2008 PROGRESS REPORT ON ALZHEIMER'S DISEASE

Moving Discovery Forward

U.S. Department of
Health and Human Services

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National Institute on Aging
National Institutes of Health
U.S. Department of Health and Human Services

The National Institute on Aging (NIA), part of the Federal Government's National Institutes of Health (NIH) at the U.S. Department of Health and Human Services, has primary responsibility for basic, clinical, behavioral, and social research in Alzheimer's disease (AD) as well as research aimed at finding ways to prevent and treat AD. The Institute's AD research program is integral to one of its main goals, which is to enhance the quality of life of older people by expanding knowledge about the aging brain and nervous system. This *2008 Progress Report on Alzheimer's Disease* summarizes recent AD research conducted or supported by NIA and other components of NIH, including:

- National Center for Complementary and Alternative Medicine (page 32)
- National Heart, Lung, and Blood Institute (pages 23, 26, 32, 35)
- National Human Genome Research Institute (page 22)
- National Institute of Diabetes and Digestive and Kidney Diseases (page 23)
- National Institute of Environmental Health Sciences (pages 19, 28)
- National Institute of Mental Health (pages 17, 18, 21, 22, 31, 37, 38, 39)
- National Institute of Neurological Disorders and Stroke (pages 17, 18, 19, 21, 29)
- National Institute of Nursing Research (pages 37, 39)

AD research efforts also are supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Cancer Institute, National Center for Research Resources, National Eye Institute, National Institute of Biomedical Imaging and Bioengineering, and John E. Fogarty International Center.

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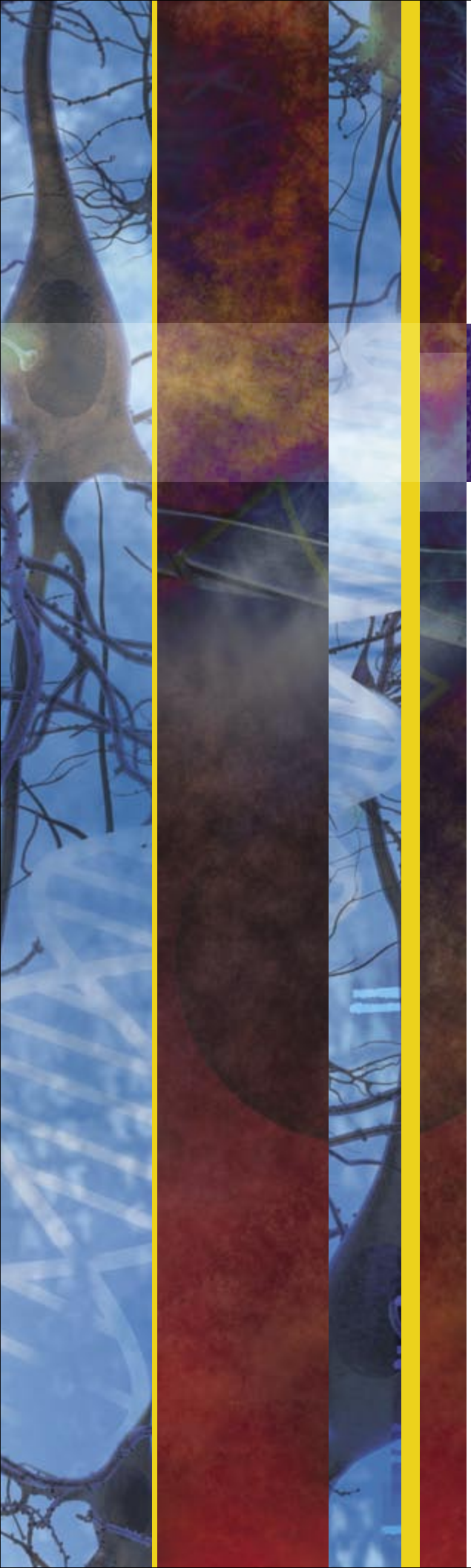


Introduction

Alzheimer's disease is an age-related, currently irreversible brain disorder that develops over many years. In the very early stage, people experience some memory loss, which may be mistaken for memory changes that happen to many people in normal aging. As the disease progresses, these symptoms gradually lead to marked memory loss and a decline in other cognitive abilities, such as decision making and language skills. Eventually, Alzheimer's leads to behavior and personality changes, a severe loss of mental function that impairs daily living, and an inability to recognize family and friends. These losses are related to the breakdown of the connections between different classes of neurons (nerve cells) in the brain and the eventual death of many of these cells.

Though the features of AD were first described by Dr. Alois Alzheimer more than 100 years ago, the scientific study of the disease intensified about 30 years ago. The course of AD varies from person to person. In most people, symptoms first appear after age 60. While AD and other dementias are caused by diseases that affect the brain, other age-related changes in the brain and body may play a role in their development. An increasingly productive research program has revealed much about the basic biology of the disease and the factors that influence its development. It is hoped that these findings will ultimately lead to effective treatment approaches and preventive strategies.

An Urgent National Health Priority

AD research today is taking place against the backdrop of an urgent demographic reality. We know that aging is the major risk factor for AD. Estimates vary, but experts suggest that as many as 5.1 million Americans may have Alzheimer's disease. In 2000, 35 million people were older than 65, and one Census projection estimates that that number will double by 2050. The large "baby boom" generation will begin to reach its 65th birthday in 2011. The ranks of the very elderly, those people 85 years old and older and at the highest risk of AD, will increase as well. Studies suggest that the prevalence of AD (the number of people with the disease at any one time) doubles for every 5-year age group beyond age 65.

The costs of AD are, of course, both societal and deeply personal. Caregivers and friends experience emotional, physical, and financial stress as they watch a loved one become more and more forgetful, frustrated, and confused. As the disease runs its course and the abilities of people with AD steadily decline, family members who have cared for a person with AD at home face difficult decisions about long-term care. Frequently, they turn to assisted living facilities, then nursing homes, for care and support. The number of caregivers—and their needs—can be expected to escalate rapidly as the population ages and the number of people with AD grows.

The National Institutes of Health has responded to this urgent public health problem with a broad program of AD research led by the National Institute on Aging. This program applies the expertise of many scientific disciplines in an attempt to answer difficult questions about what causes AD, how it can be diagnosed early and accurately, how it can be treated, and how it might ultimately be prevented. AD research is now increasingly focused on transferring knowledge gained in the laboratory to the clinical arena as quickly as possible.

About This Report

The *2008 Progress Report on Alzheimer's Disease* describes this important, multi-faceted AD research program. It begins with a brief primer that reviews the main features of the disease, discusses the causes, and describes how AD currently is diagnosed and treated. The next section, "AD Research Has Come a Long Way," looks at the remarkable achievements of the past few years and the accelerating pace of discovery. The following section, "The Rapid Pace of Discovery in Research Continues," highlights recent advances in nine major areas of investigation. The *Progress Report* concludes with an outline of the diverse ways in which NIH is building on the momentum of prior groundbreaking AD research.

A Brief Primer on ALZHEIMER'S DISEASE

The healthy human brain is made up of billions of different kinds of neurons that are connected through chemical and electrical signals. A typical neuron has a nucleus in a cell body, an axon, and many dendrites. Neuronal function is supported by other kinds of cells called glial cells. As with all cells, the nucleus of a neuron contains the cell's genetic blueprint and helps regulate the cell's activities in response to signals from outside and inside the cell. The axon transmits messages to other neurons. Dendrites receive messages from axons of other nerve cells or from specialized sense organs. The survival of neurons depends on the healthy functioning of three interdependent processes:

- **Communication.** When a neuron receives enough messages from surrounding cells, an electrical charge is generated that travels to the end of the axon. Here, it triggers the release of chemicals called neurotransmitters that move across a gap, or synapse, to the dendrites of neighboring neurons. Scientists estimate that the typical neuron has up to 15,000 synapses. The neurotransmitters bind to specific receptor sites on the dendrites of neighboring neurons, triggering chemical changes and building up new electrical charges.
- **Metabolism.** This process encompasses all the chemical reactions that take place in the cell. Efficient metabolism requires adequate blood circulation to supply the cells with oxygen and glucose (the brain's primary fuel).
- **Repair.** Neurons are programmed to live a long time—even more than 100 years—so they must constantly maintain, repair, and remodel themselves.

How Does AD Affect the Brain?

In healthy aging, most types of brain neurons are not lost in large numbers. In AD, however, many neurons stop functioning, lose connections with other neurons, and die because communication, metabolism, and repair are disrupted.

At first, AD typically destroys neurons in parts of the brain that control memory, including the entorhinal cortex, the hippocampus, and related structures. It later attacks areas responsible for language and reasoning. Eventually, many other areas of the brain are damaged, and the person becomes helpless and unresponsive to the outside world.

What Are the Main Characteristics of the AD Brain?

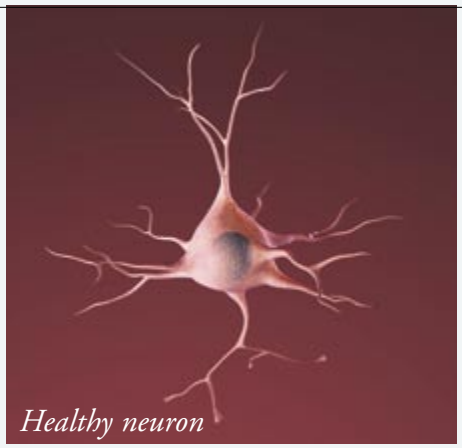
Many changes take place in the brain of a person with AD. The three major characteristics that reflect the pathology, or damage, caused by the disease are:

- **Amyloid plaques.** Found in the spaces between neurons, plaques consist of largely insoluble deposits of aggregated protein fragments called beta-amyloid peptides, other proteins, remnants of neurons, degenerating dendrites and axons, glia, and other cellular material. Scientists used to think that plaques caused most of the damage to neurons seen in AD. Now, however, many think that more soluble forms of beta-amyloid, seen earlier in the plaque formation process, may be the major culprits.
- **Neurofibrillary tangles.** Found inside neurons, neurofibrillary tangles are abnormal aggregates of a protein called *tau*. Healthy neurons are internally supported in part by structures called microtubules, which help guide nutrients and molecules from the cell body to the end of the axon. *Tau*, which normally has a certain number of phosphate molecules attached to it, binds to microtubules and stabilizes them. In AD, an abnormally high number of additional phosphate molecules attach to *tau*. As a result, *tau* disengages from the microtubules and begins to clump together with other threads of *tau*, eventually forming neurofibrillary tangles. When this happens, the microtubules disintegrate and the neuron's transport system collapses. As with beta-amyloid, some scientists think that early soluble forms of abnormal *tau* may cause the damage to neurons.
- **Loss of connections between cells and cell death.** This feature of AD likely results from the accumulation of beta-amyloid and abnormal *tau*. When neurons lose their connections, they cannot function properly and eventually die. As neuronal death spreads through the brain, affected regions begin to shrink in a process called brain atrophy. By the final stage of AD, damage is widespread and brain tissue has shrunk significantly.

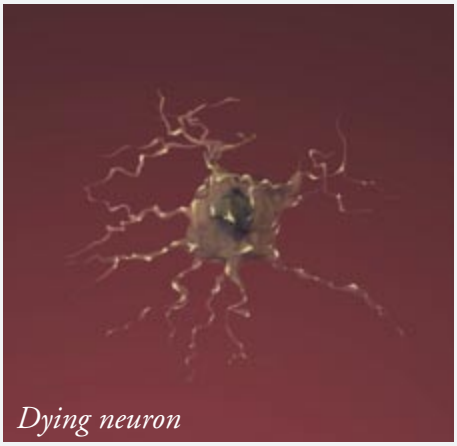
What Causes AD?

Very rarely, people develop AD in their 40s or 50s. In many of these cases, the disease runs in families and is caused by a mutation in one of three genes that a person has inherited from a parent. This form of the disease is called "early-onset" AD. Not all early-onset cases are caused by such mutations.

More than 90 percent of AD cases develop in people older than 60, however. The development and pathology of this form of AD, called "late-onset" Alzheimer's disease, are very similar to



Healthy neuron



Dying neuron

those of early-onset AD. We don't yet completely understand the causes of late-onset AD, but they probably include genetic, environmental, and lifestyle factors. The importance of these factors in increasing or decreasing the risk of developing AD differs from person to person. Scientists hope that what they learn about early-onset AD also can be applied to the late-onset form of the disease.

Perhaps the greatest mystery is why AD largely strikes people of advanced age. Why does it take 30 to 50 years or more for people to develop signs of the disease? Research on how the brain changes normally as people age will help provide answers to this important question.

How Is AD Diagnosed?

Clinicians use a range of tools to diagnose "possible AD" (dementia that could be due to another condition) or "probable AD" (no other cause of dementia can be found). These tools include a medical history, a physical exam, brain scans, and tests that measure memory, language skills, and other abilities related to brain functioning. Knowledge about the clinical and behavioral changes from the disease also helps in diagnosing AD. At this time, AD can be diagnosed conclusively only by studying the brain after death. However, in specialized research facilities, clinicians can diagnose AD in a living person with up to 90 percent accuracy.

Early, accurate diagnosis is crucial because it tells people whether they have Alzheimer's or their symptoms are caused by something else. Stroke, tumor, Parkinson's disease, sleep disturbances, or side effects of medications are all known to affect cognitive function and memory. Early diagnosis also helps families plan for the future while the person with AD can still participate in making decisions. Researchers are developing increasingly accurate diagnostic tests and techniques that may one day be used in general medical practice to detect the disease early—ideally before serious symptoms emerge.

Visit the NIA Alzheimer's Disease Education and Referral (ADEAR) Center website at *www.nia.nih.gov/Alzheimers/ADvideo* to view a short animated video about AD and the brain.

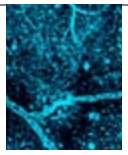
How Is AD Treated?

A variety of treatments address behavioral and psychiatric problems that occur as AD progresses. Only a few medications have been approved by the U.S. Food and Drug Administration (FDA) to help control the cognitive loss that characterizes AD. Donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®, formerly known as Reminyl® and now available as a generic drug) are prescribed to treat mild to moderate AD symptoms. Donepezil also is approved to treat severe AD. These drugs act by stopping or slowing the action of acetylcholinesterase, an enzyme that breaks down acetylcholine (a neurotransmitter that helps in memory formation). The drugs maintain some people's abilities to carry out activities of daily living and may maintain some thinking, memory, or speaking skills. They also may help with certain behavioral symptoms. However, they do not stop or reverse AD and appear to help only for months to a few years.

Another type of AD medication, memantine (Namenda®), is prescribed to treat moderate to severe AD symptoms. This drug appears to work by regulating levels of glutamate, another neurotransmitter involved in memory function. Like the cholinesterase inhibitors, memantine does not stop or reverse AD.

In addition to these medications, physicians use drugs and nondrug approaches to treat behavioral and psychiatric problems associated with AD. These problems include agitation, verbal and physical aggression, wandering, depression, sleep disturbances, and delusions. ■

AD Research *Has Come a Long Way*



Research has accelerated rapidly, resulting in an explosion of knowledge about AD, other neurodegenerative diseases, and normal aging.

In 1906, Dr. Alois Alzheimer, a German psychiatrist and neuropathologist, first described the features of what we now know as AD when he reported the case of 51-year-old Auguste D. At the time, few took notice, and for 50 years afterwards, knowledge about the disease grew slowly. One reason AD was overlooked was because relatively few people lived long enough to develop it in old age. Forgetfulness and symptoms of senility in those who did reach their older years were accepted as a normal part of aging and due to "hardening of the arteries."

