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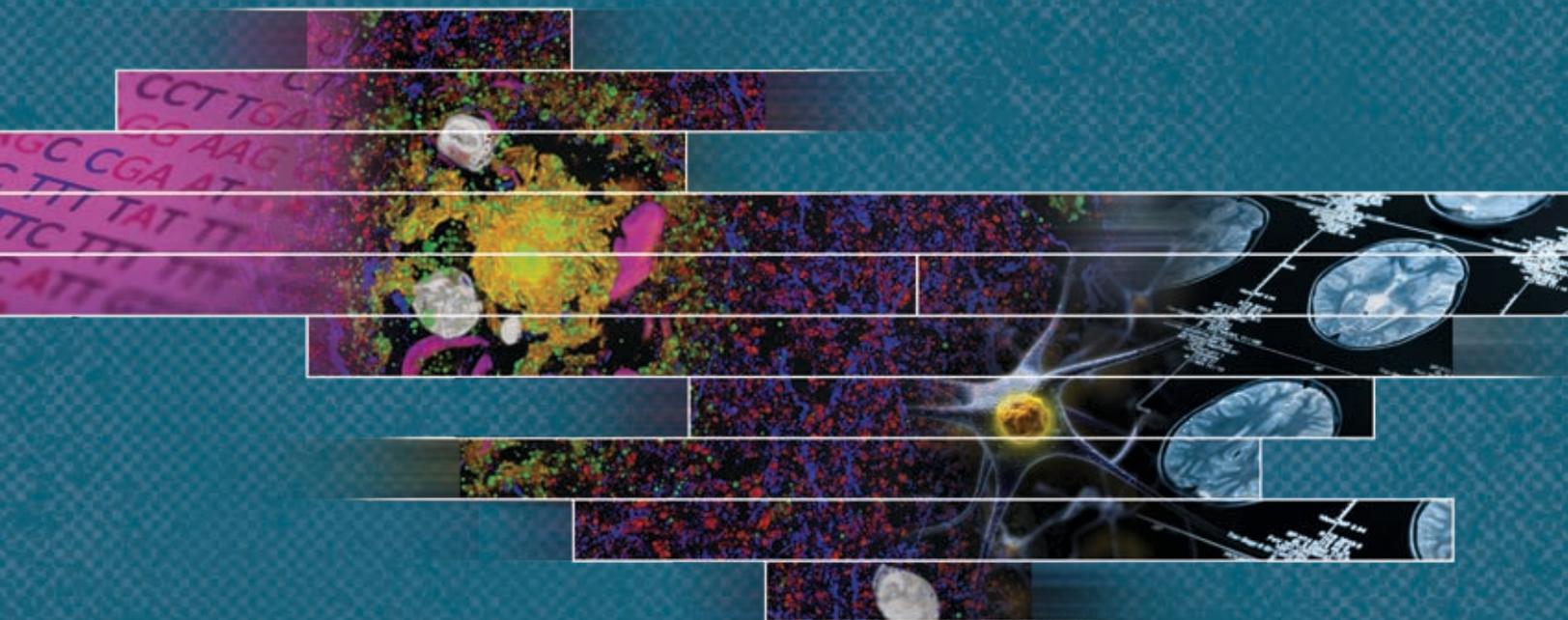


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2009 PROGRESS REPORT ON ALZHEIMER'S DISEASE

