

WOMEN & ALZHEIMER'S



Alzheimer's disease devastates its victims and their families, and disrupts their lives in many, complicated ways.

Women experience the disease at twice the rate of men.

We want to know why.



Women and Alzheimer's Disease

The first person ever diagnosed with Alzheimer's disease—Auguste Deter—was a woman.

Alzheimer's disease (AD) is often described as a simple loss of memory and a natural part of the aging process. Both characterizations are wrong and harmful to those who are, and those who will become, affected by what is truly a dreadful disease.

The early symptoms of Alzheimer's are lapses with memory, at first infrequent and inconsistent. But over time, they become more profound.

As the disease progresses, new symptoms present themselves. Anxiety, fear, confusion, anger. Mood swings for no apparent reason. Impaired judgment. Difficulty with familiar—even simple—tasks, such as boiling water. Misplacing possessions.

But the damage wrought by Alzheimer's disease goes beyond such inconveniences of mild cognitive impairment. In later stages of the disease, mobility becomes limited. You forget to eat. You lose your ability to speak. Neurological deficits can result in heart attack, stroke and other more common causes of death. The degradation of the brain manifests in many different ways.

Throughout the world more than 50 million people have been diagnosed with Alzheimer's disease, and it is estimated that there are another 150 million who have the disease but have not yet been diagnosed.

Two-thirds of those who are afflicted are women, and women develop the disease at twice the rate of men. Researchers are working to understand why.



The Main Elements of the Pathology of Alzheimer's Disease

Scientists think a combination of genetic, lifestyle and environmental factors influences when Alzheimer's begins and how it progresses. Many molecular and cellular changes occur in the brain of a person with Alzheimer's disease. These changes can be observed in brain tissue under the microscope upon autopsy.

AMYLOID PLAQUES

The amyloid plaques involved in Alzheimer's disease come in several different molecular forms that collect between neurons and are formed from the breakdown of a larger protein, amyloid precursor protein. In the Alzheimer's brain, abnormal levels of this naturally occurring protein clump together to form plaques that collect between neurons and disrupt cell function.

NEUROFIBRILLARY TANGLES

Neurofibrillary tangles are abnormal accumulations of the protein tau that collects inside neurons. Healthy neurons, in part, are supported internally by structures called microtubules. In healthy neurons, tau normally binds to and stabilizes microtubules. In Alzheimer's disease, however, abnormal chemical changes cause tau to detach from microtubules and stick to other tau molecules, forming threads that eventually join to form tangles inside neurons. These tangles block the neuron's transport system, harming the synaptic communication between neurons.

Emerging evidence suggests that Alzheimer's-related brain changes may result from a complex interplay among abnormal tau and amyloid plaque proteins and several other factors. It appears that abnormal tau accumulates in specific brain regions involved in memory. Amyloid clumps into plaques between neurons. As the level of amyloid plaques reaches a tipping point, there is a rapid spread of tau throughout the brain.

CHRONIC INFLAMMATION

Research suggests that chronic inflammation may be caused by the buildup of glial cells normally meant to help keep the brain free of debris. One type of glial cell, microglia, engulfs and destroys waste and toxins in a healthy brain. In Alzheimer's, microglia fail to clear away waste, debris and protein collections, including amyloid plaques.