However, steady improvements in scientific methods and instruments allowed scientists to study the abnormal structures that Dr. Alzheimer described. In the 1960s and 1970s, scientists began to realize that the plaques and tangles they saw in younger people diagnosed with "Alzheimer's disease" were actually the same as the structures often found in the brains of older people who had died with dementia. Slowly, AD became recognized as a distinct disease state associated with aging (Katzman, 1976). Since then, Alzheimer's research has accelerated rapidly, resulting in an explosion of knowledge about AD, other neurodegenerative diseases of aging, and even normal aging itself.

Advances in many scientific areas have made significant advances in knowledge possible. Several of these advances, described below, have been particularly valuable in helping scientists study this complex disease.

Basic Science Tools and Techniques and AD Animal Models

Scientists cannot conduct research without the right tools and methods. In AD research, these tools and methods have developed rapidly, allowing scientists to probe the where, why, and how of AD at the cellular, molecular, and genetic levels. At the same time, new technology has allowed scientists to process and analyze vast quantities of data at impressive speeds.

Animal models, such as rodents, often are used for basic research to study human diseases because they are biologically similar to humans. These animals have a shorter lifespan than humans and therefore allow scientists to study disease development over brief time periods—a critically important advantage in AD research because the disease takes decades to develop in the human brain. In addition, scientists can control the animals' environment, which allows them to focus on particular aspects of the disease.

Advances in basic science and animal models have given scientists considerable knowledge about AD's three defining characteristics: beta-amyloid plaques, *tau* tangles, and loss of connections between neurons. Scientists have detailed the steps by which beta-amyloid plaques and *tau* tangles are formed and have improved their understanding of the roles that various enzymes and other proteins play in these processes. In the past 5 years, scientists also have come to recognize that early, soluble forms of plaques and possibly tangles may actually be more damaging to neurons than full-blown plaques and tangles. They are learning more about how these early forms actually do their damage.

These advances also have helped scientists correlate what they know about damaging changes inside the brain with outward changes they see in a person, such as memory loss, losses in other cognitive abilities, and behavior and personality changes. These "clinicopathologic" correlations provide clues about biological pathways that lead to AD and generate insights into potential therapeutic targets.

Genetics

In the early days of AD research, investigators realized that some cases of the disease ran in families. They found that in these families, the disease occurred at an early age, when people were in their 40s or early 50s, indicating that AD had some genetic basis. These findings opened an entire area of AD research that continues to be highly productive today. Genetics research has helped to reveal much about the biological basis of the disease, the interrelationship of genetic and environmental factors in causing AD, and pathways amenable to prevention or treatment. As medical science progresses into individualized medicine based on a person's unique genetic makeup, this knowledge may help to identify which risk factors and preventive and treatment strategies are best suited to particular individuals.

Four genes affecting the development of early- and late-onset AD have been defined. Mutations in three genes—the amyloid precursor protein (APP)

gene found on chromosome 21, the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1—cause the rare early-onset forms of familial AD. Mutations in each of these genes promote the breakdown of the large APP protein in a way that leads to increased production of harmful beta-amyloid fragments.

The fourth gene, APOE, found on chromosome 19, is linked to the far more common late-onset AD. APOE has three forms, or alleles—ε2, ε3, and ε4. These alleles do not cause AD. Rather, they influence the risk of developing the disease. The ε2 form may provide some protection against AD, and ε3 is thought to play a neutral role. The ε4 form increases a person's risk of developing AD.

Most experts believe that additional genes may influence the development of late-onset AD in some way. Geneticists around the world are searching for these genes. Genome-wide association studies (GWAS), which use methods that can rapidly test up to a million sites in one person's genes, will help find those elusive genetic variations. Since 2007, several international research groups conducting GWAS have identified variants of the SORL1, CLU, PICALM, and CR1 genes that may play a role in risk of late-onset Alzheimer's.

Epidemiology

Epidemiology is the study of disease in a population setting. Epidemiologic research may lead to estimates of the number of individuals living with the disease (prevalence) or the number of individuals who develop the disease during a particular period of time (incidence).

Epidemiologic research also focuses on identifying personal characteristics or attributes, such as lifestyles or behaviors, that relate to developing the disease. Once scientists realized that AD was a distinct disease and not an inevitable consequence of aging, they began to search for factors that caused or were related to its development. Scientists turned to epidemiology to relate AD to lifestyle and environmental factors as well as to basic personal characteristics and other factors hypothesized to change the likelihood of developing the disease. Such studies have paved the way for

NIA's ADEAR Center Offers Free AD Information and Resources

Efforts to educate and inform people with AD, their families, the public, providers, and others interested in the disease complement NIH's research initiatives. The NIA Alzheimer's Disease Education and Referral (ADEAR) Center provides free information and publications for families, caregivers, and professionals on research, diagnosis, treatment, patient care, caregiver needs, long-term care, and education and training related to AD. For example, the publication *Alzheimer's Disease: Unraveling the Mystery* explains the disease, highlights ongoing research, and describes efforts to support caregivers of people with AD. An animated companion video—*Inside the Brain: Unraveling the Mystery of Alzheimer's Disease*—brings to life the latest knowledge about AD and the brain.

Other ADEAR Center publications include *Can Alzheimer's Disease be Prevented?,* which summarizes the latest research findings on AD risk factors and potential prevention strategies, and *Caring for a Person with Alzheimer's Disease: Your Easy-to-Use Guide from the National Institute on Aging,* which provides caregiving information and advice. ADEAR fact sheets cover a variety of topics, including basic information, AD genetics, and participating in AD clinical trials and studies. Many ADEAR publications also are available in Spanish.

ADEAR staff members answer telephone, email, and written requests and can suggest local and national resources. In addition, the ADEAR Center website offers email alerts, the online *Connections* newsletter, the AD clinical trials database, and the AD Library database.

To read and order these publications, view the AD video, and take advantage of many other resources, visit the ADEAR Center at *www.nia.nih.gov/Alzheimers* or call toll-free at 800-438-4380. ■

additional research in test tube and animal studies and in clinical trials.

If one theme in AD research predominates today, it is the pathological and clinical complexity of the disease. It is likely that AD has no single cause but develops from multiple processes that interact over many years. Epidemiologic studies have helped to make that fact abundantly clear, and they also have provided many valuable clues about specific factors that may affect the development of the disease. These clues, in turn, have opened up entire new areas of productive research.

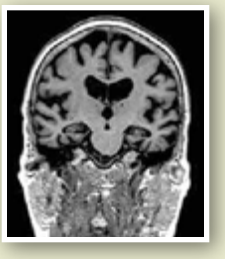
A growing body of epidemiologic research, for example, suggests that the metabolic changes that occur in a variety of age-related chronic diseases, such as heart disease, stroke, high blood pressure, and type 2 diabetes, may contribute to the development and affect the severity of AD or cause vascular dementia. (Vascular dementia occurs when a series of strokes or changes in the brain's blood supply leads to the death of brain tissue.) Epidemiologic studies also suggest that several lifestyle factors—a healthful diet and physical activity, not smoking, and having strong social networks—may reduce AD risk. Scientists are conducting animal studies and clinical trials to determine whether changing lifestyle factors can alter a person's chances of developing AD—and how this might happen.

Neuroimaging

Until recently, scientists could "see" the characteristics of AD in the brain only at autopsy, after a person with the disease had died. However, autopsies present a static picture, usually revealing only the very advanced stage of the disease. Scientists had no way to observe the disease in the living brain at early stages or to see how the disease affected the brain over time. The

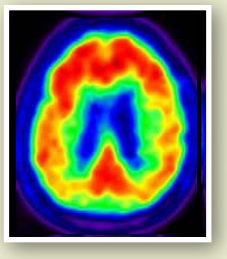
Neuroimaging: Opening New Windows on the Brain

Three neuroimaging tests are commonly used in AD research:



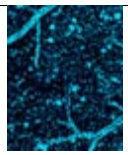
Magnetic Resonance Imaging (MRI). This type of scan uses magnetic fields to generate computer images of body structures. In AD research, MRI is used to create detailed maps of the brain, showing the size and anatomy of brain regions and structures. As AD progresses and neurons die in large numbers, regions of the brain shrink and fluid-filled spaces called ventricles enlarge. MRI has been used extensively to track this process.

Functional Magnetic Resonance Imaging (fMRI). An fMRI is a type of MRI that allows scientists to measure brain activity during a cognitive task, such as remembering or learning. These scans are providing many insights into how AD affects the brain's ability to function and how the brain tries to compensate for damage caused by the disease.



Positron Emission Tomography (PET). In a PET scan, a small amount of a short-lived radioactive substance is attached to another molecule and injected into the body. The radioactive molecule travels through the blood and becomes concentrated in the organs and tissues where it is normally found. The PET machine measures the energy given off by the radioactive material and translates that information into pictures that can be viewed on a computer screen. PET scans frequently are used in brain research because they allow researchers to observe and measure activity in different parts of the brain by monitoring blood flow and the concentrations of the radioactive material in different areas of the brain.

In a PET scan breakthrough, researchers reported in 2004 on their development of a radioactive substance, Pittsburgh Compound B (PiB), that binds to beta-amyloid in the brain (Klunk et al., 2004). Investigators can use radioactive PiB in PET scans to measure the concentration of beta-amyloid in brain regions that are particularly vulnerable to AD. These concentrations can then be compared to outward changes in memory or other cognitive abilities. ■



Translational research serves as a crucial means for collaboration among scientists who focus on understanding the cellular, molecular, and pathologic dimensions of disease and clinicians who focus on treating people.

development of neuroimaging techniques, including magnetic resonance imaging (MRI), functional MRI (fMRI), and positron emission tomography (PET), and their application to AD radically changed all that.

Researchers can now observe and measure the size and structure of specific brain regions in people who are healthy or have symptoms of AD. They also can measure the accumulation of beta-amyloid plaques in brain tissue. In addition, neuroimaging technologies allow scientists to observe brain function in people performing cognitive tasks. Importantly, these technologies allow researchers to track changes in these dimensions over time.

Developments in neuroimaging techniques have greatly increased our knowledge about how AD progresses. They have helped us understand that damage in the brain begins long before any clinical symptoms are evident and that this process develops slowly over many years. By the time a person is diagnosed, the disease is well-established, with current treatment options limited or effective for only a short time. In combination with results of the traditional battery of tests given to people suspected of having dementia, neuroimaging has been essential in helping researchers understand and chart brain changes that occur during the evolution from healthy aging to mild cognitive impairment to Alzheimer's. (Mild cognitive impairment, or MCI, is a condition of memory loss but without the other cognitive problems of AD. People with MCI are an important group for researchers because many of them go on to develop AD.) Understanding these changes opens the door to earlier and more accurate diagnosis, new intervention points for therapies, and improved methods for tracking responses to treatment.

Translational Research

Translational research is a multidisciplinary effort that creates a two-way loop between basic science laboratory studies and clinical research. It allows valuable knowledge from the laboratory to be applied to potential new tests or interventions in clinical trials, and findings from clinical trials to be taken back to the lab and investigated in basic science studies to refine the nature of future clinical trials. Translational research also serves as a crucial means for collaboration among scientists who focus on understanding the cellular, molecular, and pathologic dimensions of disease and clinicians who focus on treating people.

HBO's *The Alzheimer's Project* Showcases Recent AD Research Progress

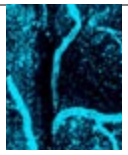
In May 2009, HBO Documentary Films launched a multimedia initiative highlighting the groundbreaking discoveries of leading AD researchers and poignantly depicting the effects of the disease on those with AD and their families. *The Alzheimer's Project* was co-presented by HBO Documentary Films and NIA, in association with the Alzheimer's Association, Fidelity® Charitable Gift Fund, and Geoffrey Beene Gives Back® Alzheimer's Initiative.

The Alzheimer's Project features a four-part documentary series, 15 short supplemental films, a companion book published by Public Affairs Books, a dedicated website, and a nationwide community-based information and outreach campaign. HBO and other participating television service providers offered the documentary series for free to viewers when the series debuted May 10–12, 2009. The documentary series and the 15 supplemental films can now be viewed free on the HBO and NIA websites, as well as on YouTube, Facebook, and iTunes. An additional 18 films, geared toward the scientific community, are hosted on the Alzheimer's Research Forum website.

The documentary films include THE MEMORY LOSS TAPES, which enters the lives of seven individuals living with AD and shows the full spectrum of the progression of the disease; MOMENTUM IN SCIENCE, a two-part, state-of-the-science film, which takes viewers inside the laboratories and clinics of 25 leading scientists and physicians, revealing some of the most cutting-edge research advances; 'GRANDPA, DO YOU KNOW WHO I AM?' WITH MARIA SHRIVER, which captures what it means to be a child or grandchild of a person with Alzheimer's; and CAREGIVERS, which highlights the sacrifices and successes of people who ex-perience their loved ones' descent into dementia.

THE MEMORY LOSS TAPES has received an Emmy for Exceptional Merit in Nonfiction Filmmaking, 'GRANDPA, DO YOU KNOW WHO I AM?' WITH MARIA SHRIVER won an Emmy for Outstanding Children's Nonfiction Program, and MOMENTUM IN SCIENCE garnered an Emmy nomination. *The Alzheimer's Project* also has received the Television Critics Association award for Outstanding Achievement in News and Information. For more information on *The Alzheimer's Project*, visit *www.nia.nih.gov/Alzheimers/HBO*.

The Rapid Pace of Discovery in RESEARCH



AD research focuses on central issues—what occurs during the disease process, what we can do to promote brain health and prevent AD, and what we can do once the disease has taken hold.

In 2008, scientists supported by NIH made advances in a number of areas important to AD:

- Epidemiology
- Basic research
- The interface between healthy cognitive aging and AD
- Genetic causes and risk factors
- Nongenetic risk and protective factors
- Diagnosis
- The search for effective therapies
- Clinical trials
- Coping and caregiver support

These areas of investigation focus on the central issues of AD—what occurs during the disease process, what we can do to promote healthy cognitive aging and prevent AD, and what we can do once the disease has taken hold. The following sections describe new knowledge that may hold the key to future prevention, treatment, and coping and caregiving strategies.

Continues

Epidemiology of AD and Related Dementias

The ability to tackle a major public health problem depends in part on understanding the dimensions of the problem. For example, how many people have the condition in question? How many people develop it each year? How many people have a precursor to the condition, or some variant of the condition? Having an accurate-as-possible picture of the scope of AD, related dementias, and age-related cognitive impairment helps scientists, policy makers, health care providers, and health care insurers determine the costs of caring for people with these conditions and develop appropriate services and resources.

This information also helps investigators reliably track trends in prevalence and incidence and correlate those trends with changes in environmental and biological factors. These correlations may provide insights into potential risk and protective factors and inform the design of prevention and treatment interventions.

The prevalence of Alzheimer's and related dementias, such as vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia, and frontotemporal lobar degeneration, increases exponentially with age. Of people with late-onset dementia, about half have Alzheimer's, 16 percent have vascular dementia, and 30 percent have other forms of dementia (Kester and Scheltens, 2009). The prevalence of AD in the United States has been variously estimated, ranging from as high as 5.1 million among people 65 or older to about half that many, depending on how the condition was defined and what methods were used to find people with AD. The public health problem presented by AD is large and, with age the best known risk factor for AD, the numbers will likely increase as the elderly segment of the population grows, at least until effective interventions to prevent the disease or halt its progress are found.

In 2007, 2008, and 2009, several groups of researchers reported what they learned from studies examining the prevalence of AD and related dementias and the prevalence of age-associated cognitive impairment.