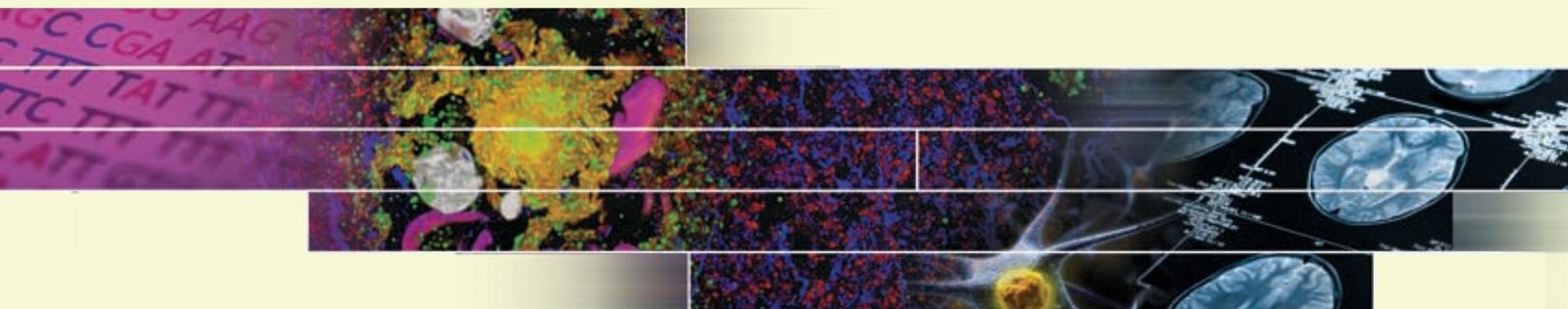
Translating New Knowledge



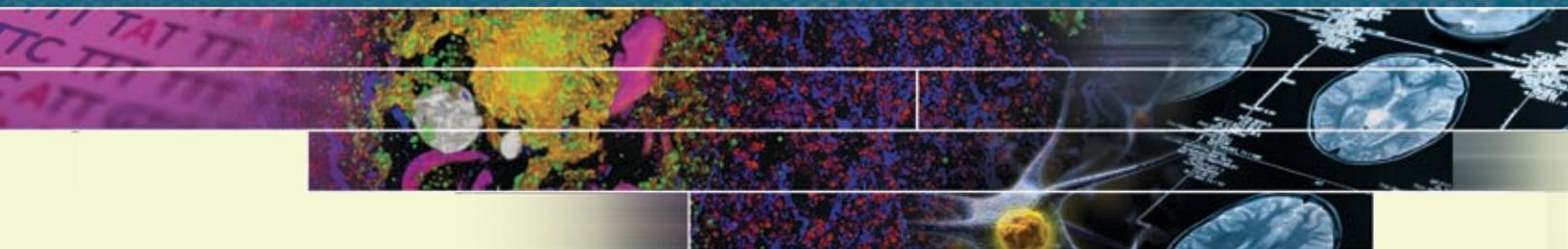


2009
PROGRESS REPORT ON
**ALZHEIMER'S
DISEASE**

Translating New Knowledge



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

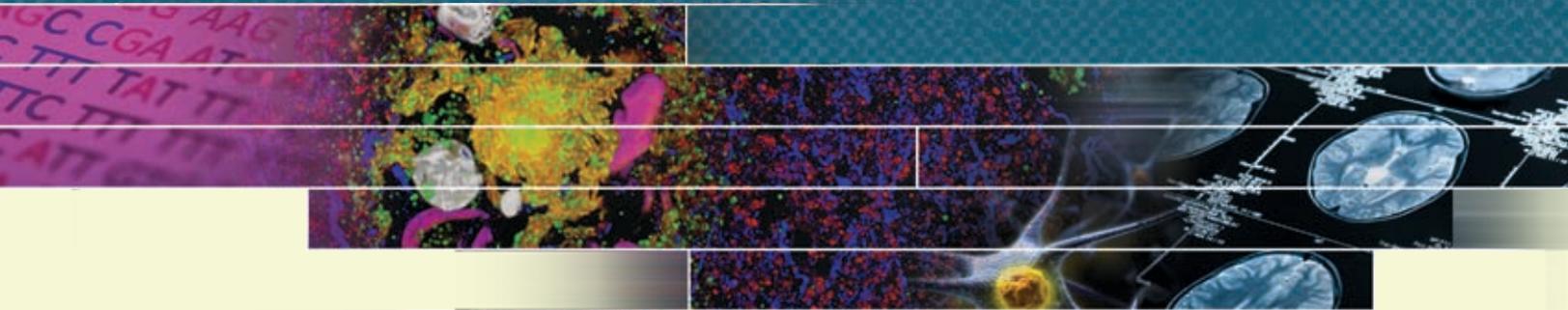


The National Institute on Aging (NIA), part of the Federal Government's National Institutes of Health (NIH) at the U.S. Department of Health and Human Services, has primary responsibility for basic, clinical, behavioral, and social research in Alzheimer's disease (AD), aimed at finding ways to treat and, ultimately, prevent this disease. The Institute's AD research program is integral to its mission, which is to enhance the health and well-being of older people. This *2009 Progress Report on Alzheimer's Disease* summarizes recent AD research conducted or supported by NIA and other components of NIH, including:

- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)—pages 18 and 22
- National Center for Complementary and Alternative Medicine (NCCAM)—pages 34, 37, 39, and 56
- National Center for Research Resources (NCRR)—pages 16, 31, 34, 39, 47, and 51
- National Eye Institute (NEI)—page 18
- National Heart, Lung, and Blood Institute (NHLBI)—pages 25, 37, 39, and 41
- National Human Genome Research Institute (NHGRI)—pages 23 and 24
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)—pages 27 and 37
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)—pages 22 and 51
- National Institute of Environmental Health Sciences (NIEHS)—pages 14, 18, 26, and 38
- National Institute of General Medical Sciences (NIGMS)—pages 16 and 26
- National Institute of Mental Health (NIMH)—pages 17, 18, 19, 23, 27, and 51
- National Institute of Neurological Disorders and Stroke (NINDS)—pages 16, 17, 18, 22, 23, 25, 26, 34, 36, 37, 41, and 47
- National Institute of Nursing Research (NINR)—pages 51 and 56
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)—page 26
- National Institute on Deafness and Other Communication Disorders (NIDCD)—page 32

AD research efforts also are supported by the John E. Fogarty International Center, National Cancer Institute, National Institute of Allergy and Infectious Diseases, National Institute of Biomedical Imaging and Bioengineering, National Institute on Drug Abuse, and NIH Common Fund.

Throughout this report, studies with no funding attribution were funded by NIA. Funding by other Institutes and Centers is noted.



In Remembrance

NIA warmly remembers two groundbreaking leaders in aging and Alzheimer's disease research who died in 2010 as this *Progress Report on Alzheimer's Disease* was being produced.

Robert N. Butler, M.D. (1927-2010), NIA's founding director and founder of the International Longevity Center USA, was a tireless advocate for older people and aging research. At NIA, he set in place a visionary research endeavor, building a rationale and organization for a broad program of basic, biomedical, social, and behavioral research that remains at the core of our efforts today. After leaving NIA, he was the founding chairman of the Department of Geriatrics at Mount Sinai School of Medicine. A geriatric psychiatrist, Dr. Butler was particularly proud of focusing public and research attention on Alzheimer's disease and other dementias.

William R. Markesbery, M.D. (1933-2010), considered among the top researchers in the world for the productivity and impact of his scientific study of Alzheimer's disease, received NIH support for nearly 30 years. Dr. Markesbery led the University of Kentucky Sanders-Brown Center on Aging from its founding in 1979 and was director of the UK Alzheimer's Disease Center. A special issue of *NeuroMolecular Medicine* honoring Dr. Markesbery's career and legacy will be published in March 2011, edited by NIA Neurosciences Lab Chief Mark Mattson, Ph.D.

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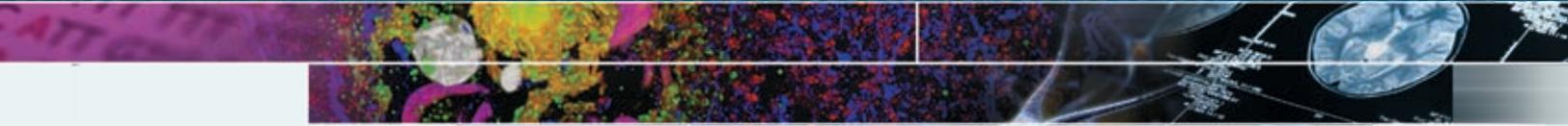


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INTRODUCTION

Alzheimer's disease (AD) is an age-related brain disorder that develops over many years. Its symptoms typically first appear after age 60. The course of AD varies from person to person, but in most people, the first symptom is memory loss. Memory decline becomes more serious as the disease progresses, and people often begin having problems with other cognitive functions, such as decision making (including financial) and language skills. People with Alzheimer's may also experience behavior and personality changes. Eventually, the loss of mental function becomes so severe that it impairs daily living and the ability 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 associated death of many of these cells.

Although AD was first described by Dr. Alois Alzheimer more than 100 years ago, scientific study of the disease began in earnest only in the early 1970s. Since then, a broad and increasingly productive research program led by the National Institute on Aging (NIA) at the National Institutes of Health (NIH) has revealed much about the basic biology of the disease and the factors that influence its development and progression. This program applies the expertise of many scientific disciplines in an attempt to answer complex questions: What causes AD? How can it be diagnosed early and accurately? How can it be treated? How might it ultimately be prevented? A current focus of research seeks to accelerate the pace of "translational research"—the transfer of knowledge gained in the laboratory to the clinical arena.

An Urgent National Health Priority

The search for more effective ways to treat or prevent AD is increasingly urgent. Today, it is estimated that 2.4 million to 5.1 million people in the United States have AD. While estimates vary, depending on how AD is measured, scientists agree that without scientific breakthroughs in prevention or early treatment of the disease, the number of people with AD will increase significantly as society ages.