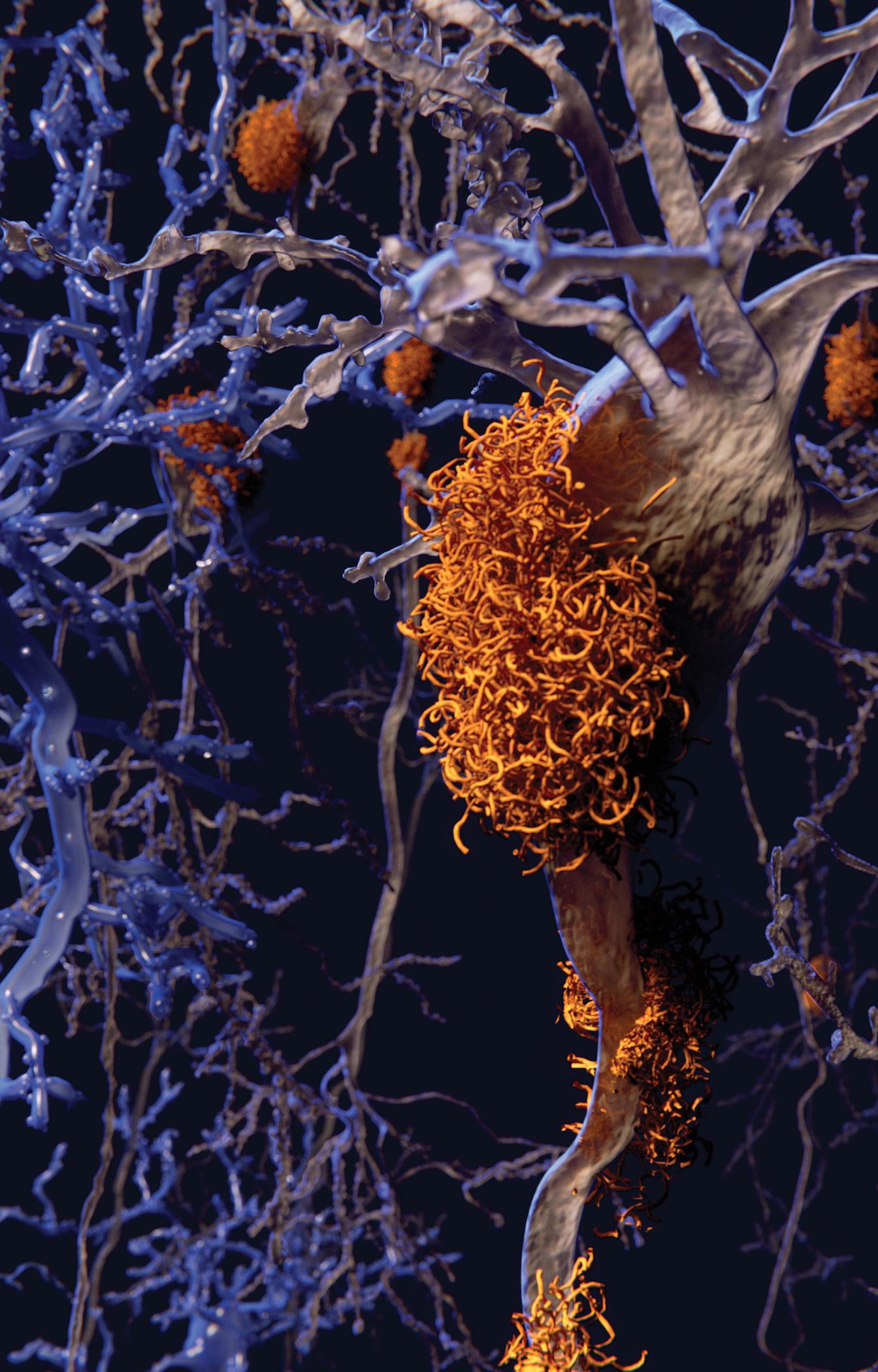
VASCULAR CONTRIBUTIONS TO ALZHEIMER'S DISEASE

People with dementia seldom have only Alzheimer's-related changes in their brains. Any number of vascular issues—problems that affect blood vessels, such as beta-amyloid deposits in brain arteries, atherosclerosis (hardening of the arteries), and mini-strokes—may also be at play.

Vascular problems may lead to reduced blood flow and oxygen to the brain, as well as a breakdown of the blood-brain barrier, which usually protects the brain from harmful agents while allowing in glucose and other necessary factors. In a person with Alzheimer's, a faulty blood-brain barrier prevents glucose from reaching the brain and prevents the clearing away of toxic beta-amyloid and tau proteins. This results in inflammation, which adds to vascular problems in the brain.