- A research team analyzed the prevalence of cognitive impairment that does not meet the threshold for a diagnosis of dementia (Plassman et al., 2008). Knowing how many people have cognitive impairment has important health care policy implications because that condition is associated with an increased risk of disability, increased health care costs, and progression to dementia. The investigators determined that 5.4 million people, or 22.2 percent of Americans age 71 and older, had cognitive impairment without dementia. This first-ever population-based national study also identified 12 subtypes of cognitive impairment without dementia and found that the subtypes varied in prevalence and outcomes.

- Investigators at the Rush Alzheimer's Disease Center in Chicago focused on the spectrum of neuropathological abnormalities found in several major dementing disorders, such as AD, Parkinson's disease dementia, Lewy body disease, and stroke (Schneider et al., 2007). An examination of brain tissue from deceased participants in the Rush Memory and Aging Project showed some differences in the occurrence of neuropathological abnormalities observed in those who died with dementia and those who died without dementia. More specifically, the study found that the majority of community-dwelling older people had some brain pathology; those with dementia most often

had multiple brain pathologies. The presence of multiple pathologies greatly increased the odds of dementia.

- Investigators at the University of Michigan assessed the influence of recent medical, demographic, and social trends on the cognitive health of older adults (Langa et al., 2008). Using data from the nationally representative longitudinal Health and Retirement Study (HRS), they compared the prevalence of "cognitive impairment consistent with dementia" among survey participants in 1993 and 2002. Results showed that fewer older Americans reached the threshold of significant cognitive impairment in 2002 compared with 1993, although those who reached that threshold, on average, died earlier than the others. These findings suggest that rates of very severe cognitive impairment may be decreasing. One major difference between the 1993 and 2002 groups was the higher education, on average, of the latter group. It may be that, compared to people with less education, individuals with more education are able to sustain greater damage from AD or other dementia-related pathology before clinical signs of impairment appear. Other factors, such as improvements in treatment and prevention for stroke, heart disease, and vascular conditions from 1993 to 2002, also may have influenced these results. The study authors suggest that building and maintaining cognitive reserve through formal education in childhood and continued cognitive stimulation through work and leisure in adulthood could limit the burden of cognitive impairment consistent with dementia among the growing number of older adults.

- The Indianapolis-Ibadan Dementia Project, established in 1991, continues to search for risk factors and protective factors for AD and other cognitive impairment by comparing two groups of community-dwelling elderly who live in vastly different environments: a group of African Americans in Indianapolis, Indiana, and a group of Yoruba in Ibadan, Nigeria. The study periodically conducts assessments of the two groups, employing the same research design, methods, and investigators. One study from this project compared prevalence rates for African Americans in the 1992 community-based sample to a newly enrolled sample in 2001 (Hall et al., 2009). The overall age-adjusted prevalence rate for AD at age 70 years and older in 2001 was 6.8 percent, and in the 1992 cohort, the prevalence rate was 5.5 percent. These rates, however, were not significantly different despite differences in risk factors between the two cohorts. The 2001 cohort had higher mean years of education, and fewer lived in rural areas during childhood. However, this later cohort also had higher rates of hypertension and history of depression, and more cohort members were taking antihypertensive medications, anti-diabetic medications, and statins.

Both the HRS and Indianapolis-Ibadan studies suggest that prevalence rates of dementia are not increasing in the United States, at least for individuals who live in the community. The latter study, from Indianapolis, was restricted to African Americans and also showed no significant increase over time in the prevalence rate of AD. More studies from U.S. populations, over longer periods of time, are needed to get a clearer picture of changes in incidence and prevalence rates for dementia and AD. If prevalence and incidence rates remain constant over time and the U.S. population of older people continues to increase, then there will be more and more cases of dementia and AD in the future.

Improving Our Basic Understanding of AD

AD-related studies at the cellular and molecular levels historically have focused on understanding the wide range of processes that interfere with, or enhance, the function and survival of neurons and their connections. The overarching aim of these studies is to identify molecular targets that can be translated and developed into AD therapies. Many investigators are continuing to study basic mechanisms and to examine the potential roles of different forms of beta-amyloid and other factors that contribute to neuronal damage and death.

Beta-amyloid

It has long been accepted that beta-amyloid plaques are a major feature of AD and their mere physical presence distorts the architecture of the brain. The effects of this structural distortion on the function and activity of neuronal networks are only now beginning to be measured. Scientists also understand the basic steps by which beta-amyloid fragments are produced and have begun to understand how the fragments clump together in aggregates to form insoluble

plaques. More recent data point to small, soluble aggregates of beta-amyloid peptides, not the insoluble late-stage plaques, as the main culprits in neuronal damage. These small beta-amyloid aggregates, called oligomers, consist of two or three and sometimes up to a dozen such small fragments excised from amyloid precursor protein (APP), the parent protein. Several reports published in 2008 revealed new evidence about the toxic effects of oligomers.

- A research team from Brigham and Women's Hospital and Harvard Medical School compared forms of soluble beta-amyloid oligomers—those with only one peptide (monomer), two peptides (dimer), and three peptides (trimer)—to see whether their toxic effects on neurons were different (Shankar et al., 2008). The researchers extracted beta-amyloid from autopsied human brains of people with and without confirmed AD and processed it to isolate soluble beta-amyloid monomer, dimer, or trimer oligomers. They then examined the effects of the different oligomers on various types of brain functioning in rats. Only the beta-amyloid dimers significantly impaired these functions. The researchers also chemically synthesized a pure beta-amyloid dimer and found that it produced the same harmful effects on neuronal function. In contrast, the large extracellular beta-amyloid plaques did not show these toxic effects unless they were treated to release dimers. These data strongly support a new view of the role of beta-amyloid in the AD disease process—as soluble toxic dimers. These results point to the need to focus on therapeutic approaches that interrupt the transition of the beta-amyloid molecules from single beta-amyloid monomers to dimers.

- Investigators from the Scripps Research Institute in La Jolla, California, studied the biochemical process by which synthetic and naturally occurring beta-amyloid fragments form aggregates and fibrils (an intermediate stage of beta-amyloid aggregation between soluble oligomers and insoluble plaques) (Bieschke et al., 2008). They found that beta-amyloid monomers were not toxic but became toxic as they aggregated into spherical or incompletely aggregated fibrils. These findings support the hypothesis that an intermediate oligomeric configuration of beta-amyloid is toxic to neurons in AD. An implication from this research is that other toxic oligomeric proteins or peptides—*tau*, synuclein, and prion proteins, for example—might behave similarly.

- Researchers from Massachusetts General Hospital and Harvard Medical School traced the formation of beta-amyloid plaques in living transgenic mice (Meyer-Luehmann et al., 2008). A highly sophisticated microscopic technology (*in vivo* multiphoton microscopy, which allows visualization of structures within the brain) enabled scientists to visualize the formation of amyloid plaques in real time. The amyloid plaques grew very quickly—from small microplaques to their final size—within 24 hours and stayed that final size for at least the remainder of the 1-week period of observation. The researchers also observed that in the days following their formation (the extent of this study), microplaques could rapidly damage the axons and dendrites of nearby nerve cells. They could not determine the underlying processes that resulted in the development of amyloid plaques. These results have led to speculation that beta-amyloid oligomers may be precursors to this sudden growth, that the plaques act as a local source of soluble beta-amyloid, and that the soluble beta-amyloid may be inducing alterations in neighboring dendrites and axons. This published report, the first to describe the rapid and progressive development of amyloid plaques in living animals, differs from the traditional view that had evolved from studies in autopsy material. In the traditional view, amyloid plaques develop through a slow and extended process.

In the mid-1970s, scientists discovered that levels of the neurotransmitter acetylcholine fell sharply in people with AD. Acetylcholine is used by neurons in the hippocampus and cerebral cortex, areas of the brain involved in memory formation. Three of the drugs currently approved to treat AD act by stopping or slowing the action of an enzyme that degrades the acetylcholine neurotransmitter. However, these drugs have adverse side effects, and investigators continue to study this neurotransmitter in hopes of identifying more effective agents with fewer side effects.

- A scientific team at Vanderbilt University, supported largely by the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), the Alzheimer's Association, and the NIH Roadmap Molecular Libraries Screening Centers Network, found a novel small molecule in rat brain cells

(Jones et al., 2008). This molecule, TBPB, selectively bound one of the two types of acetylcholine receptors in neurons and increased the use of a non-amyloidogenic pathway through which APP was processed. As a result, the production of toxic beta-amyloid was reduced. Further, TBPB enhanced the efficiency of acetylcholine-mediated communication in the hippocampus. TBPB's binding and its fidelity for one subtype of acetylcholine receptor also suggested that molecules based on its structure may have fewer adverse side effects than the earlier compounds used in AD treatment. Additional studies in AD animal models are needed to determine whether TBPB can decrease beta-amyloid production and lessen cognitive decline in living brains with fewer side effects. Successful studies in animals one day may lead to human clinical trials of a new drug candidate.

Other 2008 advances in beta-amyloid research include:

Banwait S et al. C-terminal cleavage of the amyloid-beta protein precursor at Asp664: A switch associated with Alzheimer's disease. *Buck Institute for Age Research, Novato, California. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18334752

Cenini G et al. Elevated levels of pro-apoptotic p53 and its oxidative modification by the lipid peroxidation product, HNE, in brain from subjects with amnestic mild cognitive impairment and Alzheimer's disease. *University of Kentucky Lexington. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18494939

Chen K et al. Cooperation between NOD2 and Toll-like receptor 2 ligands in the up-regulation of mouse mFPR2, a G-protein-coupled Abeta42 peptide receptor, in microglial cells. *Research supported by NCI.* www.ncbi.nlm.nih.gov/pubmed/18299458

Jin JJ et al. Toll-like receptor 4-dependent signaling in animal model of Alzheimer's Disease. *University of Illinois, Chicago. Research supported by NEI.* www.ncbi.nlm.nih.gov/pubmed/18510752

Kuchibhotla KV et al. Abeta plaques lead to aberrant regulation of calcium homeostasis *in vivo* resulting in structural and functional disruption of neuronal networks. *Massachusetts General Hospital. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18667150

Parikh V et al. Cholinergic mediation of attention: Contributions of phasic and tonic increases in prefrontal cholinergic activity. *University of Michigan. Research supported by NIMH and NINDS.* www.ncbi.nlm.nih.gov/pubmed/18591483

Zheng J et al. Annular structures as intermediates in fibril formation of Alzheimer Aβ17–42. *University of Akron. Research supported by NCI.* www.ncbi.nlm.nih.gov/pubmed/18457440

See the References section for complete citations.

Other Basic Science Advances

Although beta-amyloid remains a major focus of AD basic science research, investigators recognize that other factors also likely play a role in the pathogenesis of the disease. During 2008, scientists reported on studies demonstrating progress in several areas unrelated to amyloid.

- Researchers at the University of California Irvine investigated the effects of exercise on inflammation and the immune system in AD transgenic mice (Nichol et al., 2008). Chronic stimulation of the immune response by beta-amyloid appears to activate special cells in the brain, called microglia, that release the inflammatory cytokines (a type of protein) IL-1b and TNF-a in toxic concentrations. These inflammatory proteins could be contributing to the neurodegeneration and progression of AD-like pathology rather than the removal of beta-amyloid (as might be expected of an adaptive immune response evolved to protect an organism from foreign material). The researchers found that levels of IL-1b and TNF-a were higher in sedentary 18-month-old AD transgenic mice than in sedentary 18-month-old non-AD mice. After the aged sedentary AD transgenic mice were allowed 3 weeks of exercise in running wheels, the researchers found the mice had significantly lowered levels of IL-1b and TNF-a. In fact, the levels were no different from the non-AD aged sedentary control mice. The lowered levels of cytokines also correlated with improved learning. Exercise decreased the levels of pro-inflammatory markers in these older AD transgenic mice, and increased the markers of the adaptive immune response. The overall impact of this was to remove beta-amyloid from the brain. The research suggests that in mice even in the later stages of AD, exercise can help clear toxic beta-amyloid through stimulation of anti-inflammatory mechanisms.

Studies Look at Early-Life Environmental Exposures and Risk of AD

Scientists generally agree that AD develops over many years as a result of genetic and environmental factors. However, much is still unknown about the exact nature of these factors, how they interact, and how the interactions may differ from person to person. Two studies, the first funded by National Institute of Environmental Health Sciences (NIEHS) and NIA, the second by NIEHS alone, have taken a close look at the possible effects of early-life environmental exposures on risk of AD.

■ Rodent studies have shown that exposure to lead during early-life brain development predetermined the expression and regulation in old age of amyloid precursor protein, or APP, and its beta-amyloid product. Researchers at the University of Rhode Island, Kingston, looked at whether the same events occurred in female monkeys (Wu et al., 2008). They added lead acetate to the diet of a group of monkeys during their first year of life, and 23 years later found extensive evidence of AD-like pathology in their brains after death. This change was not evident in the brains of monkeys whose diets had not been supplemented with lead acetate. These findings implicate an environmental agent—lead—in AD pathogenesis and suggest that infancy is an important period of vulnerability in the brain to agents that could increase future susceptibility to neurodegeneration and AD pathology.

■ In another environmental-exposures study, scientists at University of Montana, Missoula, studied whether living in cities with high levels of air pollution was associated with brain inflammation and neurodegeneration in a group of healthy children and young adults who had died suddenly (Calderón-Garcidueñas et al., 2008). Examination of the children's brain tissue revealed indicators of neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of beta-amyloid and alphasynuclein (a protein found in an abnormal form in Parkinson's disease). The researchers suggest that exposure to air pollution should be considered a risk factor for AD and Parkinson's disease, and that carriers of the APOE ε4 allele who live in polluted environments could have an increased risk of developing AD. ■

■ In a series of experiments involving phospholipase A2 (PLA2), a protein involved in the production of fatty acids, researchers at the Gladstone Institute of Neurological Disease in San Francisco and the University of California San Francisco observed that many of the changes in the brain tissue of people with AD may involve changes in membrane excitability at the synapse, induced by the breakdown products of fatty acids (Sanchez-Mejia et al., 2008). These scientists, who were funded by NINDS and NIA, asked whether modifying fatty acid metabolism could affect AD progression and identified a subset of fatty acids that are present at higher levels in AD mouse models and in people with AD compared to their healthy counterparts. The investigators crossbred genetically engineered mice—mutant human APP mice and mice with one or two copies of PLA2—to generate AD transgenic mice in which PLA2 was lower than normal. This latter group of mice showed improvements in cognitive and behavioral tests and lived longer than the short-lived AD transgenic mice. These results suggest that inhibition of PLA2 may offer an opportunity to intervene therapeutically in AD.

Other 2008 advances in AD basic sciences include:

Greco SJ et al. Leptin reduces Alzheimer's disease-related tau phosphorylation in neuronal cells. *Neurotez Inc., Bridgewater, New Jersey. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18801339

Lim J et al. Pin1 has opposite effects on wild-type and P301L *tau* stability and tauopathy. *Beth Israel Deaconess Medical Center and Harvard Medical School. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18431510

See the References section for complete citations.

Normal Cognitive Aging, Cognitive Decline, and AD: What's the Difference?

Improvements in public health, medical care, nutrition, and living standards have resulted in our now living longer than ever before. Many older adults enjoy active, productive lives, but they also face the risk of memory and other cognitive problems. This challenge has provided a major impetus for research into healthy cognitive aging. Scientists—and the public—want to know how and why some people remain cognitively healthy all their lives while others do not. Answers to these questions also can help researchers understand what goes wrong in AD or other neurodegenerative diseases and can point the way to interventions that might maintain successful brain and cognitive aging.