Studies suggest that the number of people with the disease doubles for every 5-year age interval beyond age 65. The U.S. Census Bureau estimates that the 65-and-older population will double to about 72 million during the next 20 years, starting with the oldest "baby boomers" who turn 65 in 2011. The ranks of the very elderly, those 85 years old and older and at the highest risk of AD, will increase as well, potentially tripling their numbers by 2050.

The costs of AD are at the same time deeply personal and broadly societal. Families, friends, and caregivers experience emotional, physical, and financial stress as they watch a loved one become more and more forgetful, frustrated, confused, and lost. As the disease runs its course and the person with AD loses the ability to live or function independently, family members and other caregivers 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 need for practical and psychological support—is expected to escalate rapidly as the population ages and the number of people with AD grows.



EXECUTIVE SUMMARY

The U.S. investment in Alzheimer's disease (AD) research through the National Institutes of Health (NIH) has resulted in accelerating progress on several research fronts and has laid the groundwork for future discovery. This report highlights key AD research findings and activities in 2009, conducted or supported by public funding for the National Institute on Aging (NIA) at NIH and other NIH Institutes and Centers. NIA leads the Federal Government's research effort to understand and combat this devastating disease and is mandated by Congress to prepare this report.

2009 Highlights

New AD Genes

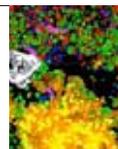
International teams studying AD genetics have identified three new genes that are associated with increased risk of late-onset AD. Two of these genes contain instructions for the synthesis of proteins that may be involved in clearing beta-amyloid from the brain and preventing its interference with communication among brain cells, which is thought to be a major factor in the development of AD. These genetic discoveries come at a time when researchers are increasingly interested in harnessing the brain's own beta-amyloid clearance mechanisms as a therapeutic strategy. (See the sections *New human AD genes identified*, page 23, and *Clearing out beta-amyloid*, page 37.)

Earlier AD Diagnosis

Researchers from the Alzheimer's Disease Neuroimaging Initiative (ADNI) showed that changes in the levels of certain proteins in cerebrospinal fluid (CSF) may correlate with the risk and progression of AD. These biomarkers may be used in the future to identify individuals at risk of developing AD. In addition, measuring amyloid in the brain may prove promising as a diagnostic tool. A preliminary study showed that the presence of high levels of brain amyloid in cognitively normal people is linked with greater risk of later cognitive decline. (For details, see the sections *Biomarkers and ADNI*, page 33, and *Brain Amyloid an Early Warning Sign of Possible Cognitive Decline in "Normal" Individuals*, page 19.)

Vascular Disease Linked to AD

AD is typically a disease of old age, which means that many people with AD also suffer from other age-related diseases and conditions, such as high blood pressure, cerebrovascular disease, or diabetes. Researchers are learning that these "co-morbid" conditions may increase the risk of AD and speed its clinical progression. For example, there is now a growing body of evidence that the cellular abnormalities associated with vascular disease feed into and exacerbate those associated with AD. Researchers are exploring in clinical trials whether the therapeutic interventions known to reduce risk of heart disease and diabetes may also reduce risk of AD. Reports published in



This Progress Report highlights key 2009 Alzheimer's disease research findings and activities supported by public funding.

2009 suggest that the Mediterranean diet, exercise, and controlling high blood pressure may be associated with reduced risk of AD. (See the sections *Links with Other Diseases*, page 14; *Interactions Between AD and Vascular Disease*, page 28; and *AD Clinical Trials*, page 38.)

Cognitive Exercise and Successful Cognitive Aging

The popularly held belief that brain exercise can improve cognitive function in older people is now being tested. In two different clinical trials, significant cognitive performance gains were seen in people over 65 who received training interventions aimed at improving either attention or speed and accuracy of verbal information processing. (See *Clinical Trials to Maintain or Improve Cognitive Function with Age*, page 46.) However, as in previous trials, there was no evidence that training in one dimension improved function in another, so questions remain about the overall usefulness of this type of training in real-world settings.

AD Is Not Just a Memory Disorder

Our view of AD is undergoing a transformation. In the past, AD was seen primarily as a memory disorder, and intervention focused on memory symptoms. However, mood and behavioral problems, such as depression, anxiety, and displays of socially inappropriate behavior, are increasingly recognized as co-occurring conditions with AD. Mood and behavioral disturbances also appear to be associated with more rapid progression from mild cognitive impairment (MCI) to dementia, and early treatment of these symptoms may help slow that

progression. For example, treatment with the drug donepezil reduced the risk of progression to AD among MCI patients with depressive symptoms. (See the sections *Other Early Signs and Symptoms*, page 32, and *Slowing progression to AD in people with MCI and depression*, page 39.)

Sleep and AD

AD may also be linked to sleep problems. Many people with AD suffer from sleep disturbances, which can contribute to cognitive impairment through a variety of mechanisms. Researchers are starting to study the possibility that therapeutic interventions to improve sleep quality may help alleviate some symptoms of AD. (See the sections *Amyloid and Sleep*, page 17, and *Treatment of sleep apnea may slow cognitive decline*, page 39.)

AD Caregiving

Two clinical trials, REACH I and REACH II, were previously funded to develop and test strategies for helping caregivers manage the stress and emotional burden of caring for people with dementia. The REACH OUT Program is beginning to implement these strategies through local social service agencies. The first such study showed a significant improvement in caregivers' sense of burden, social support, depression, and health, as well as in care recipients' behavior problems and mood. (See *Supporting AD Caregivers*, page 51.)

Recovery Act Funds Advance Research on AD and Age-Related Cognitive Decline



In 2009, the American Recovery and Reinvestment Act (ARRA) provided a novel opportunity to spark additional Alzheimer's disease research. NIA targeted promising areas of research in awarding more than 100 Alzheimer's or Alzheimer's-related ARRA research grants, totaling \$77 million. Projects conducted within a short timeframe (2009-2010) included both new and ongoing studies to understand the biological mechanisms of the disease, identify additional risk-factor genes associated with Alzheimer's, improve diagnostic tools, find biomarkers, develop therapies, conduct clinical trials, and explore preventive measures. ARRA funding also provided an opportunity to support research on age-related cognitive decline, a condition even more prevalent than AD in the older population.

Basic Research

Basic research to better understand the development and progression of AD will lay the foundation for new prevention and treatment interventions. ARRA-supported researchers are:

- Investigating how AD and vascular disease may influence and exacerbate one another. Findings may suggest strategies for preventing dementia.
- Investigating how amyloid, a protein implicated in AD brain changes, contributes to the formation of clots in the brain and blood vessels.
- Examining how energy metabolism influences brain aging by looking for correlations among the loss of brain

volume, metabolic measures, and dementia status in aging and in people with AD.