LOSS OF NEURONAL CONNECTIONS AND CELL DEATH

In Alzheimer's disease, as neurons are injured and die throughout the brain, connections between networks of neurons may break down, and many brain regions begin to shrink. By the final stages of Alzheimer's, this process—called brain atrophy—is widespread, causing significant loss of brain volume.



Glossary of Scientific Terms

APOE4: One of the variants of the APOE gene, the presence of the APOE4 gene is the second-highest risk factor for developing Alzheimer's disease. The highest risk factor is old age.

COHORT: A group of people who share a common characteristic, such as age or disease risk.

GENE: The basic unit of inheritance, passed from parents to offspring; a gene contains specific physical and biological traits.

GLIAL: Support cells that hold neurons in place and have a variety of functions, including facilitating neurotransmission and immune response.

MICROGLIA: A type of glial cell that acts as the primary line of defense and immunity for the brain.

NEURONS: Specialized impulse-transmitting cells that are the fundamental working units of the brain and nervous system.

OXIDATIVE STRESS: When free radicals (unstable, highly reactive molecules) and antioxidants (compounds that neutralize free radicals) are out of balance, the result is oxidative stress. This may result in damage to organs and tissue, potentially leading to disease and contributing to the aging process.

PATHOLOGY: Structural and functional changes that result in disease.

PROTEIN: Biomolecules made of chains of amino acids with numerous functions in cells, tissues and the body.

SEX-BASED DIFFERENCES: In scientific investigations, the terms sex and gender are not interchangeable. Gender refers to social constructs such as norms, behaviors and roles associated with being a man, woman, girl, boy and other gender diverse people. Sex is a biological classification based on anatomy, physiology, genetics and hormones.

Discoveries

The Effect of Menopausal Transition on the Brain

Throughout a single lifetime, the brain undergoes many changes. In early development, brain circuits are connected and pruned; in adolescence, circuits mature and, in midlife, the menopause transition impacts a host of brain functions—from energy metabolism to synaptogenesis. Despite the clear link between menopause transition and brain function, very little data exists on how the different stages (pre-, peri- and post-menopause) impact the brain. The results of this study make it clear that the menopausal transition period is a dynamic period of change that impacts key brain biomarkers.

Read More: <https://bit.ly/3QT756A>

Lisa Mosconi, Ph.D., Weill Cornell Medicine

The Framingham Heart Study Reveals Sex Differences in AD

The Framingham Heart Study (FHS) has tracked more than 14,000 men and women and gathered extensive information about these participants, including their demographics, cardiovascular risk factors, biomarker data, coexisting medical conditions and the occurrence of diseases, including Alzheimer's disease. The data was analyzed to find clues to explain differences in AD risk between men and women.

The data highlighted that women are 96% more likely to receive a diagnosis of AD dementia at a younger age than men. However, this discrepancy disappears by age 70. Interestingly, education was linked to a decreased risk in women. The study also revealed that blood levels of A β 42, a longer,

toxic form of amyloid beta, were a greater predictor for future memory decline in women than men. This study suggests that factors both early in life (education) and later (pathological amyloid beta) may contribute to the higher AD risk for women.

Read More: <https://bit.ly/3QVSB5N>

P. Murali Doraiswamy, M.B.B.S., Duke University



A Western Diet May Affect Men and Women with APOE4 Genes Differently

Recent Alzheimer's disease (AD) research has taken a new approach by looking at how various factors like genetics, sex and lifestyle choices come together to impact the progression and severity of the disease. The most significant genetic risk factor for late-onset AD is the gene APOE4. When combined with a high-fat, high-sugar Western diet, APOE4 carriers had worse outcomes, and the effects differed for males and females.

In this study, scientists fed a Western diet to mice specially bred to have two copies of APOE4. While both sexes showed cognitive impairments, the effect was more pronounced in males. Males also had larger livers and signs of oxidative stress and brain inflammation. Female APOE4 carriers did not have these signs, yet they still had cognitive impairments.