As knowledge about the spectrum of stages from healthy cognitive aging to AD grows, it has become increasingly evident that no clear distinctions separate a healthy brain and a diseased brain. Most people develop some plaques and tangles in their brains as they get older, but not everyone develops cognitive problems, MCI, or AD. At what point does an age-related process become a disease-causing process? Several studies published in 2008 and 2009 explored this question.

- Researchers at the University of Pittsburgh School of Medicine conducted PiB PET scans to image amyloid deposits in the brains of 43 adults, 65 to 88 years old, who did not have clinical AD or MCI (Aizenstein et al., 2008). The 9 participants with beta-amyloid deposits in at least one brain region performed as well on cognitive tests as the 29 participants who had no amyloid deposits and the 5 participants with "intermediate" evidence of amyloid deposits. The finding that an older person with "significant amyloid burden" can be cognitively normal suggests either that some people may have a high level of cognitive reserve or that beta-amyloid deposition alone does not explain cognitive impairment. (See page 25 for more information about cognitive reserve.) Another possibility is that some of these individuals will go on to develop AD, even though they are cognitively normal to start. In that case, PiB PET may be useful in identifying AD before clinical symptoms appear. These findings mirror those previously found in post-mortem studies, where the brains of some people with normal cognition were found to have significant amyloid deposits.

- A team of scientists at the Banner Alzheimer's Institute in Phoenix, Arizona, conducted PiB PET scans in 28 cognitively normal older people, correlating the results with the presence of the APOE ε4 gene (Reiman et al., 2009). The researchers found higher levels of beta-amyloid deposits in people with one and two copies of the APOE ε4 gene than in those without this version of the gene. These results echo earlier findings showing that APOE ε4 carriers have higher levels of amyloid in their brains at death than do people without this risk factor. Findings from these two studies suggest the possible usefulness of PiB PET scans to detect AD before clinical signs and symptoms appear. This will be crucial for testing promising prevention therapies.

Longitudinal studies also are being conducted to determine the long-term consequences of beta-amyloid deposits in brain and whether they invariably lead to AD.

- University of California Berkeley scientists looked at the relationship between extent of brain amyloid deposits (measured using PiB PET scans), hippocampal volume (measured using MRI), and episodic memory (for example, memory of times or places) in three groups: cognitively healthy participants in the Berkeley Aging Cohort, cognitively healthy participants in the AD Neuroimaging Initiative (ADNI), and ADNI participants with MCI (Mormino et al., 2009) (see page 41 for information about ADNI). In the Berkeley Aging Cohort participants and ADNI participants with MCI, brain amyloid deposits were associated with smaller hippocampal volumes and worse episodic memory. In the healthy ADNI participants, brain amyloid deposits were associated with smaller hippocampal volumes but normal episodic memory. The researchers conducted analyses suggesting that beta-amyloid deposition, hippocampal atrophy,

and declines in episodic memory occur sequentially in elderly subjects, with beta-amyloid deposition being the triggering event. In other words, declining episodic memory in older individuals may be caused by hippocampal atrophy induced by beta-amyloid.

Other 2008 advances in normal cognitive aging, cognitive decline, and AD include:

Geda YE et al. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and normal cognitive aging: Population-based study. *Mayo Clinic, Rochester, MN. Research supported by NIMH, NIA, NINDS, and the Agency for Healthcare Quality and Research*. www.ncbi.nlm.nih.gov/pubmed/18838636

Iacono D et al. Neuronal hypertrophy in asymptomatic Alzheimer disease. *Johns Hopkins University. Research supported by NIA and the Burroughs Wellcome Fund for Translational Research*. www.ncbi.nlm.nih.gov/pubmed/18520776

Sojkova J et al. Longitudinal cerebral blood flow and amyloid deposition: An emerging pattern? *NIA Intramural Research Program*. www.ncbi.nlm.nih.gov/pubmed/18703614

See the References section for complete citations.

Accelerating the Search for Genetic Causes and Risk Factors

It is clear that AD has genetic links. Finding those links and learning how they play out over time is an enormous job, however, given the complexity of the human genome. Further complicating the study of AD genetics is the fact that late-onset AD is probably influenced by many risk and protective factor genes, each conferring a small measure of harm or safety and affecting a variety of biochemical pathways. These pathways may influence the age at onset and the risk of getting the disease or its progression.

In recent years, computer and other technology advances have made an astounding contribution to progress in genetics research. Developments in these technologies now permit scientists to conduct studies, such as genome-wide association studies, that involve rapid processing of vast amounts of genetic data. A GWAS is a study of genetic variations across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or

New International Early-Onset Network Helps Scientists Search for Biological Clues to AD

People with early-onset AD and their families have contributed enormously to our overall knowledge of the disease. A new NIA-funded research network is now asking adult children of people with early-onset AD to join the Dominantly Inherited Alzheimer's Disease Network (DIAN) study, a 6-year, multimillion dollar effort that aims to identify the sequence of brain changes in early-onset AD, even before symptoms appear.

Until now, research into inherited early-onset AD was hindered by the rarity of the condition and geographic distances between patients and research centers. DIAN is designed to overcome those challenges. Study participants will undergo genetic analyses, cognitive testing, and neuroimaging scans and will provide blood and cerebrospinal fluid samples. These assessments, images, and samples should enable researchers to determine the type and sequence of changes in the brain in early-onset inherited AD. By understanding this process, scientists hope to learn about the more common late-onset form of the disease. Knowledge gained also may eventually lead to targets for therapies that can delay or even prevent progress of the disease.

This collaborative, international effort will link a network of research sites in the United States, England, and Australia to family members of people with these rare forms of AD. The study is being led by scientists at Washington University School of Medicine in St. Louis. Collaborators include Massachusetts General Hospital; Brigham and Women's Hospital; Brown University; Columbia University; Indiana University; the University of California Los Angeles; University College, London Institute of Neurology at Queen's Square; and a consortium of the Universities of Melbourne and New South Wales and Edith Cowan University in Australia.

For more information about DIAN, visit *www.dian-info.org.*

absence of a disease or condition. This technology associates single nucleotide polymorphisms (SNPs), which are single changes in nucleotides (the building blocks of DNA), in specific locations on a strand of DNA when compared to the same location in other DNA strands from other individuals. Used to study human genetic variation, SNPs are a powerful way to investigate genetic predispositions to health or disease. GWAS, as well as other sophisticated analytic techniques, are being used to look for associations between genes and late-onset AD and are highlighted in recent advances in this area of AD research.

- Using several familial collections of DNA and clinical data collected as part of the NIMH Genetics Initiative Study, the NIA National Cell Repository on Alzheimer's Disease, and the Consortium on Alzheimer's Genetics, (supported by the Cure Alzheimer Fund), investigators at Massachusetts General Hospital conducted a GWAS to identify SNPs that might be linked to AD (Bertram et al., 2008). In addition to confirming the well-established APOE risk factor gene on chromosome 19, the researchers identified a new SNP on chromosome 14 that showed a strong association with AD as well as several other possible candidates. None of these new markers had previously been associated with AD. Additional whole genome analyses in larger sample sets will be needed to confirm these loci.

- A research team from the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University studied well-characterized clinical and genetic data from people with AD and age-matched healthy individuals participating in the NIA Late-Onset Alzheimer's Disease Family Study (Lee et al., 2008). The scientists used several approaches to analyze the data to identify genetic locations associated with increased risk of late-onset AD. In addition to confirming the strong connection to the APOE gene, the researchers found several promising genes on chromosomes 7, 16, 17, 20, and 22. As with the previous study, these findings must be replicated using other genetic analyses before candidate genes for follow-up analysis are identified, and the functions of these genes are elucidated. Recently, researchers conducting GWAS have identified variants of the SORL1, CLU, PICALM, and CR1 genes that may play a role in risk for late-onset Alzheimer's.

These two studies demonstrate that AD is a complex disease that involves the interaction of a number of genes that influence risk of the disease and its manifestations. Sample sets including several thousand cases and controls, and the use of large independent confirmatory sample sets will be necessary to identify risk genes with low effect size. A number of such collaborative GWAS studies are underway.

As knowledge grows about genetic links to AD, scientists are hoping to use this knowledge to help predict future risk of developing the disease.

- The APOE gene directs the formation of the ApoE protein, which is involved in transporting cholesterol in the blood and the central nervous system. A study conducted at the Banner Alzheimer's Institute and Banner Good Samaritan PET Center (Reiman et al., 2008) looked at the relationship between an aggregated cholesterol-related genetic risk score (CREGS, based on seven cholesterol-related genes associated with AD risk) and regional brain glucose metabolism measured with FDG PET in 141 cognitively normal, late middle-aged individuals. The scientists found a significant inverse correlation between the CREGS score and regional glucose metabolism in brain regions known to be involved in AD. This relationship held even after factoring out the effects of the APOE ε4 gene. These findings further suggest that cholesterol metabolism has a role in the risk of developing AD and support the role of cholesterol-lowering approaches in AD prevention.

The ability to discern possible genetic links to diseases means that scientists also need to develop genetic risk assessment and risk communication strategies to help people understand what these risks may mean in their own lives. The REVEAL (Risk Evaluation and Education for Alzheimer's Disease) Study is a multicenter series of clinical trials supported by the National Human Genome Research Institute (NHGRI) and NIA that aims to examine the psychosocial and behavioral effect of providing close relatives of people with AD with genetic susceptibility testing and information about their chances of developing the disease.

- The REVEAL study assessed the ethical issues involved in genetic testing of African Americans and the ways in which this group interpreted and responded to genetic information (Christensen et al., 2008). Using data from the long-term, NIA-funded Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study,

Examining Diabetes and AD from Two Angles

Type 2 diabetes has emerged as a major focus of interest for AD researchers, and the following studies illustrate the diverse avenues of investigation being conducted to understand the relationship between the two diseases. All of these avenues—from test tube studies to studies in laboratory animals to epidemiologic studies in groups of people—lay the groundwork for clinical trials that can test possible therapeutic or prevention strategies in humans.

■ Scientists at the Salk Institute for Biological Studies in La Jolla, California, induced diabetes in a strain of young AD transgenic mice (Burdo et al., 2009). The diabetic mice displayed a significant loss in both learning and memory compared to control animals. Furthermore, the mice were found to have damaged blood vessels well before pathologic signs of AD appeared. The findings of this study, which was supported by the National Institute of Diabetes and Digestive and Kidney Diseases, suggest that damage to the brain's blood vessels caused by uncontrolled diabetes, in concert with increasing beta-amyloid accumulation, appears to contribute to brain pathology and cognitive defects.

■ People with type 2 diabetes are known to be at increased risk of cognitive decline, but less is known about which cognitive abilities are affected and how undiagnosed diabetes and impaired fasting glucose relate to cognitive performance. A study by researchers at the University of Massachusetts Medical School analyzed data from the intramural NIA Age, Gene/Environment Susceptibility-Reykjavík Study (AGES-Reykjavík) (Saczynski et al., 2008). This study was designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. The research team found that study participants with type 2 diabetes had poorer cognitive performance than did healthy people, particularly with respect to the speed at which they were able to process information. Participants with undiagnosed diabetes had the lowest cognitive performance compared to all other participants in the study.

■ Researchers supported by the National Heart, Lung, and Blood Institute (NHLBI) and NIA analyzed data from the ongoing Cardiovascular Health Study Cognition Study to examine the combined effect of type 2 diabetes and the APOE ε4 gene on the risk of AD, AD with vascular dementia, and vascular dementia without AD (Irie et al., 2008). Compared with those who had neither type 2 diabetes nor the APOE ε4 gene, study participants with both factors had a significantly higher risk of AD. The study found that having both diabetes and APOE ε4 increased the risk of dementia, especially for AD and mixed AD, more than each risk factor alone. Several clinical trials are underway to determine whether various diabetes-related treatments will slow the onset of AD or its progression. ■

the research team found that African Americans responded well to having genetic risk susceptibility information available to them when culturally appropriate education strategies were employed. This study is among the first to include ethnicity in a genetic risk assessment for AD and suggests protocols that can be used to develop culturally appropriate risk communication strategies.

Other 2008 advances in AD genetics include:

Bekris LM et al. Multiple SNPs within and surrounding the apolipoprotein E gene influence cerebrospinal fluid apolipoprotein E protein levels. *Geriatric Research, Education, and Clinical Center, VA Puget Sound Health Care System, Seattle. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18430993

Berchtold NC et al. Gene expression changes in the course of normal brain aging are sexually dimorphic. *University of California Irvine. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18832152

Kauwe JS et al. Variation in MAPT is associated with cerebrospinal fluid *tau* levels in the presence of amyloid-beta deposition. *Washington University School of Medicine, St. Louis. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18541914

See the References section for complete citations.

Understanding Nongenetic Risk and Protective Factors

Genetic studies have shed considerable light on genes involved in the development of the familial forms of early-onset AD and on genetic risk factors for late-onset AD. It is apparent, however, that genetic risk factors cannot fully explain the initiation and

progression of this complex disease. A number of nongenetic factors may contribute to or lessen AD risk. Many epidemiologic and experimental studies have been conducted to identify and understand these factors. The biggest value of the knowledge gained from this research is that it points to new therapeutic approaches, both pharmacological and lifestyle. In the past year, a number of scientific teams reported on their findings in this exciting area of AD research.

Metabolic and Vascular Risk Factors

Over the past decade, considerable evidence has emerged that the body's network of blood vessels—the vascular system—may contribute significantly to the disease process in AD. A growing number of researchers are studying how the brain microvasculature changes during aging and as part of the disease process in AD, and how these changes impinge on disease progression. Other scientists are focusing their research on understanding the relationship between AD and a variety of risk factors associated with vascular and metabolic diseases, such as heart disease, stroke, obesity, and type 2 diabetes.

■ Aging is accompanied by a decrease in brain volume and by an increase in cerebrovascular diseases, such as stroke. A study conducted by scientists at Columbia University examined the effects of age, sex, race/ethnicity, and vascular disease history on brain volume, ventricular volume, hippocampus and entorhinal cortex volumes, and white matter hyperintensity (WMH) burden (Brickman et al., 2008b). (White matter is the part of the brain that is made up of axons, the projections from neurons that transmit messages to other neurons. WMH is seen on MRI scans and is thought to indicate cerebrovascular injury.) This study was conducted in a large community-based population of racially/ethnically diverse older adults without dementia. The team found that older age was associated with decreased brain volume and with increased ventricular and WMH volumes. Hispanic and African American participants had larger relative brain volumes and more WMH than did white participants. However, the associations of these variables with age were similar across racial/ethnic groups. Compared with men, women had larger relative brain volumes. Vascular disease was associated with smaller

Of Mice and Menopause: Studies Look at Estrogen and the Risk of AD

Production of estrogen, a hormone made by women's ovaries, declines dramatically after the childbearing years. During the past 25 years, laboratory and animal research and human observational studies have suggested that estrogen may protect the brain. Experts have wondered whether using estrogen could reduce the risk of AD or slow its progression.

Clinical trials have shown that estrogen does not slow the progression of already-diagnosed AD and does not effectively treat or prevent the disease if treatment begins in later life. However, questions remain as to whether some forms of estrogen might have helpful neuroprotective and anti-inflammatory effects if started somewhat earlier than the older ages already tested (i.e., nearer menopause). A recent study, conducted at the University of Washington Seattle, focused on this question (Suzuki et al., 2007).

This study, conducted in mice, found that estrogen given immediately after the removal of ovaries had a profound neuroprotective action and suppressed inflammation after a stroke. The beneficial effects did not occur when the estrogen was given 10 weeks after ovary removal, when the mice's estrogen levels had been low for a long time.