Genetic and Other Risk Factors

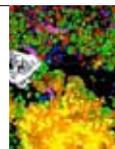
The ability to identify people at risk for AD is increasingly important as preventive measures are developed and as we learn more about how those at risk may reduce their odds of developing the disease. ARRA-supported investigators are:

- Using genome-wide association studies to compare the entire genomes of individuals with and without the disease to identify potential genetic risk factors for cognitive decline and AD.
- Investigating whether changes to the brain "histone code," which helps determine the activity of specific genes, can mediate the effect of life experiences on the development of age-related cognitive decline and AD.
- Exploring the association of AD with vascular risk factors (e.g., high blood pressure), markers of inflammation, and pathology pathways in diverse populations.

Biomarkers for Detection and Diagnosis

Research suggests that the earliest AD damage begins to develop in the brain long before clinical symptoms appear. Finding ways to diagnose AD as early as possible is critical so that researchers can test interventions and, ultimately, treat the disease as early as possible. ARRA-supported investigators are:

- Building on the highly successful ADNI to determine the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics of MCI, often a precursor to AD.
- Identifying best practices for collecting samples of CSF and its analysis for proteins that may be associated with AD onset and progression, with the goal of identifying biomarkers that appear before cognitive symptoms do.



The American Recovery and Reinvestment Act (ARRA) provided a novel opportunity to spark additional Alzheimer's disease research.

- Comparing the effectiveness of brain imaging and blood biomarkers to diagnose AD.

Possible Prevention and Treatment Strategies

ARRA-supported investigators are studying a range of potential strategies to prevent MCI or AD. This research includes:

- Evaluating the drug levetiracetam in a clinical trial as a treatment for MCI, potentially preventing progression to AD by reducing the hyperactivity of neurons in the hippocampus, a part of the brain important to learning and memory.
- Evaluating the effects of exercise in combination with two dietary supplements—the omega-3 fatty acid DHA and curcumin—on AD biomarkers and cognition in an animal model.
- Testing whether blocking a key inflammation pathway alleviates the consequences of high cholesterol on the brain in mouse models of AD. High cholesterol is believed to increase AD risk by triggering inflammation pathways that ultimately damage brain cells.
- Studying how the outer shell, or capsid, of certain viruses might be used to carry protective or therapeutic molecules into the brains of AD patients. This early work is being carried out in a mouse model of AD and, if successful, might be used in other neurodegenerative diseases as well.
- Studying the drug methylphenidate as a treatment for apathy, one of the most common behavioral symptoms of AD and one for which there is currently no effective treatment.
- Closely following participants who were enrolled in the Alzheimer's Disease Anti-inflammatory Prevention

Trial (ADAPT) to assess the long-term effects of naproxen and celecoxib on cognitive health.

Understanding Normal Aging and Preventing Loss of Cognitive Function

A growing body of evidence suggests that various interventions may exert a protective effect on the brain in older age, but little is known about the underlying mechanisms and more intervention testing is needed. ARRA-supported researchers are working to:

- Understand the role that neurotrophic factors (proteins that promote the development of new neurons and the repair of damaged ones) play in healthy and abnormal brain aging. Animal and human studies have shown that circulating levels of neurotrophic factors increase with exercise and also with a calorie-restricted diet or one rich in fruits and vegetables.
- Elucidate the neural mechanisms that contribute to robust age-related decline in prospective memory—the act of remembering to carry out an intention such as sending a grandchild a birthday card, paying bills on time, or taking needed medication.
- Develop automated technologies to map functional activity of brain networks, which will help expand our understanding of the neural basis of episodic and semantic memory and how this function changes with normal aging.
- Test a home-technology based cognitive health coaching approach to improve function and quality of life for older adults.

A Brief Primer on ALZHEIMER'S DISEASE and the BRAIN

The healthy human brain is made up of tens of billions of neurons that are connected through chemical and electrical signals. The function of these neurons is supported and regulated by other brain cells, called glial cells, and by the brain's rich supply of blood vessels. A typical neuron has a *cell body*, an *axon*, and many *dendrites*. The cell body contains the cell's nucleus. As in other cell types, the *nucleus* contains the neuron's genetic blueprint and helps regulate changes in the neuron's activity, metabolism, and structure in response to signals from outside and inside the cell. The *axon* is a cable-like structure that extends from one end of the neuron's cell body and transmits messages to other neurons. *Dendrites* are branch-like structures that radiate from the other side of the neuron's cell body and receive messages from the axons of other neurons.



View a short video showing the progression of Alzheimer's disease in the brain.

The function and survival of neurons depends on several interdependent processes:

■ **Communication.** When a neuron receives enough messages from surrounding cells, an electrical charge is generated that travels from the cell body to the end of the axon. There, it triggers the release of chemicals called neurotransmitters that move across a gap, or *synapse*, to the dendrites of neighboring neurons. The neurotransmitters bind to specific receptor sites on the dendrites of neighboring neurons, triggering chemical or electrical changes in those neurons. In some cases, neurotransmitter binding stimulates a neuron. In others, it inhibits the neuron's activity. Scientists estimate that at any one time the average neuron makes 7,000 synaptic connections to other neurons.

■ **Metabolism.** This process encompasses all the chemical reactions that take place in the cell. These reactions require chemical energy in the form of oxygen and glucose, which is supplied by the brain's blood circulation. The brain has an exceptionally high energy demand and so has one of the richest blood supplies of any organ.

■ **Repair.** Unlike many short-lived cells in the body, neurons have evolved to live a long time—more than 100 years in humans—so they must constantly maintain and repair themselves. Neurons also continuously remodel themselves—for example, by breaking down synaptic connections with one neighboring neuron and forming new ones with a different neighbor.

How Does AD Affect the Brain?

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

At first, AD typically destroys neurons and their connections in parts of the brain that control memory, including the *entorhinal cortex* and the *hippocampus*. It later attacks areas in the *cerebral cortex* responsible for language and reasoning. Eventually, many other areas of the brain are damaged, and a person with AD 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. Some of these changes can be observed under the microscope after death. The three abnormalities most evident in the brains of people who have died with AD are:

■ **Amyloid plaques.** Found in the spaces between neurons, plaques consist of largely insoluble deposits of a protein fragment called *beta-amyloid*, which is generated from a protein called *amyloid precursor protein* (APP). Plaques also contain other proteins, remnants of degenerating neurons and glia, and other cellular material. Scientists used to think that amyloid plaques were the primary

cause 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. Normally, tau binds to microtubules and helps stabilize them. In AD, tau undergoes abnormal chemical changes that cause it to disengage from microtubules and come together with other threads of tau, eventually forming neurofibrillary tangles. 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 most damage to neurons.