The study suggests that male APOE4 carriers are more vulnerable to the harmful effects of a Western diet than females. It is also further evidence that AD risk factors affect males and females differently, and it is critical to research both sexes.

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Paula Grammas, Ph.D., Tribute Senior Living

The Protein DUSP4 Affects Neuroinflammation in Females

In the autopsied brains of individuals who died from Alzheimer's disease (AD), researchers discovered lower levels of the signaling protein DUSP4. The same decrease was replicated in a laboratory model of AD, where it was found to be linked to learning and memory problems. When brain DUSP4 levels were artificially increased, females, but not males, saw an

improvement in their cognitive abilities. Although both sexes experienced drops in amyloid and tau brain levels (hallmarks of AD), only females also had a reduction in neuroinflammation. This might explain why males showed no cognitive improvement. Targeting DUSP4 could unlock a unique therapeutic strategy for treating AD in females.

Read More: <https://bit.ly/4697Z3K>

Stephen R. Salton, M.D., Ph.D., Michelle E. Ehrlich, M.D., and Sam Gandy, M.D., Ph.D., Icahn School of Medicine at Mount Sinai

Altering the Gut Microbiome Impacts Amyloid in the Brain

There are four main groups of bacteria in the human gut, and the level of each type is constantly changing. This component of the human microbiome is essential in maintaining the body's normal functions, such as resistance to infection and inflammation. Advances in understanding the connection between the gut microbiome and the brain have brought to light that an imbalance in the diversity of gut microbes may trigger neuroinflammation in the brain. Short-term experimental treatment with high-dose antibiotics administered early in the life stage of specialized mice changed the composition of the microbiome and led to a significant reduction of amyloid beta later in life. Interestingly, the manipulation had an effect in male but not female mice. The research also suggests that the gut microbiome-brain connection relies on microglia. Depletion of microglia after the antibiotic treatment overturned the amyloid-reducing effect of the antibiotics, and amyloid persisted.

Read More: <https://bit.ly/3ErtlZQ>

Sangram Sisodia, Ph.D., University of Chicago; Rudolph Tanzi, Ph.D., Massachusetts General Hospital



Women & Alzheimer's: The ZBTB7C Gene

In a study scanning the whole genome of more than 2,000 individuals from 605 families, four novel sex-specific AD genes were identified that had opposite effects on AD risk for men and women. Variations in three of these genes increased AD risk in men but seemed to be protective in women. However, the strongest association with AD risk was with the ZBTB7C gene, variants of which conferred high risk for women but protection for men. The type of protein that the ZBTB7C gene encodes has been shown to play a role in blood-brain barrier function, potentially linking increased female risk of AD to the state of the brain's vasculature.

Read More: <https://bit.ly/3Cl0oBk>

Lars Bertram, M.D., University of Lübeck; Winston Hide, Ph.D., Beth Israel Deaconess Medical Center; Christoph Lange, Ph.D., Harvard Medical School; and Rudolph Tanzi, Ph.D., Massachusetts General Hospital

Sex Differences in the Brain's Debris Removal System and Interaction with Amyloid Plaques

Recent studies evaluate how two well-established risk factors for Alzheimer's disease—being female and having the APOE4 gene—affect the interactions between microglia, the natural debris removal cells in the brain, and amyloid plaques.

Studies find that microglia affect Alzheimer's disease (AD) pathogenesis in opposing manners, by protecting against amyloid accumulation in early phases of the disease and promoting neuropathology in advanced stages. These findings suggest a possible mechanism by which microglia may contribute to the increased AD risk associated with APOE4 genotype and female sex.