These findings demonstrate that a prolonged period of low estrogen levels in mice, such as that which occurs after menopause, disrupts both neuroprotective and anti-inflammatory actions of estrogen, and they may help to explain the results of earlier studies, such as the Women's Health Initiative. In that study, which found no beneficial effect of estrogen against stroke, participants began estrogen therapy after an extended period of low estrogen levels.

Based on the results of these human and animal studies, several ongoing clinical trials are now testing the effects of different kinds and delivery of hormones on cognition in perimenopausal women. This is a good example of the "bench to bedside to bench and back to bedside again" approach of AD translational research. ■

relative brain volume and with higher WMH burden, particularly among African Americans. Future studies will examine these results in more detail to understand what leads to them and their importance to cognitive health and cognitive declines.

■ Many studies show that an accumulation of belly fat is a more dangerous risk factor for heart disease and type 2 diabetes than is fat that is distributed elsewhere in the body. A research team at Kaiser Permanente Division of Research in Oakland, California, examined the association between belly fat in midlife and late-life dementia in 6,583 members of Kaiser Permanente in Northern California (Whitmer et al., 2008). The investigators were struck by the finding that people who had excess belly fat in midlife (ages 40 to 45 years) were three times as likely to develop dementia 30 to 36 years later compared to those with low levels of this fat. Even more striking was the finding that people who had an excess of belly fat but were not obese during midlife were twice as likely to develop dementia late in life compared to those with low levels of belly fat. The highest risk of late-life dementia was found in individuals who had excess belly fat and were obese during mid-life.

Personality Traits and the Risk of AD

One of the most intriguing observations in clinical research that is focused on identifying new risk or protective factors for AD comes from studying the associations between various personality traits exhibited throughout life and the development of AD in late life.

■ A research team from the Rush Alzheimer's Disease Center in Chicago has carried out a series of seminal studies in this area and continues to break new ground. In their previous work, they identified that neuroticism and proneness to psychosocial distress were associated with elevated risk of AD. In a recent epidemiologic study (Wilson et al., 2007), the Rush team explored the association between the development of AD and conscientiousness, a personality trait previously linked to morbidity and mortality in old age. The study participants were members of the Religious Orders Study, a long-running study involving 997 nuns, priests, and brothers. At the beginning of this 12-year study, the participants completed a 12-item measure of conscientiousness. In the course of the study, a number of participants were diagnosed with AD and others died with or without having the disease. The brains of clinically diagnosed participants were evaluated for the presence of AD pathology. The study found that a higher level of conscientiousness was associated with reduced risk of developing clinical AD, even after controlling for other personality traits and risk factors for AD. Similar to observations for other personality traits and AD, conscientiousness did not have any correlation with the pathologic hallmarks of AD. This suggests that the mechanisms by which these factors elevate or reduce AD risk have yet to be discovered and that novel neurodegenerative and neuroprotective processes may be at play.

The Mystery of Cognitive Reserve

Scientists have long been fascinated by the question of why some people develop dementia while others remain cognitively healthy all their lives. Another conundrum is why some people remain cognitively healthy even though they may have significant AD-related lesions such as deposits of amyloid plaques in their brains. One possible explanation for these puzzling observations revolves around the concept of "cognitive reserve." This term refers to the brain's ability to operate effectively despite apparent damage. Variations in reserve may reflect genetic differences or differences in life experience, such as education, occupational experience, or leisure activities. A recent study has focused on the role of education in cognitive reserve.

■ A research team from the Washington University School of Medicine evaluated the cognitive reserve hypothesis by examining whether people with greater educational attainment have better cognitive function than individuals with less education when both have elevated beta-amyloid plaque levels (Roe et al., 2008). The investigators studied 198 people between 2003 and 2008 at the Washington University Alzheimer's Disease Research Center. Study participants were divided into two groups—participants without dementia and participants with AD. All participants underwent cognitive and neuropsychological testing. The extent of beta-amyloid deposition in their brains was measured with PiB PET scans. The study found that the participants with greater education maintained better global cognitive functioning in the presence of beta-amyloid pathology. These findings support the cognitive reserve hypothesis and present evidence that education could be used as an indicator of cognitive reserve.

Extinguishing the Flares of the Disease Process

Inflammation is a dynamic and complex biological process that affects cells and tissues throughout the body. It occurs in response to many types of injuries and abnormal situations, from a scrape on the knee to rheumatoid arthritis. Chronic inflammation in the brain is part and parcel of AD pathology, and many scientists are examining its role in the development and progression of the disease. They do not always agree on its significance, however. Some scientists believe that inflammation is part of a vicious cycle that harms neurons. Others think that aspects of inflammation may be valuable to the brain by counteracting the detrimental aspects of the AD process. Epidemiologic studies have suggested that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen, ibuprofen, and indomethacin, are associated with decreased AD risk. However, clinical trials have not yet detected any beneficial effect of NSAIDs on AD prevention or progression. A recent study examined epidemiological findings on NSAIDs and AD.

■ Scientists at the Johns Hopkins University Bloomberg School of Public Health conducted a study funded by NHLBI and NIA to analyze data from six prospective epidemiologic studies (Szekely et al., 2008) to test the hypothesis that only NSAIDs known to have beta-amyloid-lowering activity would be associated with diminished AD risk. The investigators confirmed previous observations that study participants who used NSAIDs were less likely than those who did not use NSAIDs to develop AD. However, NSAIDs with beta-amyloid-lowering activity were no better than other NSAIDs when it came to their association with lower AD risk. The researchers concluded that all conventional NSAIDs, including aspirin, are associated with a similar lowered AD risk in humans. Studies are continuing to determine whether NSAIDs might lessen the risk of AD if given earlier in the disease process.

Other 2008 advances in AD nongenetic risk and protective factors include:

Buchman AS et al. Physical frailty in older persons is associated with Alzheimer disease pathology. *Rush Alzheimer's Disease Center in Chicago. Research supported by NIA*. www.ncbi.nlm.nih.gov/pubmed/18695161

Dai W et al. Abnormal regional cerebral blood flow in cognitively normal elderly subjects with hypertension. *University of Pittsburgh School of Medicine. Research supported by NIA*. www.ncbi.nlm.nih.gov/pubmed/18174483

Martin B et al. Conserved and differential effects of dietary energy intake on the hippocampal transcriptomes of females and males. *NIA Intramural Research Program*. www.ncbi.nlm.nih.gov/pubmed/18545695

Troncoso JC et al. Effect of infarcts on dementia in the Baltimore Longitudinal Study of Aging. *NIA Intramural Research Program*. www.ncbi.nlm.nih.gov/pubmed/18496870

See the References section for complete citations.

Exploring All Possibilities to Improve AD Diagnosis

The only way to diagnose AD definitively is after death, when a clinical examination of the brain can reveal the defining characteristics of the disease—an abundance of beta-amyloid plaques and *tau* tangles, atrophied brain tissue, and enlarged ventricles. However, scientists know that damage to the brain caused by AD begins to develop long before clinical symptoms are readily apparent. Finding a way to detect the disease early in its development would allow clinicians to intervene as soon as they can.

Ambitious efforts are underway to develop sensitive screening instruments and neuropsychological tests to diagnose cognitive decline, MCI, and AD as early as possible. In a complementary effort, many investigators are seeking new ways to measure changes in the structure and function of the brain and in biomarkers, such as substances in cerebrospinal fluid (CSF) and blood. These methods may hint at pathological changes that occur before MCI or AD becomes evident.

Improvements in a third area—brain imaging—also are yielding exciting results. For example, the development of PiB has enabled scientists to visualize beta-amyloid plaques in the living brain. Advances like

this may lead to very early diagnosis of AD and will help researchers and clinicians monitor the effectiveness of experimental treatments. Following are just a few highlights from studies concerned with early diagnosis that were reported in 2008 and 2009.

- Many studies have demonstrated that the hippocampus and entorhinal cortex (structures deep in the brain) shrink when a person has AD. Changes in the cerebral cortex (the outer surface of the brain) have been harder to study in living people. A research team at Massachusetts General Hospital and Harvard Medical School used MRI scans to map the thinning of gray matter in the cerebral cortex (a "signature" of abnormal cortical anatomy in living people with AD) in people with mild AD (Dickerson et al., 2009). The signature paralleled cortical regions already known to be involved in AD. Thinning in the cerebral cortex was associated with severity of symptoms even in the earliest stages of clinical decline, and subtle thinning also was present in older adults without cognitive symptoms who had beta-amyloid deposits detected by PiB. Cortical thinning may potentially be useful as an imaging biomarker.

- Not everyone with MCI develops AD, and scientists have long been interested in determining indicators that might reliably predict which people with MCI will go on to develop AD. A research team at Columbia University assessed 148 people with MCI every 6 months for 3 years (Devanand et al., 2008). Five baseline measures, when combined, strongly and accurately predicted whether a person with MCI would develop AD. The five measures were performance on verbal memory tests, reports by a family member or close friend of functional impairments, performance on a smell identification test, MRI scan of hippocampal volume, and MRI scan of entorhinal cortex volume. If the results of this study are replicated, this five-measure combination could be useful in early AD detection.

- White matter hyperintensities called periventricular hyperintensities (PVH) can be found in axons next to the ventricles and in axons deep in the brain. Recently, investigators at the VU Medical Center in Amsterdam, The Netherlands, as well as NIA-funded investigators conducted a study of the role of WMH in the progression from MCI to AD. They used data from a 3-year clinical trial conducted as part of the Alzheimer's Disease Cooperative Study, which compared the effectiveness of vitamin E, donepezil (Aricept®), and a placebo in delaying the onset of AD in people with MCI (van Straaten et al., 2008). The researchers found that only PVH, not deep WMH, was associated with an increased risk of developing AD. Cerebrovascular disease, particularly PVH, may contribute to the onset of AD in vulnerable individuals.

As scientists have sharpened their focus on the early stages of AD, they have begun to discover hints that changes other than memory loss may signal a developing AD process. For example, movement difficulties, trouble identifying odors, and hearing problems may indicate that the AD process is underway. These findings suggest possible new targets for diagnostic tests for MCI and AD. Such tools can help scientists answer questions about causes and very early development of AD, track changes in brain and cognitive function over time, and track responses to treatments. Two studies reported in 2008 focused on such early changes.

- A University of Wisconsin–Madison team followed 1,920 participants in a population-based study of sensory loss and aging (Schubert et al., 2008). The researchers found a significant association between difficulty identifying smells at baseline and incidence of cognitive impairment 5 years later, and the association remained even after adjusting for possible confounders. The authors concluded that their findings are promising and may be useful clinically but cautioned against using olfaction as a screening test in the general population.

- Researchers at the University of Washington Seattle examined the effects of memory impairment on the brain's ability to understand and interpret speech among 313 older adults participating in a dementia surveillance research program (Gates et al., 2008). The scientists divided the participants into three groups: cognitively healthy participants, participants with MCI, and participants with diagnosed dementia. Results showed that even after adjusting for age and peripheral hearing loss, ability to understand and interpret speech was poorest in the dementia group and moderately reduced in the MCI group compared with the cognitively healthy group.

Other 2008 advances in AD diagnosis include:

Brickman AM et al. Measuring cerebral atrophy and white matter hyperintensity burden to predict the rate of cognitive decline in Alzheimer disease. *Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University. Research supported by NIA*. www.ncbi.nlm.nih.gov/pubmed/18779424

Davatzikos C et al. Detection of prodromal Alzheimer's disease via pattern classification of magnetic resonance imaging. *University of Pennsylvania. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/17174012

Desikan RS et al. MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD. *Boston University School of Medicine. Research supported by NIA*. www.ncbi.nlm.nih.gov/pubmed/18672473

Esposito G et al. Imaging neuroinflammation in Alzheimer's disease with radiolabeled arachidonic acid and PET. *NIA Intramural Research Program*. www.ncbi.nlm.nih.gov/pubmed/18703605

Fan Y et al. Structural and functional biomarkers of prodromal Alzheimer's disease: A high-dimensional pattern classification study. *University of Pennsylvania. Research supported by NIA*. www.ncbi.nlm.nih.gov/pubmed/18400519

O'Bryant SE et al. Detecting dementia with the Mini-Mental State Examination in highly educated individuals. *Texas Tech University Health Sciences Center. Research supported by NIA*. www.ncbi.nlm.nih.gov/pubmed/18625866

Pan S et al. Application of targeted quantitative proteomics analysis in human cerebrospinal fluid using a liquid chromatography matrix-assisted laser desorption/ionization time-of-flight tandem mass spectrometer (LC MALDI TOF/TOF) platform. *University of Washington, Seattle. Research supported by NIEHS*. www.ncbi.nlm.nih.gov/pubmed/18186601

Ringman et al. Biochemical markers in persons with preclinical familial Alzheimer disease. *University of California Los Angeles. Research supported by NIA*. www.ncbi.nlm.nih.gov/pubmed/18509095

Whitwell JL et al. MRI correlates of neurofibrillary tangle pathology at autopsy: A voxel-based morphometry study. *Mayo Clinic, Rochester, Minnesota. Research supported by NIA*. www.ncbi.nlm.nih.gov/pubmed/18765650

See the References section for complete citations.

Boosting the Search for Effective AD Therapies

NIA has a longstanding interest and commitment to supporting research aimed at ensuring that promising new leads in basic science are developed into drugs that can be clinically tested in people. These efforts shifted into high gear in 2004 when NIA launched a set of translational research initiatives focused on supporting early drug discovery and preclinical drug development for AD. NIA is in a unique position to support the translation of basic research into new therapies because its funded academic research is fertile ground for the discovery of potential therapeutic targets. These research initiatives have resulted in a diverse portfolio of funded projects aimed at the discovery and preclinical development of novel compounds for a variety of therapeutic targets in AD. In addition, the program supports the repurposing and reformulation of existing drugs already approved for other disease conditions as well as the development of therapeutics based on natural products.

Since the inception of the AD translational research initiatives, NIA has supported more than 60 projects aimed at discovering and developing novel compounds for more than a dozen different therapeutic targets.

- Evidence from numerous clinical observations and experimental studies has indicated that some antihypertensive medicines might be useful in AD treatment. Researchers at the Mount Sinai School of Medicine examined the ability of the antihypertensive drug valsartan (Diovan®) to alleviate AD pathology in a transgenic mouse model of AD. The study showed that valsartan reduced the amount of beta-amyloid plaques and attenuated the learning deficits that accompany this pathologic feature (Wang et al., 2007).

- Curcumin, the yellow pigment of the spice turmeric, has been shown in studies with mice to have multiple neuroprotective activities, such as anti-inflammatory and antioxidant properties. In addition, in mouse models of AD exhibiting plaque pathology and learning deficits, curcumin reduced the deposition of beta-amyloid and diminished the learning deficits. A considerable challenge in developing curcumin as an AD therapeutic is its chemical instability and a tendency to change metabolically in the human body. A research team at the

University of California Los Angeles is working to develop a curcumin formulation with more desirable physico-chemical properties and is investigating whether one of curcumin's more stable metabolites (known as tetrahydrocurcumin, THC) mediates curcumin's neuroprotective activities (Begum et al., 2008). The study found that despite the structural similarities between curcumin and THC, THC had few of the neuroprotective properties of curcumin, further emphasizing the need for a more refined curcumin formulation.