■ **Loss of neuronal connections and cell death.** In AD, the synaptic connections between certain groups of neurons stop functioning and begin to degenerate. 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 injury and death spreads through the brain, connections between neurons break down, and 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?

In some rare cases, people develop AD in their 40s or 50s. This form of the disease, called “early-onset” AD, often runs in families and is caused by a mutation in one of three genes that a person has inherited from a parent. The causes of other early-onset cases are not yet understood.

More than 90 percent of AD cases occur in people older than 60. The development and pathology of this “late-onset” form of the disease are very similar to those of early-onset AD. The causes of late-onset AD are not yet completely understood, but they probably include a combination of genetic, environmental, and lifestyle factors. The importance of any one of these factors in increasing or decreasing the risk of developing AD may differ from person to person.

Much basic research in AD has focused on the genes that cause early-onset AD, and how mutations in these genes disrupt cellular function and lead to disease. Scientists hope that what they learn about early-onset AD 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 60 to 80 years or more for people to develop signs of the disease? Research on how the brain changes normally as people age will answer this important question, as will studying the disease itself.

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). Some people with memory problems have a condition called amnesic *mild cognitive impairment* (MCI) that often precedes AD. People with MCI have more memory problems than normal for people their age, but their symptoms are not as severe as those seen in AD. Importantly, not all people with MCI develop AD.

Tools for diagnosing AD include a medical history, a physical exam and tests—preferably over time—that measure memory, language skills, and other abilities related to brain functioning. The physician may also perform a brain scan. Information provided by family members or other caregivers about changes in a person's day-to-day function and behavior also help in diagnosis. At this time, AD can be diagnosed conclusively only by an autopsy of the brain after death. However, in specialized research facilities such as the NIA-funded Alzheimer's Disease Centers, 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 whether 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, and some of these conditions are reversible. When AD is diagnosed, knowing early on can help families plan for the future while the person with AD can still participate in making decisions. Researchers are developing increasingly accurate diagnostic tests for telltale biomarkers that may one day be used in general medical practice to detect the disease before memory loss or cognitive impairment is evident.

How Is AD Treated?

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 patients' abilities to carry out everyday activities and may slow down symptoms related to 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 patients only for months to a few years.

Another type of medication, memantine (Namenda®), is prescribed to treat

moderate to severe AD symptoms. This drug appears to work by blocking receptors for glutamate, another neurotransmitter involved in memory function. Studies in animals suggest that memantine may have disease-modifying effects, although this has not yet been demonstrated in humans.

In addition to these medications, physicians may use other 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. (It is important to note, however, that since *no* drugs are specifically approved by the FDA to treat behavioral or psychiatric symptoms in dementia, this practice constitutes "off-label" usage.) ■

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 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, an 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 the Center toll-free at 800-438-4380. ■



RESEARCH ADVANCES

The NIH scientific portfolio for AD covers a wide range of disciplines and research programs. In 2009, NIH-supported researchers forged new understanding of the disease that could lead to future breakthroughs in how to prevent, treat, and cope with its impact. The following pages highlight important findings and explore their potential relevance to the field.

1 Recognizing the Scope of AD

A first step toward curing or preventing a disease is to get a clear picture of how the disease appears in individuals and across large populations. Critical questions for physicians, research scientists, and public policy makers involved in AD treatment and prevention include: How widespread (or prevalent) is the disease? Is it more or less common in certain populations? What is the relationship of AD to other chronic or age-related diseases? How is it different from normal cognitive aging?

Prevalence of Dementia

As the average age of the U.S. population rises, developing a reliable estimate of the current and future prevalence of AD becomes increasingly urgent. Knowing how many people have or are likely to develop AD can help manage private and public health resources in the coming years. For example, the number of people living to 100 or beyond is expected to be 15 times greater in 50 years than it is today. Since the risk of AD increases with age, pertinent questions are: What proportion of centenarians will be affected by AD? How many more relatives will be impacted?

Data are available on the current prevalence of AD in a number of communities and on a national level,

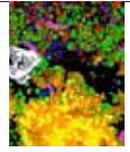
but specific data are lacking for the over-97 age group, or “oldest old,” living in rural communities. Compared with those living in and near cities, people living in rural communities are relatively isolated and may have different lifestyles, decreased access to some resources, and potentially different rates of dementia. Researchers at Oregon Health & Science University in Portland assessed dementia prevalence in a sample of people aged 97 or older living in the Klamath Basin, a large rural region in southern Oregon (Kaye et al., 2009). The study showed this population to be within the typical range for people of advanced age. Sixty-one percent of the sample had dementia, 29 percent suffered from MCI, and 10 percent were still cognitively intact. Better understanding of factors that enable nearly 40 percent of people age 97 and older to remain dementia-free could help identify strategies for preventing progress to dementia in younger elders.

Additional advance in estimating prevalence:

- Wilson et al. (2009a) Biracial population study of mortality in mild cognitive impairment and Alzheimer disease. Rush Alzheimer's Disease Center. Supported by NIA and NIEHS.

Links with Other Diseases

Plaques and tangles are usually the most obvious disease features seen under the microscope in brain tissue from deceased AD patients. However, individuals diagnosed with AD also often suffer from other diseases affecting the brain, such as vascular disease. In a postmortem study of 349 people who had been diagnosed before death with either AD or MCI, neuropathologists at the Rush University Alzheimer's Disease Center in Chicago, IL, found evidence of other disease processes in almost half of the AD brains and 20 percent of the MCI brains



Is AD more or less common in certain populations? What is the relationship of AD to other chronic or age-related diseases?

(Schneider JA et al., 2009). Most common were microinfarcts—small spaces in brain tissue where cells have died due to blockage of blood vessels that once nourished them—which are associated with cerebrovascular disease. The next most common disease signature was Lewy bodies in the cortex. Lewy bodies are abnormal clumps of protein often found in the brains of older people that differ in structure and composition from plaques and tangles. They are associated with dementia with Lewy bodies, and are also found in the brains of people with Parkinson’s disease.

A key finding was that people whose brains showed “mixed” disease (plaques and tangles *plus* microinfarcts, for example) were more cognitively impaired when they died than those whose brains contained only comparable levels of plaques and tangles. Microinfarcts and Lewy bodies may compound the negative effects of plaques and tangles on neural function, so that fewer plaques and tangles are required to produce noticeable cognitive decline. This study highlights the need to understand how other disease processes contribute to brain dysfunction in people diagnosed with AD. In addition, the finding that microinfarcts seem to exacerbate the negative impact of plaques and tangles on neural function is consistent with increasing evidence of overlap between risk factors for AD and vascular disease (see *Interactions Between AD and Vascular Disease*, page 28).

