 50 percent of the 5 million Americans with Alzheimer’s disease carry a particular version, or allele, of the apolipoprotein gene, which produces a cholesterol-carrying compound in the blood. “Research over the years has demonstrated that having the apolipoprotein E4 allele, known as ApoE4, greatly enhances your chance of developing Alzheimer’s,” says Gilman. “We also know that people who have the allele have greater density of beta-amyloid deposition in blood vessels and in brain tissue.”

When data from the immunization trial were re-examined in light of the subjects’ genetic make-ups,

it turned out that presence or absence of the ApoE4 allele made all the difference.

“People with the allele showed no beneficial effect in this phase II trial, but those without the allele showed a highly significant beneficial effect, a remarkable effect,” says Gilman, who presented results of the trial at the International Conference on Alzheimer’s Disease in Chicago last summer. “Moreover, their MRI scans showed less brain atrophy.”

So, while results of this early bapineuzumab trial suggest better effects in the subgroup of ApoE4 non-carriers, the overall results were encouraging enough for the drug’s developers, Elan and Wyeth, to proceed with a phase III trial involving both subgroups, at sites including the U-M.

## RUNNING INTERFERENCE

**A**nother approach to nipping Alzheimer's disease in the bud is turning off genes believed to underlie the disease. Paulson's research group is employing a powerful technique known as RNA interference, the discoverers of which received a Nobel Prize in 2006. Paulson's lab has used the technique to silence two key proteins: amyloid precursor protein (APP), from which beta-amyloid is made, and tau. In addition, they're exploring protein "quality control machinery," says Paulson, who is the Lucille Groff Professor of Neurology for Alzheimer's Disease and Related Disorders.

"In the same way that we must clean our houses to keep them from getting messy," Paulson says, "the cell has dedicated machinery that recognizes and cleans up abnormal proteins. Some of that machinery clearly is involved in the Alzheimer's disease pathway, and we're doing a range of studies to identify protein quality control components,

roimaging Initiative, a nationwide project in which the U-M is a partner. In a study involving 800 subjects at more than 50 centers, researchers are investigating a number of indicators, or biomarkers, associated with an elevated risk of developing Alzheimer's disease. For example, positron emission tomography (PET) scans that employ a particular contrast agent known as Pittsburgh Compound B, or PIB, reveal the location and extent of amyloid plaque deposits in subjects' brains. Other markers are found in spinal fluid, blood, and subjects' genetic profiles.

Three groups of volunteers are being studied: individuals with confirmed Alzheimer's disease, people with mild cognitive impairment (noticeable problems with memory, language and thinking that are not severe enough to interfere with daily life), and subjects with no signs of either Alzheimer's or cognitive problems. "The idea is to observe changes in the various markers over time and correlate them with standard cognitive assessments," says Heidebrink.

Early findings are promising. "One thing we're seeing is

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how they're regulated and how they might be enhanced to block the disease."

If any — or all — of these efforts hit pay dirt and successful therapies are developed, another big question remains: At what point in the disease process should they be given?

"By the time people have the full-fledged dementia of Alzheimer's, the underlying biochemical processes have probably been accumulating for years, if not decades," says Heidebrink. So, to be effective, perhaps treatments should be started when symptoms are extremely subtle, or even before any symptoms develop.

But who should receive such preventive therapy? Everyone? Probably not, says Paulson.