- A research team at the Center for Drug Discovery and Chemical Biology at Northwestern University in Chicago is seeking to develop a novel class of anti-inflammatory drug that can halt the progression of the disease process in the brain without altering the body's ability to fight infection. One result of these efforts is a candidate therapeutic called Minozac. Given that persistent brain inflammation is a hallmark of a number of neurodegenerative diseases, including AD, the team initiated a preclinical study to test the effectiveness of Minozac in curtailing the deleterious consequences of traumatic brain injury (TBI). These consequences include a marked increase in inflammatory molecules such as cytokines, which are thought to cause acute and long-term damage to the brain (Lloyd et al., 2008). Mice treated with Minozac up to 9 hours after TBI showed suppressed inflammatory response in the brain. This response precluded the long-term neurological consequences of the injury and abolished the neurobehavioral deficits measured up to 1 month after injury. TBI is gaining recognition as a condition of major public health concern and an enormous unmet medical need because effective therapies for TBI are currently lacking.

NIA-funded investigators also continue to take on the challenge of developing safe and effective gene therapy and immunotherapy for AD.

- **Gene therapy.** A research team from the University of San Diego has been pursuing a gene-vector therapy to deliver nerve growth factor (NGF) to brain areas showing loss of cholinergic transmission, which is critical for cognitive function (Nagahara et al., 2008). Most recently, these investigators reported on the efficacy and safety of long-term NGF therapy using a new lentiviral vector for NGF delivery to the cholinergic basal forebrain neurons of aged rhesus monkeys. This area is very vulnerable in AD, with neurons subject to shrinkage in normal aging as well. The result was a reversal of age-related neuronal shrinkage, compared to that of untreated aged monkeys. Importantly, the delivery method did not lead to any adverse side effects, which had previously hindered the effectiveness of this approach. These findings support the safety and feasibility of lentiviral NGF gene transfer for potential testing in human clinical trials.

- **Immunotherapy approaches.** Two recent advances highlight the progress made in developing a safe and effective AD immunization therapy. The goal of immunization therapies is to remove the toxic beta-amyloid peptides from the brains of people with AD without causing dangerous brain inflammation. NINDS- and NIA-supported researchers from the Institute for Molecular Medicine in Huntington Beach, California, and the University of California Irvine sought to achieve this goal by developing a novel vaccine that used DNA as an immunogen. The DNA drove the synthesis of a fragment of the beta-amyloid peptide as well as an inflammatory mediator that stimulated a strong anti-inflammatory response (Movsesyan et al., 2008). AD transgenic mice exhibiting both beta-amyloid and *tau* lesions were prophylactically immunized at a young age. Seven days later, the researchers tested the animals' cognitive performance, and then analyzed their immunological response and changes in amyloid and *tau* pathology. In the short period after the immunization, the vaccine produced a robust anti-beta-amyloid immune response associated with reduced levels of toxic beta-amyloid oligomers as well as reduction in amyloid plaques. *Tau* pathology remained unaltered. Notably, the vaccine treatment led to improved cognitive function in the treated mice and resulted in reduced brain inflammation without adverse effects. Using a related approach, a research team at the University of Rochester School of Medicine and Dentistry used a modified herpes simplex virus (HSV) that makes beta-amyloid, along with the inflammatory mediator interleukin-4 (IL-4), to help the body generate the desired anti-inflammatory immune response (Frazer et al., 2008). The team tested this approach in the same AD transgenic model used by researchers in the previous study. The transgenic mice that expressed both amyloid and *tau* pathology received an initial vaccination at 2 months of age, before the development of the AD pathologic hallmarks, and two additional booster injections. The treated mice showed an anti-inflammatory, anti-beta-amyloid immune

response, improved learning and memory, and reduced AD-related amyloid and *tau* pathology 9 months after the initial vaccination. Brain neuroinflammation also was reduced without signs of micro-bleeding in the brain. These two preclinical studies are important steps toward the development of a safe and effective AD vaccine.

In addition to funding initiatives that support early drug discovery and preclinical drug development for AD, NIA continues to provide investigational new drug (IND)-enabling toxicology services for novel therapeutics and imaging ligands through a longstanding contract. This contract supports the development of the amyloid imaging agent PiB, which enables visualization of beta-amyloid pathology in living human brains. AL-108, a drug that was evaluated for safety under that contract to help provide the data for IND approval from the FDA, is now being tested in human clinical trials. AL-108, or davunetide, is the intranasal formulation of NAP (an eight amino acid peptide). The Allon Therapeutics Phase IIa clinical trial results showed intranasal davunetide positively affected memory function in people with MCI. A Phase IIb clinical trial in people with AD is under development.

NIA also co-funds a number of aspects of preclinical development for AD through the trans-NIH Rapid Access to Interventional Development (NIH-RAID) Program *(http://nihroadmap.nih.gov/raid/).* NIA and the NIH-RAID Program co-funded the completion of critical IND-enabling steps for the novel AD therapeutic MCD-386, discovered by Dr. William Messer at the University of Toledo. MCD-386 belongs to a second generation of drugs that activate particular receptors for acetylcholine on neuronal cells. These drugs are more effective than the first generation of drugs and are very specific for the receptors they are targeting. As a result, they lack some of the side effects that prevented the development of the first generation of the drugs. MCD-386 was licensed by the Wisconsin-based biotech company Mithridion, Inc., and is in early stages of clinical testing for AD treatment.

Other 2008 advances in AD translational research include:

Faghihi MA et al. Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of beta-secretase. *The Scripps Research Institute, Jupiter, Florida. Research supported by NIA.* http://www.ncbi.nlm.nih.gov/pubmed/18587408

Ghosh AK et al. Potent memapsin 2 (beta-secretase) inhibitors: Design, synthesis, protein-ligand X-ray structure, and *in vivo* evaluation. *Purdue University. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18180160

Head E et al. A two-year study with fibrillar β-amyloid (Aβ) immunization in aged canines: Effects on cognitive function and brain Aβ. *University of California Irvine. Research supported by NIA.* www.ncbi.nlm.nih.gov/pubmed/18385314

See the References section for complete citations.

Supporting the Gold Standard: AD Clinical Trials

Clinical trials, which compare a potential new treatment with a standard treatment or with a placebo (an inactive substance), are the only way to demonstrate whether a drug or other type of treatment is safe and effective in people. These complex and expensive studies can involve hundreds or even thousands of people and often are conducted over a long period of time. Some clinical trials are focused on prevention—strategies to help reduce the risk of developing AD in the future. Other clinical trials are focused on AD treatment—strategies to preserve cognitive function for as long as possible, slow disease progression, delay progression from MCI to AD, or alleviate behavioral or psychiatric problems. In 2008, several research teams reported on studies in this latter area.

- Sleep disturbances and disordered breathing during sleep are common in the elderly. Sleep apnea (a sleep disorder characterized by pauses in breathing during sleep) affects nearly 42 percent of older adults. Scientists have already demonstrated a strong relationship between severity of sleep apnea and cognitive impairment in older adults and in people with dementia. A large study of nursing home residents showed that those with severe dementia had significantly more-severe sleep apnea, and those with more-severe sleep apnea had significantly more-severe dementia. The continuous positive airway pressure (CPAP) mask is an inexpensive and effective treatment for sleep apnea. In a clinical trial, researchers from the University of California San Diego demonstrated

that CPAP treatment in people with AD significantly improved their ability to learn and memorize, as well as to adapt their cognitive processing strategies to face new and unexpected conditions in the environment (Ancoli-Israel et al., 2008). The researchers also found a significant enhancement of mental processing speed in AD patients after CPAP treatment.

■ The Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD), funded by NIMH, examined atypical antipsychotic medications (olanzapine, quetiapine, and risperidone) or placebo in 421 outpatients with AD and psychosis or agitated/aggressive behavior (Sultzer et al., 2008). Results indicated that some clinical symptoms improved with atypical antipsychotic use and suggest that they may be especially effective for particular symptoms, such as anger, aggression, and paranoid ideas. However, these drugs do not appear to improve functioning, care needs, or quality of life in people with AD.

Although results may not demonstrate that a particular treatment is effective, scientists can gain a wealth of knowledge from clinical trials for use in future trials. A good case in point is the recently concluded Ginkgo Evaluation of Memory Study.

■ Early studies suggested that extracts of leaves from the *Ginkgo biloba* tree have beneficial effects on brain function, especially those related to dementia and AD.

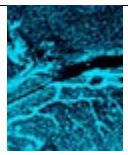
Decisionmaking Capacity: An Issue for Clinical Trials Participation

Researchers conducting clinical trials with people who may have memory problems, MCI, or AD must consider the declining memory and cognitive capacity of the participants. They must evaluate the ability of potential participants to understand, consent to, and participate in the research. Three studies reported in 2008 examined this issue.

■ Researchers from the University of Pennsylvania School of Medicine developed a semistructured interview technique that assesses four decisionmaking abilities (Karlawish et al., 2008). They found that scores from this instrument, called the MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR), and especially scores on the "understanding" domain, can be used to help determine which people with mild to moderate AD are capable of giving informed consent. However, the researchers caution that results could vary depending on the risk of the study and the techniques interviewers use to administer the MacCAT-CR. Therefore, the tool should not be used alone but in concert with other measures to determine a person's ability to provide informed consent.

■ A study led by scientists at the Boston University Alzheimer's Disease Center and funded by NIMH and NIA compared 40 older adults (ages 60-90) with MCI to 40 with normal cognitive functioning. They looked at participants' scores on a comprehensive neuropsychological battery of tests and their capacity to provide informed consent for participation in a hypothetical clinical trial (Jefferson et al., 2008). The results showed that many of those with MCI performed more poorly than the normal controls on most of the decisional capacity measures examined. People with MCI who were deemed to be capable of providing informed consent had higher education levels than those rated as not capable. These findings suggest that impaired capacity to provide informed consent for research participation may be present relatively early in the trajectory of cognitive decline to AD and that researchers should be cautious when evaluating the decisional capacities of potential research participants who are at risk of AD. The researchers further note that methods used to obtain research consent should take into account the participants' educational background.

■ Scientists at the University of Alabama at Birmingham assessed changes over time in the medical decisionmaking capacity of people with MCI (Okonkwo et al., 2008). The investigators were interested in determining participants' capacity at the beginning of the study and investigating the impact of progressing from MCI to AD on this capacity. Participants were followed for up to 3 years. The researchers found that the decline in medical decisionmaking capacity in people with MCI is a relatively slow but detectable process. Over a 3-year period, participants with MCI also showed progressive decline in their ability to understand consent information. This decline accelerated after diagnosis of AD, reflecting increasing vulnerability to decisional impairment. The study authors suggest that clinicians and researchers working with MCI patients should give particular attention to the informed consent process when progression to AD is suspected or confirmed. ■



Discoveries and progress would not be possible without the many thousands of volunteers who participate in research.

In 2000, the National Center for Complementary and Alternative Medicine, NIA, and NHLBI funded a clinical trial to compare ginkgo to placebo in people older than 75 who were cognitively healthy or had MCI (DeKosky et al., 2008). The main goal was to determine whether ginkgo was helpful in preventing or delaying the onset of dementia, but researchers also were interested in assessing participants' rate of cognitive and functional decline, the incidence of cardiovascular and cerebrovascular events, and causes of death. In 2008, the University of Pittsburgh research team leading the trial reported that ginkgo did not reduce the incidence of dementia or AD in either the cognitively healthy participants or those with MCI. Despite these results, the investigators learned much about subgroups of participants who may have been at increased risk of developing dementia, and they learned about ginkgo's effects on diseases other than dementia and AD. They also gained insights into ways of designing and conducting large dementia prevention trials in older adults, such as the number of participants needed to yield clinically significant results. These trial findings and lessons learned will be used in planning and conducting future AD prevention trials.

A number of other NIA-funded Phase II and Phase III clinical trials have been completed, and publication of the primary results is pending. These trials include:

- Cholesterol Lowering Agent (Simvastatin) to Slow Progression of AD (CLASP)—Alzheimer's Disease Cooperative Study (ADCS); Mary Sano, Principal Investigator (PI)
- Docosahexaenoic Acid (DHA, Omega 3 fatty acid) in AD—ADCS; Joseph Quinn, PI
- Antioxidants (vitamins E and C, alpha lipoic acid, coenzyme Q) in AD—ADCS; Douglas Galasko, PI
- Valproate in Dementia (VALID)—ADCS; Pierre Tariot, PI
- Huperzine A in AD—ADCS; Paul Aisen, PI
- Transdermal Nicotine Treatment of MCI—Paul Newhouse, PI

Federal and non-Federal agencies and industry are supporting more than 50 AD-relevant clinical trials. Table 1, beginning on page 33, lists ongoing prevention and treatment trials funded by NIA, as well as several jointly supported by NIA and other NIH Institutes. The ADCS, a consortium of about 75 sites in the U.S. and Canada (see page 41 for more on the ADCS), is a cornerstone of NIA's efforts in clinical trials research.

Table 2, beginning on page 36, lists NIA-funded clinical trials examining prevention of age-related cognitive decline. Currently, it is unclear whether any intervention that effectively slows age-related cognitive decline also will slow the onset of AD.

TABLE 1. Ongoing NIA-Funded AD/MCI Prevention and Treatment Clinical Trials (as of November 2009)

Trial Name	Principal Investigator	Intervention	Population
Antioxidants			
PREADVISE (Prevention of Alzheimer's Disease by Vitamin E and Selenium)*	William Markesbery	Vitamin E, selenium, Vitamin E + selenium	Men ages 60-90
Vitamin E in Aging Persons With Down Syndrome	Arthur Dalton	Vitamin E	People ages 50+ with Down syndrome, at high risk of developing AD
Cardiovascular			
ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes—Memory in Diabetes)*	Lenore Launer	Intensive glucose, blood pressure, and lipid management	People ages 40-79 with type 2 diabetes mellitus
Effects of Simvastatin on CSF AD Biomarkers	Cynthia Carlsson	Simvastatin	People ages 45-65 at high risk of AD (family history, APOE ε4)
ESPRIT (Evaluating Simvastatin's Potential Role in Therapy)	Cynthia Carlsson	Simvastatin	People ages 35-69 at high risk of AD (family history)
SPRINT-MIND (Systolic Blood Pressure Intervention Trial-MIND)*	Lawrence Fine	Blood pressure lowering to <140 mm Hg versus <120 mm Hg	Adults age 55 years or older with systolic blood pressure of 130 mm Hg or higher, history of cardiovascular disease, high risk for heart disease
Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for AD	Gail Li	Simvastatin	Cognitively normal people ages 45-64
Hormones			
Alzheimer's Disease: Potential Benefit of Isoflavones	Carey Gleason	Novasoy (soy isoflavones–phytoestrogens)	People with AD
ELITE (Early versus Late Intervention with Estradiol)	Howard Hodis	17β-estradiol	Healthy early (less than 6 years) or late (10 years +) menopausal women
KEEPS-CA (Kronos Early Estrogen Prevention Study–Cognitive and Affective Study)*	Sanjay Asthana	Oral conjugated equine estrogen (CEE or Premarin®) and transdermal 17β-estradiol (tE2)	Healthy perimenopausal women ages 42-58
Raloxifene for Women with Alzheimer's Disease	Victor Henderson	Raloxifene (selective estrogen receptor modulator or SERM)	Older women with AD
SMART (Somatotrophics, Memory, and Aging Research Trial)	Michael Vitiello	Growth hormone releasing hormone (GHRH)	People with MCI and healthy older adults ages 55-80
Testosterone Supplementation in Men with MCI	Monique Cherrier	Testosterone	Older men with MCI and low testosterone