Read More: <https://bit.ly/3Y08lo5>

Caleb E. Finch, Ph.D., and Christian Pike, Ph.D., University of Southern California

Removing Astrocytic APOE4 May be Beneficial for Late-Stage Alzheimer's Disease

APOE4 is linked to an earlier age of onset of Alzheimer's disease and worsened pathology. In the brain, astrocytes are the major producer of APOE. Removing astrocytic APOE4 in the lab at the onset of abnormal tau deposition is neuroprotective; levels of toxic tau were lower and so was resulting neurodegeneration. The study also demonstrated that removing astrocytic APOE4 is more beneficial to females than males. The results suggest the deleterious effects of APOE4 may be greater in females than in males, and that a future therapy may be treatments to modify APOE4.

Read More: <https://bit.ly/3SXUPzK>

Oleg Butovsky, Ph.D., Brigham and Women's Hospital; and Jason Ulrich, Ph.D., and David Holtzman, M.D., Washington University School of Medicine in St. Louis

Brain Microbleeds May Cause Amyloid Plaques

Brain microbleeds are the result of small hemorrhages in the brain. In a laboratory model of AD, amyloid plaques developed near microbleeds, suggesting that the damage caused by microbleeds may seed amyloid plaques and lead to AD pathology.

Age, sex and APOE4 status influenced the size and number of microbleeds. With increasing age, the number of microbleeds increased, but their size did not. Females fared worse than males, with more and larger microbleeds. The presence of the APOE4 gene increased the number of microbleeds further, with females once again affected to a greater extent.

This study demonstrates that microbleeds, and therefore amyloid plaques, are exacerbated by the risk factors of age, sex and APOE4 status.

Read More: <https://bit.ly/3EWA3LJ>

Caleb E. Finch, Ph.D., University of Southern California



Sex and APOE4 Affect Cognitive Decline

In 2004, the Alzheimer's Disease Neuroimaging Initiative (ADNI) was founded to develop tools to aid in the early detection and tracking of Alzheimer's disease (AD). The ADNI gathers and analyzes brain scans, genetic profiles, and blood and cerebrospinal fluid biomarkers from its participants.

Over 10 years, researchers tracked how sex and APOE4 status impacted cognitive decline in participants with mild cognitive impairment. They found the following:

- Cognition declined more in females than males.
- Inheriting the APOE4 gene sped up the decline in both sexes.
- Female APOE4 carriers declined faster than male carriers.

These data show that a person's sex and APOE4 status influence the pace and severity of cognitive decline.

Read More: <https://bit.ly/3r5T8YF>

*P. Murali Doraiswamy, M.B.B.S., Duke University School of Medicine; and
Rudolph Tanzi, Ph.D., Massachusetts General Hospital*