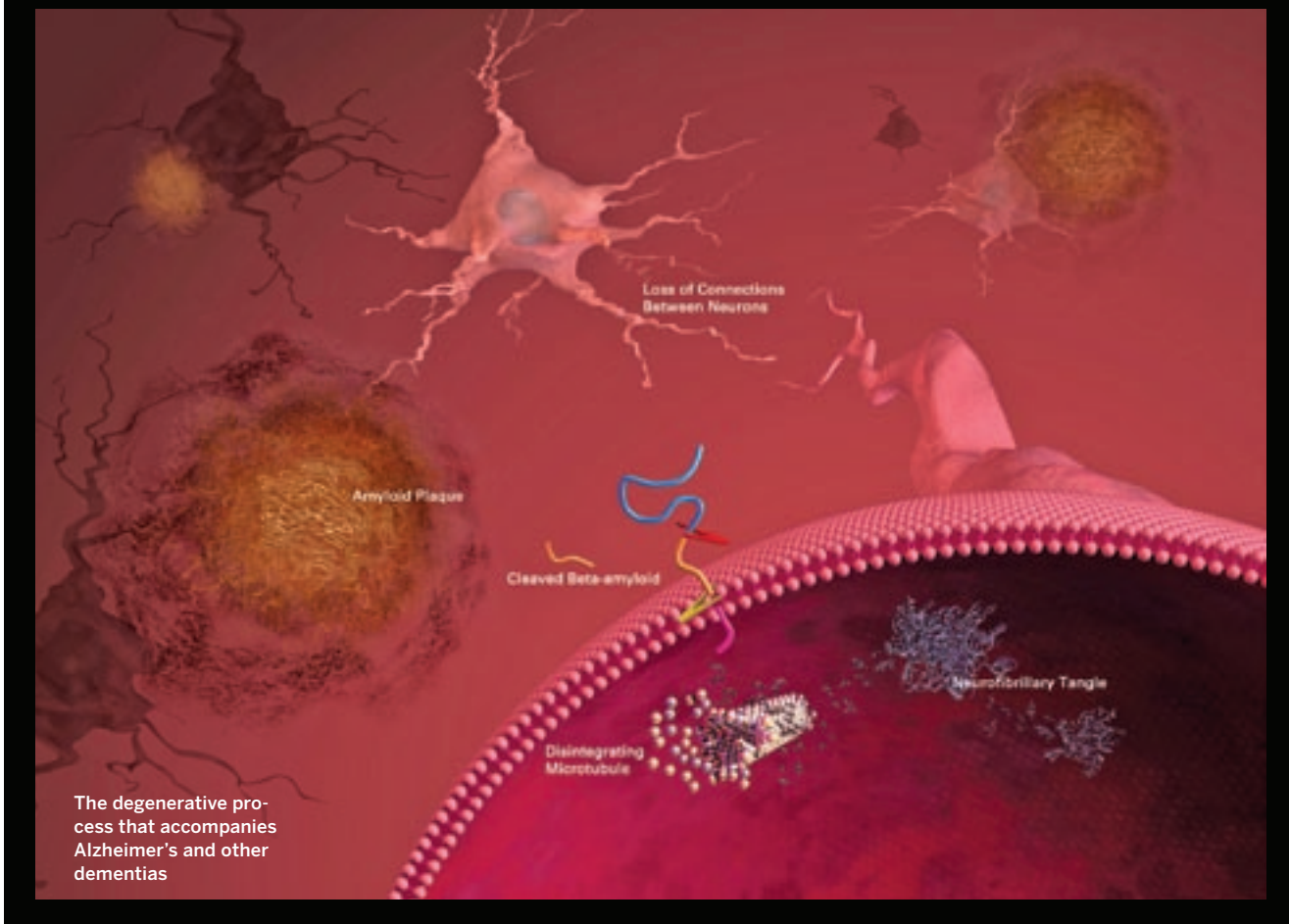
"The ideal preventive therapy would be completely safe, cheap and totally effective," he says. "In reality, preventive therapy is probably not going to be cheap, and it's going to have the risk of potential side effects. So we only want to give it to people who really need it. If we can identify those at greatest risk, then we'll be in a position to do that."

That's exactly the goal of the Alzheimer's Disease Neu-

that a high percentage of those in the mild cognitive impairment group have amyloid accumulation," Heidebrink says. "That's not so surprising, but as many as 50 percent of the normal subjects also appear to have it. So the question is, are we really beginning to identify people with no hint of cognitive impairment at present who might — five, 10 or more years later — be the ones coming in with symptoms of Alzheimer's disease? We may not be able to answer that question within the timeframe of the initial neuroimaging initiative, but we hope to continue studying some of these subjects so that those types of questions can be answered."

Developing accurate biomarkers will not only help pinpoint who should be treated and when, but also give physicians better ways of assessing disease progression and treatment effectiveness. The current gold standard is cognitive testing, which isn't always an accurate gauge.

"Someone might be sleep deprived or have emotional issues going on when they're tested, so when you look at changes in their test scores over time, you may see a lot of variability that isn't measuring the disease itself," Heidebrink says.



## COLLABORATION KEY TO RESEARCH AND CARE

While exciting results are emerging from the various clinical trials and patient studies underway at the U-M, a constant challenge is enlisting enough qualified participants to obtain meaningful results, says Nancy Barbas, M.D., M.S.W., director of the Cognitive Disorders Clinic. The challenge has become even greater with the recognition that different subpopulations may respond differently to a given treatment, as happened in the bapineuzumab immunization trial. “That means we need even more patients to have enough within each subpopulation to draw valid conclusions,” she says.

While there’s no guarantee that people participating in therapeutic trials will benefit from the treatment being studied — or even that they will be in the group receiving the treatment — Barbas promises this: “Everyone who participates gets a lot of attention from the researchers, physicians and other personnel, as well as first-hand information about new developments in the area.”

That sort of close, personal attention extends to all patients, not just those enrolled in studies, says Heidebrink. Years ago, patients with dementia were kept in the dark, as others discussed and decided on their care. “Nowadays

we’re much more sensitive to the importance of incorporating the wishes of the patient,” says Heidebrink.

Another advance is the recognition that dementia isn’t a disease in isolation.

“There’s a huge toll on the family and other caregivers, and a lot of our clinical work is trying to determine what kind of support is available for everyone involved,” says Heidebrink. The rigorous workup that new patients to the Cognitive Disorders Clinic receive includes referrals to social workers, educational resource centers and other sources of help, as well as to appropriate medical professionals.

The integrated, multi-faceted approach applies to research, too. One of Paulson’s missions is to identify and facilitate collaboration among researchers scattered throughout the university who are doing work that relates, or could relate, to Alzheimer’s disease and other dementias. Scientists in the School of Public Health, the Life Sciences Institute, the College of Literature, Science, and the Arts, and the Institute for Social Research, as well as the Medical School, all are doing work that could advance understanding of the disease.

“One of the wonderful things about biological research on Alzheimer’s disease, throughout the country and very much at the University of Michigan,” Paulson says, “is that a wide range of research platforms, from bacteria to humans, are being studied and leading to new insights.” [M]

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