Trial Name	Principal Investigator	Intervention	Population
Diabetes			
Glucose Regulation and Memory in Alzheimer's Disease	Suzanne Craft	Diet, triglyceride emulsion, rosiglitazone	People with AD (all studies), age-matched healthy older adults (diet study)
Metformin in Amnestic MCI	Jose Luchsinger	Metformin	Overweight/obese older people with MCI
RECALL (Rosiglitazone Effects on Cognition for Adults in Later Life)	Suzanne Craft	Rosiglitazone	People with MCI
SNIFF 120 (Study of Insulin to Fight Forgetfulness, 120 Days)	Suzanne Craft	Intranasal insulin	People with MCI and AD
Diabetes and Exercise			
POEM (Pioglitazone or Exercise to Treat Mild Cognitive Impairment)	Robert Schwartz	Pioglitazone, endurance exercise training	Older people with MCI and metabolic syndrome
Exercise			
Effects of Standardized Aerobic Exercise Training on Neurocognition and Neurodegeneration	Thomas Obisesan	Aerobic exercise training	African Americans with AD
Exercise and Health Promotion for MCI: A Controlled Trial	Linda Teri	Two exercise programs	People with MCI
MCI: Cerebrovascular Dysfunction and Exercise Training	Rong Zhang	Endurance exercise training	People with MCI
Exercise and Cognitive Training			
Exercise Versus Cognitive Interventions for Elders at Risk for Dementia	David Loewenstein	Cognitive training, aerobic exercise training	People with MCI
Neural Effects of Exercise, Cognitive, or Combined Training in AD At-Risk Elders	Stephen Rao	Cognitive training, aerobic exercise training	Healthy people ages 65-85
SHARP-P (Seniors Health and Activity Research Program Pilot)	Mark Espeland	Physical activity, cognitive training	Older people ages 70-85 at risk of developing MCI
Treatment for Behavioral Issues			
ADMET (Apathy in Alzheimer's Disease Methylphenidate Trial)	Jacobo Mintzer Krista Lanctot Paul Rosenberg	Methylphenidate	People with AD
Antipsychotic Discontinuation in Alzheimer's Disease	Davangere Devanand	Risperidone	People with AD
CITAD (Citalopram Treatment for Agitation in Alzheimer Dementia)	Constantine Lyketsos	Citalopram	People with AD
Light Treatment for Sleep/Wake Disturbances in AD	Jerome Yesavage	Light treatment	People with AD and their caregivers

Trial Name	Principal Investigator	Intervention	Population
Treatment for Behavioral Issues (continued)			
Prazosin Treatment for Disruptive Agitation in Alzheimer's Disease	Elaine Peskind	Prazosin	People with AD
TREA (Treatment Routes for Exploring Agitation)	Jiska Cohen-Mansfield	Systematic approach to individualizing non-pharmacological interventions for persons with dementia	Nursing home residents with AD/dementia
Other Interventions			
AAV-NGF Gene Delivery in Alzheimer's Disease	Paul Aisen	Nerve growth factor (NGF) gene delivery	People with AD
AREDS2 (Age-Related Eye Disease Study 2)**	Emily Chew John Paul San Giovanni	Macular xanthophylls (lutein and zeaxanthin) and/or omega-3 fatty acids (DHA and EPA)	People ages 50-85 with age-related macular degeneration (AMD) in both eyes or advanced AMD in one eye
fMRI Activation in Mild Cognitive Impairment	Michela Gallagher	Levetiracetam	People with MCI
GAP (Gammaglobulin Alzheimer's Partnership)†	Norman Relkin	Immune globulin intravenous (IVIg), passive immunization	People with AD
Study on Thalidomide as BACE1 Inhibitor in Alzheimer's Disease	Yong Shen	Thalidomide	People with AD

Note: For information on new and currently recruiting trials, visit *www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials* or *www.ClinicalTrials.gov*.

* NIA-funded add-on trials: PREADVISE (add-on to National Cancer Institute's SELECT trial); ACCORD-MIND (add-on to National Heart, Lung, and Blood Institute's ACCORD trial); SPRINT-MIND (add-on to NHLBI's SPRINT trial); KEEPS-CA (add-on to Kronos Longevity Research Institute's KEEPS trial).
** NIA co-funded trial: AREDS2 (National Eye Institute, lead institute).
† Alzheimer's Disease Cooperative Study (ADCS) trial.

TABLE 2. Ongoing NIA-Funded Age-Related Cognitive Decline Trials with Healthy Older Adults (as of November 2009)

Trial Name	Principal Investigator	Intervention
Cognitive Training		
A Brain-Based Approach to Enhancing Executive Control Functions in Healthy Aging	Mark D'Esposito	Cognitive training
Active Interventions for the Aging Mind	Denise Park	Cognitive enrichment through training in digital photography or quilting
Expanding the Implementation of an Effective Cognitive Aging Intervention	Helga Noice	Cognitive enrichment through training in acting
Randomized Clinical Trial of Two Speed of Processing Modes to Prevent Cognitive Decline in Older Adults	Frederic Wolinsky	Comparison of standard versus enhanced visual processing training
The Senior Odyssey: A Test of the Engagement Hypothesis of Cognitive Aging	Elizabeth Stein-Morrow	Cognitive enhancement through participation in the Odyssey of the Mind program
Aerobic and Other Exercise		
Dose-Response Study of Exercise in Older Adults	Jeffrey Burns	Aerobic exercise
Examining the Effects of Improved Physical Fitness on Cognitive/ Psychological Function	Adrienne Morgan	Aerobic exercise
Influence of Fitness on Brain and Cognition	Arthur Kramer	Aerobic exercise
LIFE (Lifestyle Interventions and Independence for Elders)	Marco Pahor	Aerobic exercise, resistance, and flexibility exercises
Aerobic Exercise and Cognitive Training		
Brain and Cognitive Changes After Reasoning or Physical Training	Sandra Chapman	Aerobic exercise and cognitive training
Combining Exercise and Cognitive Training to Improve Everyday Function	Ellen Binder Mark McDaniel	Aerobic exercise and cognitive training
Combined Exercise and Cognitive Training Intervention in Normal Aging	Yaakov Stern	Aerobic exercise and cognitive training
Impact of Exercise and Engagement on Cognition in Older Adults	Denise Park	Addition of exercise to a cognitive enrichment trial
Improvement of Visual Processing in Older Adults	Karlene Ball	Combination of visual processing training and exercise
Tai Chi and Guided Autobiography for Remediation of Age-Related Cognitive Decline	Victor Henderson	Low-impact Tai Chi exercise and autobiographical writing

Trial Name	Principal Investigator	Intervention
Other Interventions		
ASPREE (Aspirin in Reducing Events in Elderly)	Richard Grimm John McNeil	Aspirin
Guanfacine Treatment for Prefrontal Cognitive Dysfunction	Christopher Van Dyck	Guanfacine
Hormones and Cognitive Processing	Yolanda Smith	Estradiol or progesterone in postmenopausal women
Omega-3 and Blueberry Supplementation in Age-Related Cognitive Decline	Robert Krikorian	Omega-3 and blueberry supplements
The Testosterone Trial	Peter Snyder	Testosterone gel in older men living in the community

Note: For information on new and currently recruiting trials, visit *www.ClinicalTrials.gov*.

Helping People Cope with AD

Caring for a person with AD presents unique challenges, and considerable research has explored the physical, emotional, and mental stresses on AD caregivers. This area of research is an important component of NIH's overall AD research effort. Investigators supported by NIA, NIMH, and the National Institute of Nursing Research (NINR) continue to study ways to understand the effects of caring for a loved one with AD and to find ways to support both caregivers and people with AD.

Issues with Diagnosis

■ The traditional view is that receiving a diagnosis of AD is a devastating experience for the person and his or her family. That might not always be true, however. To gauge psychological reactions to a dementia diagnosis, researchers from Washington University in St. Louis conducted telephone interviews with patients a few days after they received a dementia diagnosis (Carpenter et al., 2008). Participants with AD and their companions took two tests that measured depression and anxiety. The research team also conducted comprehensive physical and neurological examinations of the people with AD. The researchers found no significant increase in depression in individuals or their companions. The participants' anxiety also did not increase after receiving the diagnosis, and in some cases, even decreased. One explanation for this latter result is that an AD diagnosis may provide relief because it explains symptoms, and knowing the cause of the behaviors, being able to plan for the future, and having the support available at an Alzheimer's disease research center may improve people's ability to cope with their changing situation.

■ Increasingly, because of both greater numbers of patients and insufficient access to specialists, people with dementia are diagnosed and treated by primary care physicians. Previous research about dementia care in primary care settings has shown significant obstacles to optimum care. These obstacles include high rates of underdiagnosis, inappropriate use of medications, lack of referrals to social service agencies, and insufficient time to provide information. A research team at the University of California Davis interviewed 40 primary care physicians to determine challenges that clinicians face after the point of a dementia diagnosis (Hinton et al., 2007). The results suggested several possibilities for improved care. This study extended prior findings of lack of time, demonstrating that dementia creates

greater paperwork demands due to need for referrals. Further, family members can have real and intense social and psychological needs. Long delays for scheduling with a specialist, lack of feedback from specialists, and variations in insurance coverage of mental health needs were all identified as barriers to care. Some even suggested that dementia patients are excluded from certain practices due to the high demands. Medicare billing rules also were identified as problematic. Different codes are reimbursed at dramatically different rates, and many of the activities that physicians and their staff must do when caring for people with dementia (or their families) are not reimbursable. Ongoing work by other groups is beginning to produce cost-effective models for improved, proactive interdisciplinary care of dementia patients.

Advance Planning Concerns

Scientists at the University of Pittsburgh conducted a study to examine the prevalence and sociodemographic correlates of written advance planning among people who were unable to make decisions because of dementia or who were at risk of this incapacity (Lingler et al., 2008). Study participants included 112 people with MCI, 549 people with AD, and 84 cognitively healthy people. The investigators found that 65 percent of participants had a durable power of attorney and 56 percent had a living will. Advance planning rates did not vary by diagnosis. The authors conclude that a majority of persons with and at risk for the sustained and progressive decisional incapacity of AD are formally planning for the future, but a substantial minority are not.

Behavioral Problems

Disrupted sleep is a common complaint among family members who care for older adults with AD. These disturbances are often thought to be linked to the sleep disturbances in the person with AD. This study, conducted by investigators at the University of Washington and supported by NIMH, used special monitoring methods to examine the sleep patterns over 1 week of 44 older adults with probable or possible AD and the family caregivers living with them (McCurry et al., 2008). The researchers found that people with AD and care-

Kentucky's African American Dementia Outreach Partnership: A Model for High-Quality Care

Researchers at Kentucky's Sanders-Brown Center on Aging have been working closely with the local African American community to develop a model of community outreach and quality AD care. Founded in 2003, the African American Dementia Outreach Partnership (AADOP) found that a conveniently located clinic and access by study personnel to the home of a person with AD were first steps in achieving quality of care (Danner et al., 2008). During the study, research staff made 66 in-home safety checks for individuals with suspected memory loss who were living alone. Educating families about the distinction between normal aging and signs of disease was another critical component of successful care.

The Center has worked to build trust in the community by collaborating with African American churches. This collaboration has encouraged people with AD and their families to receive help with memory problems and to feel comfortable in seeking help for other medical problems. An additional benefit of this approach is earlier identification of dementia among community residents, who then have access to drug treatments that work best early in the course of the disease and the opportunity to plan future care.

The AADOP team recognizes that the next challenge for the program is to maintain the Center's involvement with and responsiveness to the community over the long term.

givers both experienced considerable variability in sleep disturbances from night to night. However, contrary to assumptions, the sleep disruptions experienced by the person with AD and the caregiver did not necessarily match. When one person was sleeping poorly, the other may have been sleeping well and vice versa. The researchers also found that whether the pair's sleeping patterns matched or not, sleep disturbance was associated with depression in the people with AD and with differences in caregivers' reported problem-management styles (criticism, encouragement, active management). More research to clarify the complex interrelationships between sleep in AD patients and their caregivers will help in developing effective personalized intervention approaches. Such research also will be essential to understand more fully the roles that depression in people with AD and caregiver management styles may play.

Supporting Caregivers

- One of the most difficult decisions families face is whether and when to place a loved one in a nursing home or other care setting. This decision is driven by the needs of the person with AD and the ability of the family to meet those needs. The costs of care in an institutional setting are always an important consideration in this decision. Two recent studies conducted by researchers at the James J. Peters Veterans Affairs Medical Center in Bronx, New York, examined this issue. Their results provide important insights that can assist communities and policymakers to determine the costs of AD and develop appropriate services. In the first study, the researchers estimated the incremental effects of dependence on others and the ability to function on costs of care during the early stages of AD (Zhu et al., 2008a). They found that dependence on others and functional ability of people with early AD related differently to direct medical and to informal caregiving costs. These results suggest that these two measures provide unique information for explaining variations in cost of care for people with AD and highlight the value of measuring both constructs.

In the second study, the VA research team examined the incremental effect of dependence on others by people with AD and the cost of medical and non-medical care and informal caregiving hours over time (Zhu et al., 2008b). They found both functional impairment and patient dependence to be associated with higher costs of care and caregiving over time. These results demonstrate that measures of functional impairment and patient dependence provide unique and incremental information on the overall impact of AD on people with the disease and their caregivers.

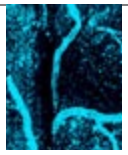
- A study by scientists at the University of North Carolina at Chapel Hill found that appropriately timed community-based support services for older adults with dementia and their caregivers may reduce caregiver burden and postpone nursing home placement (Beeber et al., 2008). This NINR-supported study also found that having adequate financial resources, private insurance, access to sufficient programs and physicians in the area, more functional and behavioral problems, or a diagnosis of AD (rather than other types of dementias) increased the likelihood of using adult day care services. Similarly, use of home-based services was more likely among households with more highly educated caregivers, older care recipients, and care recipients or caregivers with greater functional limitations. Determining the long-term outcomes of support-service use may identify specific groups and geographical locations at risk of lower quality of life outcomes, which, in turn, could inform the design of interventions to improve assessment for and delivery of community-based support services.

Other 2008 advance in AD research to help people cope with AD include:

Gitlin LN et al. Tailored activities to manage neuropsychiatric behaviors in persons with dementia and reduce caregiver burden: A randomized pilot study. *Thomas Jefferson University. Research supported by NIMH*. http://www.ncbi.nlm.nih.gov/pubmed/18310553

See the References section for complete citations.

Outlook *for the Future*



Scientists are increasingly optimistic about the promise of AD research and the hope that it brings for new treatment and prevention interventions.

Alzheimer's research continues to move ahead with purpose, always pushing against the boundaries of current knowledge. Today, scientists are increasingly optimistic about the promise of AD research and the hope that it brings for new treatment and prevention interventions. A critical element in keeping the momentum in science going is the careful cultivation of the AD research infrastructure.