Diabetes is another disease that often coexists with AD in older adults. Neuropathologists at the University of Washington in Seattle found that the brains of people who had died with diabetes and dementia had more neuroinflammation and more microinfarcts than those with dementia alone (Sonnen et al., 2009). This finding

is not surprising, given that diabetes is a risk factor for cerebral atherosclerosis (accumulation of fatty deposits inside brain blood vessels that restrict or block blood flow). Interestingly, the people who had diabetes in addition to dementia actually carried *less* amyloid on average at the time of their deaths than did nondiabetics with dementia. The brains of nondiabetics with dementia also had higher levels of free radical damage. These different patterns of injury suggest different underlying mechanisms of pathology and may have implications both for mechanisms of disease development and possible therapies.

2 Deciphering AD Biology

Scientists believe that the accumulation of beta-amyloid fragments around neurons and blood vessels interferes with communications between cells. This communication breakdown is followed by loss of synapses and death of neurons (see *A Brief Primer on Alzheimer’s Disease and the Brain*, page 11). Much research has focused on exactly how beta-amyloid disrupts intercellular communication. Key questions to be answered include:

- With which molecules does beta-amyloid interact at the synapse?
- With which specific cellular processes does beta-amyloid interfere?
- Which brain “circuits” (systems of interconnected neurons) are most affected by beta-amyloid and why?
- What mechanisms support normal cognitive function in older individuals who also display substantial levels of brain amyloid?

There is also increasing research interest in apparent points of overlap between cellular and molecular changes occurring in AD and in “normal” brain aging.

Synaptic Dysfunction

How beta-amyloid interferes with memory formation

One mechanism the brain uses to store memories is a process called “long-term potentiation” (LTP). LTP is a strengthening of the synaptic connection between two neurons that allows the second neuron to fire more readily. This process is thought to contribute to memory formation.

Beta-amyloid has been shown to interfere with this process. Understanding how it does might reveal potential molecular targets for AD drug development. In particular, researchers would like to identify the proteins involved in LTP-beta-amyloid interactions. Reports from the University of Southern California Alzheimer’s Disease Research Center, State University of New York at Buffalo, and Harvard University identified three different synaptic proteins interacting with beta-amyloid (Williams et al., 2009; Gu et al., 2009; Li et al., 2009). All three are involved in signaling by the neurotransmitter glutamate.

Another study suggests an alternative or additional beta-amyloid “receptor”: cellular prion protein (PrPc). Prion protein in its abnormal form causes mad cow disease in cattle and Creutzfeldt-Jacob disease in humans. Scientists at Yale University in New Haven, CT, supported by NIA and NINDS found that beta-amyloid binds to hippocampal nerve-cell membranes at or near sites where PrPc is found. Moreover, binding to PrPc appears to be *necessary* for beta-amyloid to disrupt LTP (Laurén et al., 2009). If it is ultimately shown that PrPc is the receptor through which beta-amyloid binds to nerve cells and disrupts LTP, then drugs that block beta-amyloid binding to PrPc could be pursued aggressively as potential AD therapeutics.

Beta-amyloid and synapse loss

Beta-amyloid appears not only to disrupt LTP, but to cause the collapse of dendritic spines (specialized protrusions on the surfaces of dendrites that receive input from other neurons). Loss of dendritic spines is evident around amyloid plaques in both human AD and transgenic mouse models of AD. Scientists at the Massachusetts General Hospital Alzheimer’s Disease Research Center in Boston sought to discover whether this loss is caused by the plaque itself or by soluble beta-amyloid shed from the plaque. Using a new microscopic imaging technique, the researchers were able to see amyloid plaques and nearby dendritic spines in greater

detail than had previously been possible. They discovered that plaques are surrounded by halos of soluble beta-amyloid, and that spines first begin to collapse upon contact with these halos (Koffie et al., 2009). Thus, plaques may serve as a reservoir for soluble beta-amyloid, which in turn triggers collapse of spines and loss of synaptic contacts.

Other advances related to synaptic dysfunction:

- López-Hernández et al. (2009) Positive modulation of alpha 7 n AChR responses in rat hippocampal neurons. University of Florida. Supported by NIA and NIGMS.
- Polydoro et al. (2009) Age-dependent impairment of cognitive and synaptic function in the htau mouse model of tau pathology. Albert Einstein College of Medicine. Supported by NINDS.
- Sun et al. (2009) Imbalance between GABAergic and glutamatergic transmission impairs adult neurogenesis in an animal model of Alzheimer’s disease. University of California, San Francisco. Supported by NIA, NINDS, and NCRR.

Selective Neuronal Death

AD affects neurons sooner and more severely in certain brain regions than in others. Particularly vulnerable are neurons in the entorhinal cortex, hippocampus, and certain other cortical regions. A key question is, Why are neurons in certain regions especially vulnerable to AD? In some cases, it may be because these neurons experience higher-than-average levels of functional activity (see *Cortical “Hubs” and Amyloid*, page 17).

Neurons may also be more affected in AD because they synthesize certain proteins that render them vulnerable. An example is neurons in the basal forebrain, a brain region severely affected in AD. These neurons synthesize high levels of a receptor for nerve growth factor, which usually helps ensure their survival. However, investigators at the Buck Institute for Age Research in Novato, California, supported by NIA and NINDS, showed that when the receptor is bound by APP, two toxic events take place: the APP is cleaved into beta-amyloid, and neurons die (Fombonne et al., 2009).

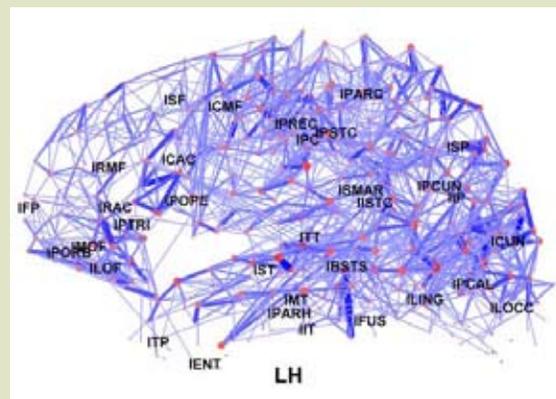
Additional advance related to selective neuronal death:

- Robertson et al. (2009) Amyloid-beta expression in retrosplenial cortex of triple transgenic mice: relationship to cholinergic axonal afferents from medial septum. University of California, Irvine. Supported by NIA and NINDS.