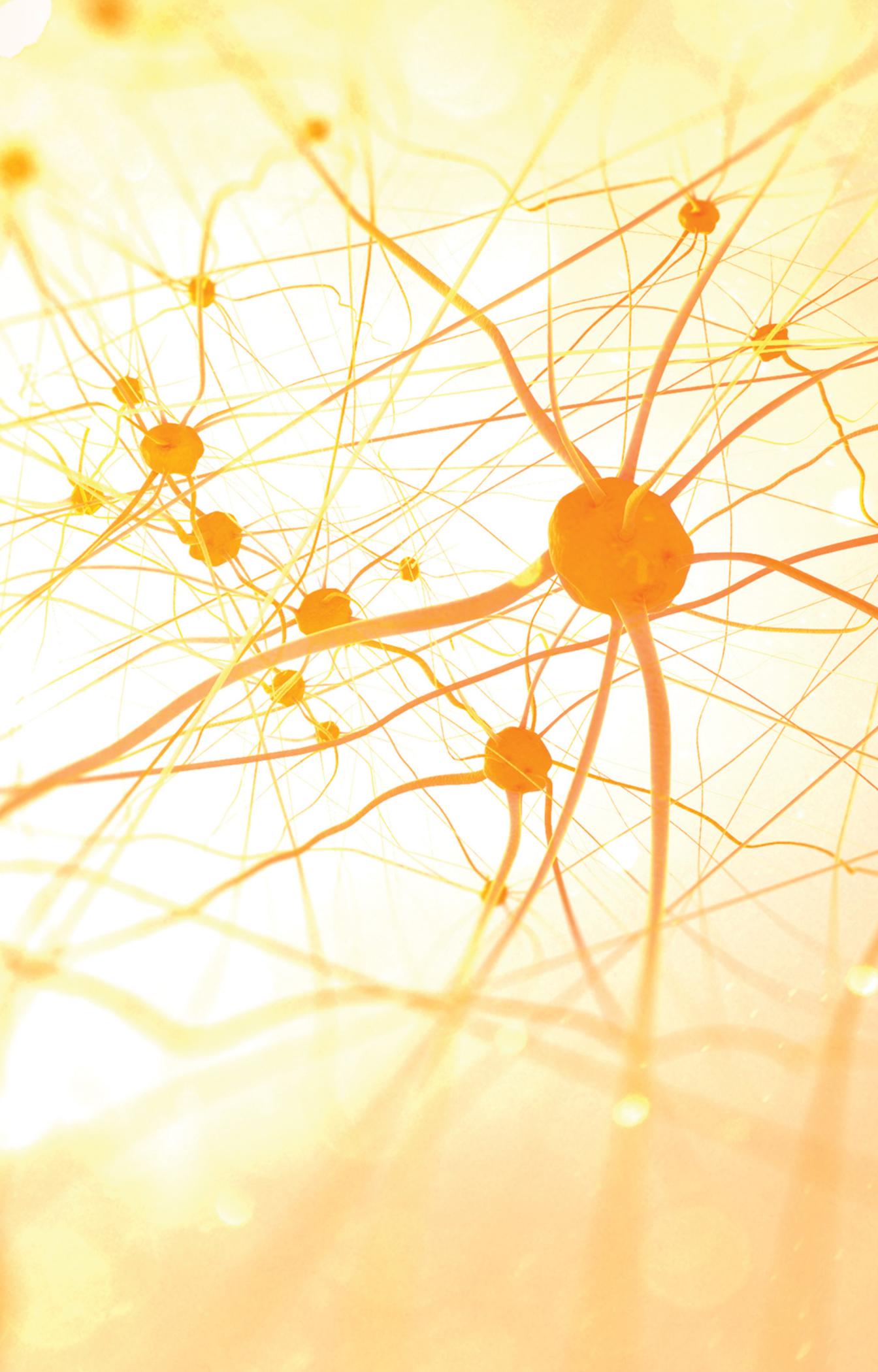
Blood Pressure Medication: A Future Treatment for AD?

The angiotensin-converting enzyme (ACE) causes blood vessels to narrow, increasing blood pressure. Patients with AD show higher levels of ACE in their brains. The Alzheimer's Genome Project™ identified rare variants of ACE that were associated with AD. One of these mutations increased the levels of the ACE1 protein in neurons of the brain and induced neuroinflammation and neurodegeneration. This research investigates the relationship between neurodegeneration and ACE1, and the potential impact of U.S. Food and Drug Administration-approved blood pressure medications—ACE inhibitors—already proven safe as potential treatments for Alzheimer's disease.

“There are three mysteries of Alzheimer's disease that really are enigmatic: why age is the primary risk factor, why women have an increased susceptibility for developing Alzheimer's and why there is selective death of neurons in regions of the brain that are important for memory. And our study, I think, provides some insight into those three mysteries,” said study principal Dr. Robert Vassar in a press release.

Read More: <https://bit.ly/3fKiTaF>

Leah Cuddy, Ph.D., Northwestern University; Winston Hide, Ph.D., Beth Israel Deaconess Medical Center; Rudolph Tanzi, Ph.D., Massachusetts General Hospital; and Robert Vassar, Ph.D., Northwestern University



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TELEPHONE: If you would like to make a donation by telephone, please call us at 781.237.3800. Our business hours are 9 a.m. to 5 p.m. ET. When calling after hours, please leave a message and we will return your call the next business day.

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Cure Alzheimer's Fund is a nonprofit organization dedicated to funding research with the highest probability of preventing, slowing or reversing Alzheimer's disease.

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