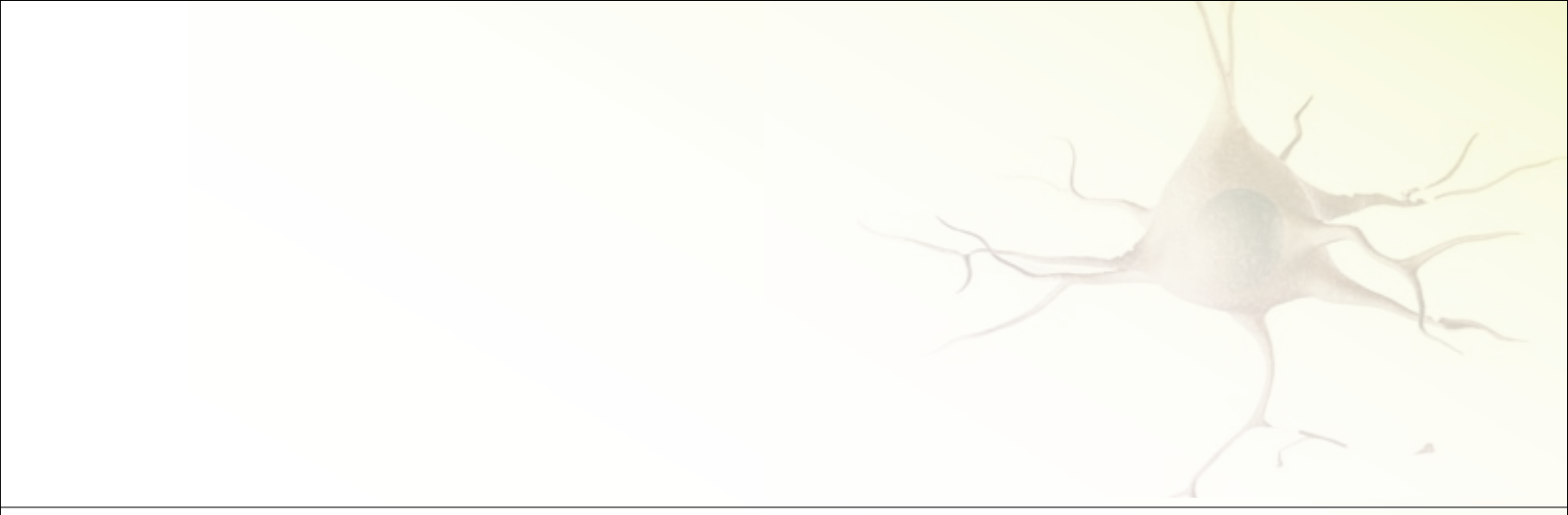
Nurturing the AD Research Infrastructure

Thoughtful development of and sustained support for the AD research infrastructure has allowed NIH to continue to make rapid progress in AD. This support takes a variety of forms.

Coordinating Mechanisms

Alzheimer's Disease Centers. The 30 NIA-funded Alzheimer's Disease Centers (ADCs) (*www.nia.nih.gov/Alzheimers/ResearchInformation/ResearchCenters*) are multidisciplinary centers that promote research, training and education, and technology transfer. With participation by the community, the Centers conduct longitudinal multicenter and collaborative studies of diagnosis and treatment in AD, age-related neurodegenerative diseases, and normal aging. Complementary studies, such as imaging studies and autopsy evaluations, also are conducted at ADCs.

National Alzheimer's Coordinating Center (NACC). In 1999, NIA established the NACC so data on participants in ADC studies could be



pooled and shared (*www.alz.washington.edu*). By 2009, information on more than 90,000 ADC study participants and neuropathologic data on more than 10,000 brains from autopsied participants had been collected. Much of this material is available to qualified AD researchers at institutions worldwide.

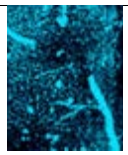
Alzheimer's Disease Cooperative Study (ADCS). The ADCS, launched in 1991, is a cornerstone of NIA's clinical trials research efforts (*www.adcs.org*). This consortium of about 75 sites in the United States and Canada was developed in response to a perceived need to advance research in the development of drugs that might be useful for treating patients with AD, particularly drugs that otherwise might not be developed by industry. The ADCS focuses on trials of compounds developed by individual investigators or small companies that have limited resources for clinical trials. A recent focus has been on partnering with larger companies. In addition to testing new compounds, the ADCS is developing new methods for conducting dementia trials.

Initiatives

Alzheimer's Disease Neuroimaging Initiative (ADNI). ADNI, a research partnership supported primarily by NIA with private-sector support through the Foundation for NIH, seeks to find neuroimaging and other biological markers that can be used to detect AD progression and measure the effectiveness of potential therapies. Begun in 2004, ADNI is following approximately 200 cognitively healthy individuals and 400 people with MCI for 3 years, and 200 people with early AD for 2 years. Participants are being evaluated using clinical and neuropsychological measures; MRI, FDG-PET, and PiB PET scans; CSF measures of beta-amyloid and *tau*; and genetic assessments. The data generated from these visits and clinical testing will help in evaluating disease progression and may reduce the time and expense of clinical trials by improving methods and developing uniform standards by which imaging and biomarkers might track the disease and measure effects of interventions. ADNI also has created a publicly accessible database containing thousands of MRI and PET scan brain images as well as clinical, genetic, and fluid biomarker data. This database is available to qualified researchers worldwide. Hundreds of researchers already have accessed ADNI data and images, and ADNI has inspired similar efforts in Europe, Japan, and Australia.

Alzheimer's Disease Genetics Initiative (ADGI) and Alzheimer's Disease Genetics Consortium (ADGC). Launched in 2003, ADGI aims to identify at least 1,000 families with members who have late-onset AD and members who do not have the disease. Investigators are collecting blood samples and other clinical data from participants to use in genetic analyses to identify additional late-onset AD risk-factor genes. The ADGC was launched in 2007 to accelerate the application of genetics technologies to late-onset AD through collaborations among leading researchers in AD genetics and genetic epidemiology. The ultimate goal of this effort is to obtain genetic material from 10,000 people with AD and 10,000 cognitively healthy people and then to scan the entire genome for the remaining AD risk-factor genes, as well as genes for age-related cognitive decline and genes associated with related risk and protective factors.

Cognitive Aging Initiative. In partnership with the McKnight Brain Research Foundation and the Foundation for NIH, NIA convened a Cognitive Aging Summit in 2007 to highlight scientific research



Solving the puzzle of this disease will depend on harnessing the power of all avenues of science and medicine. Our task is to build on recent discoveries through continued support for multidisciplinary, collaborative AD research.

on healthy brain aging and function, galvanizing the field and serving as a catalyst for two research initiatives. The first, "Remediation of Age-Related Cognitive Decline," provides funding for pilot interventions examining normal age-related decline. The second, "Neural and Behavioral Profiles of Cognitive Aging," provides funding for studies to delineate the neural and behavioral mechanisms involved in maintaining a healthy brain. This initiative also encourages projects designed to help distinguish normal age-related change from pathological decline.

Cognitive and Emotional Health Project (CEHP). A large number of people are at substantial risk for cognitive impairment and emotional disorders as they age. CEHP's goal is to assess the state of longitudinal and epidemiologic research on demographic, social, and biologic determinants of cognitive and emotional health in aging adults, and to accelerate identification of ways to maintain cognitive and emotional health.

NIH Toolbox for Assessment of Neurological and Behavioral Function. In 2006, a contract was awarded through the NIH Blueprint for Neuroscience Research to develop a set of brief, psychometrically sound measures to assess cognitive, sensory, motor, and emotional function in large cohort studies (longitudinal and epidemiological) and clinical trials. NIA has taken the lead on this project, which will produce assessments, in English and Spanish, for use in individuals from ages 3 to 85 years.

AD Translational Initiative. The AD Translational Initiative, launched in 2004, supports early drug discovery and drug development research by academic scientists and small biotechnology companies, with the goal of finding ways to treat and prevent AD, MCI, and age-related cognitive decline. This effort is broadening the range of potential treatments and expanding the number of therapeutic targets by providing support at critical steps of translational research that are traditionally not supported by the pharmaceutical industry.

Collaborations

Recent discoveries and continued progress in Alzheimer's research would not be possible without close collaboration between NIH and other Federal agencies and among NIH Institutes and Centers, scientists in laboratories and academic centers around the country and the world, non-profit education and advocacy organizations, and private-sector groups. Discoveries and research progress also would not be possible without the many thousands of people with AD and their families, as well as healthy volunteers, who participate in research studies and clinical trials. A growing emphasis on developing standardized data collection systems and sharing data and biological samples is improving the efficiency with which research is conducted today and laying the groundwork for even more productive collaborative research tomorrow.

AD Research Advances: A Look to the Future

Research advances are providing important clues to what may cause and influence the development of AD. These advances suggest a number of directions for future research:

Genetic analysis technologies. Because the genetic links to late-onset Alzheimer's, other than APOE ε4, are relatively weak, inheritance patterns are less clear than they are for early-onset AD. This means that investigators must search through the genetic profiles of thousands of people to find genes that may influence a person's susceptibility to AD. Developments in genetic analysis technologies have played a huge role in pushing forward this area of research. GWAS technologies let scientists use high-powered computers to associate individual gene variations with observable traits, such as the presence of AD. Today, for just a few hundred dollars, scientists can rapidly test 500,000 to a million sites in one person's genes using a computer chip the size of a postage stamp. These types of studies will give scientists unprecedented insights into the genetic links to AD, and thus into the earliest biochemical pathways that lead to the disease.

Biomarkers and neuroimaging. Researchers are intensely focused on developing ever more sensitive screening instruments, neuropsychological tests, biomarkers in CSF and blood, and neuroimaging methods that can be used to diagnose cognitive decline, MCI, and AD as early as possible.

Translational research and clinical trials. Translational initiatives and federally supported clinical trials should provide important new approaches for prevention and treatment because they will ensure that researchers with promising therapies have opportunities to develop them. Many compounds that test well in animal models and that have a sound theoretical basis fail in clinical trials because of safety or efficacy problems. The bidirectional collaboration between basic science and clinical application that is at the heart of translational research is essential to helping investigators understand why this happens and then to develop improved compounds. Support for this area of research will allow investigators to pursue many different therapeutic targets besides the now-obvious ones of beta-amyloid and *tau*. By funding pilot clinical trials, NIA also hopes to provide the necessary foundation for private industry or NIH to support larger follow-up clinical trials of the most promising leads.

Conclusion

In recent years, we have learned much about the aging brain, and Alzheimer's disease research has opened many new windows into our understanding. Much of what we have learned about how and why the brain ages normally can be applied to elucidating the underlying processes of AD. Studies into other neurodegenerative diseases, such as Parkinson's disease, frontotemporal dementia, and dementia with Lewy bodies, also are shedding light on AD.

We've made tremendous progress in recent years, but there is still much to learn about AD. Clearly, solving the puzzle of this disease will depend on harnessing the power of all avenues of science and medicine. Our task is to build on recent discoveries through continued support for multidisciplinary, collaborative AD research so that its promise will become a reality for all older adults.

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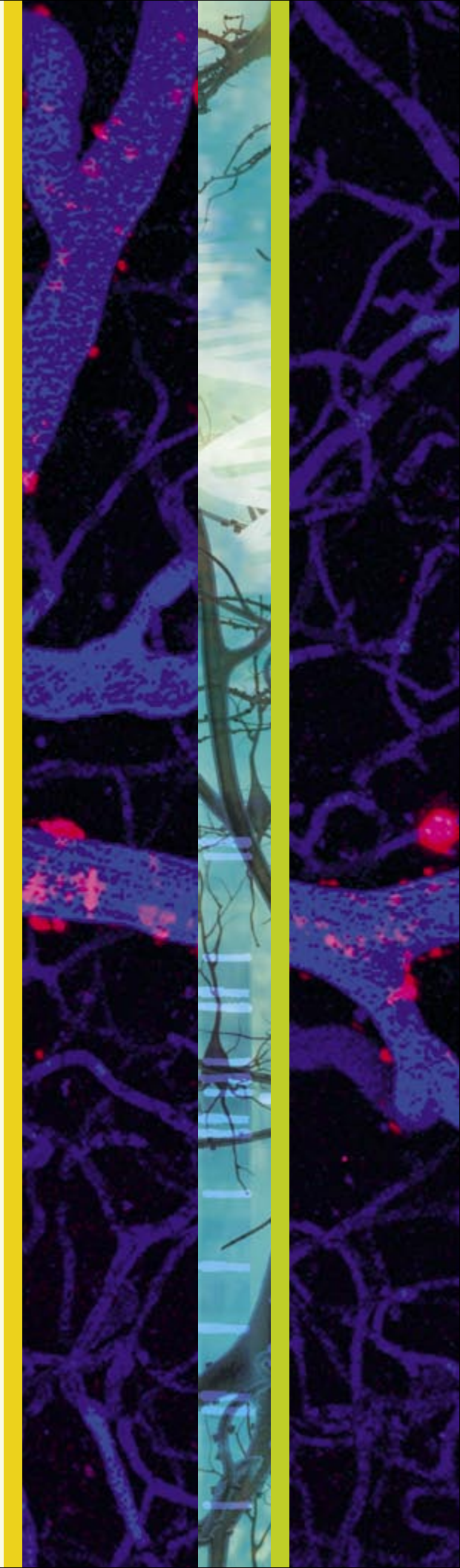
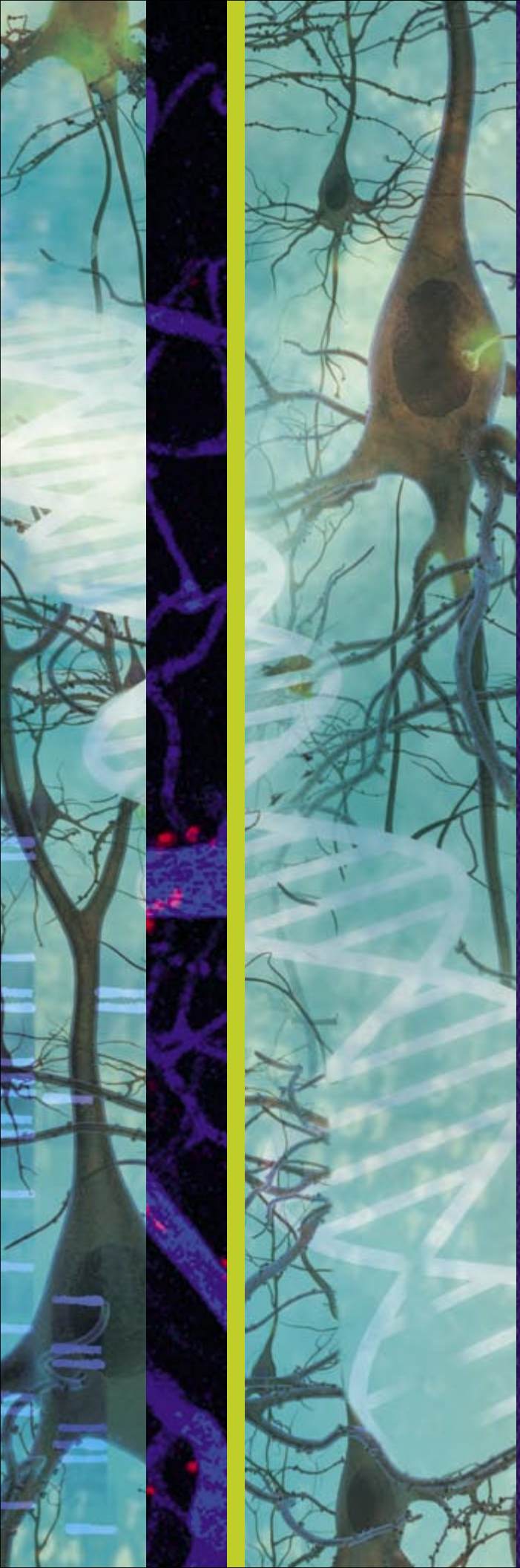
IMAGE CREDITS

The National Institute on Aging extends sincere appreciation to Brian J. Bacskai, Ph.D., and his optical imaging lab at Massachusetts General Hospital/Harvard Medical School for providing the Alzheimer's disease microscopy images shown throughout the *2008 Progress Report on Alzheimer's Disease*.

Thanks also to Stacy Jannis, Jannis Productions, for the neuron images on the covers, page 7, and throughout the report, and to Michael Weiner, M.D., of the VA Medical Center, San Francisco/University of California San Francisco, and William Jagust, M.D., of the University of California Berkeley for the images on page 11.





U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Aging
NIH Publication Number: 09-7378
December 2009