Cortical “Hubs” and Amyloid

If there were a map of the neural connections within the brain’s cortex, it would look something like an airline route map, with airport “hubs” such as Atlanta, Chicago, and Dallas serving many different routes and showing much higher activity levels than other points in the system. Human brain hubs include hot spots in several regions of the cortex. They can be observed using functional magnetic resonance imaging (fMRI), an imaging technique that monitors levels of nerve-cell activity in different brain regions. Some cortical hubs are busier when a person is at rest, others when a specific task is being performed.

Researchers at Harvard University compared patterns of this activity to patterns of amyloid deposition in people with



Like airline route maps, the human brain has “hubs” in several regions of the cortex.

AD. They found that the regions of highest amyloid accumulation coincided with the locations of highly active cortical hubs (Buckner et al., 2009). The study suggests that these amyloid-associated hubs

are active both at rest and during task performance, consistent with mounting evidence that the presence and deposition of amyloid is associated with high neuronal activity levels. ■

Amyloid and Sleep

The idea that amyloid deposition is correlated with high levels of neuronal activity has received further support from a study showing increased beta-amyloid deposition after sleep deprivation. Active neurons are known to secrete beta-amyloid into the fluid surrounding them. Investigators at Washington University in St. Louis, supported by NIA, NINDS, and NIMH, measured beta-amyloid levels in AD model mice at different points in the sleep-wake cycle. They found levels to be highest at the end of the wakeful period and decreased during sleep (Kang et al., 2009). A similar pattern was seen for beta-amyloid levels in the CSF of human volunteers (10 young healthy males). Additional studies in AD model mice showed that beta-amyloid levels and plaque deposition were increased by chronic sleep deprivation and by orexin, a neurohormone that promotes wakefulness. Treating mice with a drug that blocks orexin receptors blocked the daily rise in beta-amyloid.

The possibility that chronic sleep deprivation exacerbates amyloid deposition is especially interesting given evidence that sleep disturbances, such as sleep apnea, are

common in the elderly and cause damage to certain brain regions. This study provides further impetus for testing whether measures that promote healthy sleep also reduce risk of brain dysfunction and AD. (Read about a sleep apnea treatment study, page 39.)

Additional advance related to amyloid and sleep:

- O’Hara et al. (2009) Sleep apnea, apolipoprotein epsilon 4 allele, and TBI: mechanism for cognitive dysfunction and development of dementia. Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC), Stanford University. Supported by NIMH.

Cellular Energy Deficits

Neurons need exceptionally high levels of energy to support their signaling. Indeed, although the brain represents only about 2 percent of the body weight of an average adult human, it uses about 20 percent of the body’s energy. Neurons are also especially sensitive to energy deficits. Failures in energy-generating mechanisms that occur as neurons age may contribute to the development of AD.

Mitochondrial fission and fusion

Often called the cellular “powerhouses,” mitochondria are responsible for energy production. Mitochondria are highly dynamic—they move around inside cells and can fuse with one another or break apart into smaller pieces (fission). If the balance between mitochondrial fusion and fission tips too much toward fission, the result is abnormally small, malformed mitochondria that may not function properly. Such abnormal mitochondria have been observed in the brains of people with AD.

Researchers at Case Western Reserve University in Cleveland, OH, found that the proteins responsible for mitochondrial fission and fusion are abnormally regulated in the AD brain. They also found that applying beta-amyloid to rat hippocampal neurons caused the mitochondria in the neurons’ dendrites to break apart (Wang X. et al., 2009). Thus, abnormal mitochondrial dynamics may be a link between beta-amyloid and synaptic degeneration.

In related work, a research team at the Burnham Institute for Medical Research in La Jolla, California, supported by NICHD, NEI, NIEHS, and NINDS, showed that nitric oxide (NO), thought to be a key mediator of beta-amyloid’s neurotoxic effects, stimulates the activity of an enzyme that accelerates mitochondrial fission (Cho et al., 2009). Drugs that inhibit activity of this fission-accelerating enzyme might therefore be useful to explore as a possible therapeutic for AD.

Changes in brain metabolism in normal aging and AD

Since age is the best known risk factor for AD, it seems likely that some of the cellular changes that occur with aging contribute to the development of AD. One such change, depressed mitochondrial function, was examined by scientists at the University of Southern California in Los Angeles, supported by NIA and NIMH. The researchers investigated the possible link between mitochondrial dysfunction and events in the AD disease pathway using a mouse model of AD. They found an age-dependent decline in mitochondrial function in both normal and AD model mice, which preceded the onset of amyloid plaque formation (Yao et al., 2009). Thus, mitochondrial dysfunction might contribute to amyloid deposition, as well as vice versa.

Another finding also points to the impact of normal aging and AD on cellular energy production. While nerve cells usually use glucose as their main energy source, researchers at the University of Kentucky in Lexington, studying the brains of aging rats, observed a shift to other fuel sources, such as fats and amino acids. This metabolic shift was accompanied by the breakdown of myelin, the fat- and protein-rich sheath that insulates axons. The earliest stages of cognitive impairment in rats coincided with the changes in myelin metabolism. The investigators hypothesize that these processes damage neuron structure and deplete energy needed for cell-to-cell signaling (Kadish et al., 2009).

Insulin-like growth factor-1 (IGF-1) is a hormone that promotes cell growth. The brain IGF signaling pathway also appears to be involved in aging, as blocking this pathway prolongs lifespan in organisms ranging from worms to mammals. The pathway may also contribute to AD. Investigators at the Salk Institute for Biological Studies in La Jolla, CA, discovered that reducing IGF signaling in AD model mice prevented the development of AD-like disease symptoms, including brain inflammation, behavioral impairment, and neuronal death. Of great interest, the beta-amyloid plaques in the brains of these mice differed from those normally seen in AD: the fibrils making up the plaques were more orderly and tightly packed than usual. These more tightly packed beta-amyloid aggregates are less likely to shed the soluble form of beta-amyloid, and are therefore less likely to be toxic to neurons (Cohen E. et al., 2009).

Additional advances in brain metabolism, normal aging, and AD:

- Bishop et al. (2009) Review: Neural mechanisms of ageing and cognitive decline. Harvard University.
- Cohen AD et al. (2009b) Basal cerebral metabolism may modulate the cognitive effects of Aβ in mild cognitive impairment: an example of brain reserve. University of Pittsburgh. Supported by NIA.
- Salthouse, TA. (2009) Review: When does age-related cognitive decline begin? University of Virginia.

Brain Amyloid an Early Warning Sign of Possible Cognitive Decline in “Normal” Individuals

The year 2009 saw intense investigation of the relationship between brain amyloid deposits and cognitive function. It has been known for many years that some cognitively normal individuals had high levels of brain amyloid at autopsy. More recently, methods became available for imaging amyloid in the brains of living people using positron emission tomography (PET) and radioactive Pittsburgh Compound B (PiB) as an amyloid marker. Subsequent imaging studies supported by NIA and NIMH funding at the University of Pittsburgh, Mayo Clinic, and Banner Alzheimer’s Institute produced an important result: Amyloid deposits were found in the brains not only of people with MCI and AD, but also in some older people who were cognitively normal (Aizenstein et al., 2008; Jack et al., 2009; Reiman et al., 2009). In fact, the percentage of nondemented older adults with significant levels of brain amyloid ranged from 20 to 50 percent in different studies.

Questions to Explore

These findings opened the door to exploring the future implications of differences in amyloid levels among cognitively normal people. Could some older people who have high brain amyloid nonetheless maintain good cognitive function for decades to come? Or, if one scrutinized these apparently normal people more rigorously, would they show the very earliest signs of cognitive loss and eventually develop AD? The weight of evidence from studies supports the second scenario. Many cognitively normal people with high brain amyloid levels exhibit other abnormalities associated with cognitive decline. Further longitudinal studies will be needed to distinguish between those who will progress and those who will not.

Imaging of neuronal activity patterns in individuals with high levels of brain amyloid in three studies at Washington University, Harvard University, and

Massachusetts General Hospital indicated abnormalities in the brain’s “default network,” a system of brain regions that is most active when a person is not performing a task, but rather focused inward (e.g., during daydreaming, envisioning or planning the future, or recollecting the past) (Sheline et al., 2010; Sperling et al., 2009; Hedden et al., 2009). The pattern of network disruption seen in these cognitively normal, high amyloid load-bearing individuals is similar to that seen in people with clinical AD. It involves cortical “hubs” that participate in memory formation (see *Cortical “Hubs” and Amyloid*, page 17).

PiB-PET Scans Key

Most importantly, several studies in 2009 found that cognitively normal people with high amyloid loads were more likely to suffer eventual cognitive decline than peers with low amyloid levels. For example, one research team at the Washington University Alzheimer’s Disease Research Center (ADRC) in St. Louis, MO, longitudinally studied 135 cognitively normal people who had annual cognitive testing starting in 1985 and PiB-PET scans starting in 2004. All of these individuals scored within the normal range on cognitive tests when they first entered the study. PiB-PET scans showed that 29 participants had high brain amyloid loads. This group also showed shrinkage of brain areas typically affected by AD, as seen in MRI scans, and declining performance on visuospatial, episodic, and working memory tasks over time (Storandt et al., 2009).

In a related study, the Washington University ADRC showed that positive PiB-PET scans at baseline were predictive of developing very mild AD but not of other causes of dementia up to 5.5 years later (Morris et al., 2009). This study was limited by the small number of people who developed AD and the short followup time.

Together, the studies suggest the following sequence of disease events in AD:

- Amyloid deposition occurs first, and in its earliest stages is not associated with cognitive impairment.
- Loss of synapses, neurons, and brain volume occurs next, and is accompanied or shortly followed by loss of cognitive function (see *AD Progression figure*, page 30).

More studies are needed to determine the best ways of accurately predicting who will go on to develop AD and who will not before clinical symptoms emerge.

This scenario may seem discouraging but in fact offers hope. Because significant amyloid deposition seems to occur years before clinical diagnosis of AD, there may be a window of time in which therapeutic intervention might prevent disease progression. Accumulation of brain amyloid could serve as a warning sign that additional testing is necessary and therapeutic intervention should be considered. Thus, just as people are now routinely checked for high cholesterol and counseled about lifestyle changes and medications to reduce their risk of heart disease and stroke, in the future they may also be checked for brain amyloid and counseled about AD prevention.

Another encouraging finding is that it is possible for a person to have a lot of amyloid in his or her brain without significant cognitive decline. Thus, in some people the brain somehow compensates for the presence of beta-amyloid, at least for some period of time. The brain’s capacity to compensate for AD pathology, called “cognitive reserve,” is also being intensively studied. ■

Additional advance:

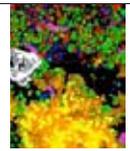
- Mormino et al. (2009) Episodic memory loss is related to hippocampal-mediated beta amyloid deposition in elderly subjects. University of California, Berkeley. (ADNI)

What Is Normal Aging?

The close association between age and risk of AD raises the question of whether AD is an inevitable consequence of aging, especially since many older people with normal cognition have substantial levels of brain beta-amyloid. Is there any such thing as “normal” cognitive aging and, if so, what does it look like?

Understanding what constitutes normal brain aging and age-related cognitive decline is an important focus of research. Cognitive decline associated with aging can compromise quality of life for older people and looking at brain aging in this way may help promote healthy cognitive outcomes. It is anticipated that such research, both in animal models and in humans, can provide critically important insight into effects of normal aging, distinct from AD, as well as providing a biological context for the abnormal brain changes in AD. More detailed descriptions of normal aging will also help in developing early and sensitive AD diagnostic tools.

Investigators at NIA’s intramural Laboratory of Personality and Cognition in Baltimore, MD, carried out an exceptionally detailed analysis of brain changes over time in 138 people who were 64 to 86 years of age and nondemented at the beginning of the study. Brain scans were conducted every year for up to 10 years, and cognitive status was evaluated. Some participants developed MCI over the course of the study, while others remained cognitively normal. Both groups experienced atrophy (shrinkage) of certain brain areas over time, but the specific patterns of atrophy differed. For example, the group who remained cognitively normal showed more atrophy in certain areas of the frontal cortex (the portion of the cortex closest to the forehead), whereas the group who developed MCI had more prominent atrophy in temporal areas (the regions on the sides of the brain, closer to the ears) (Driscoll et al., 2009).



Is there any such thing as “normal” cognitive aging and, if so, what does it look like?

These results suggest that there is a specific trajectory of brain changes that occurs during normal aging, distinct from that occurring in AD. Brain changes in cellular mitochondria and energy production also occur during normal aging (see *Changes in brain metabolism in normal aging and AD*, page 18). Moreover, a review from the University of Virginia in Charlottesville suggests that declines in certain aspects of cognitive function, such as memory and speed of processing, may begin as early as a person’s 20s or 30s (Salthouse, 2009). These observations appear to be dependent on the type of study conducted, cross-sectional or longitudinal, and debate continues as to the point at which measurable and meaningful change occurs.

Additional advance in understanding normal aging:

- Bishop et al. (2010) Neural mechanisms of ageing and cognitive decline. Harvard University.

3 Discovering New Genetic Mechanisms

In the early days of AD research, scientists realized that some cases of the disease ran in families. When it did, it appeared quite early, in the 40s or early 50s. By analyzing the patterns of inheritance of these early-onset cases of AD, researchers proved that these particular forms of the disease had a genetic basis. Those findings opened an entire area of AD research that continues to be highly productive today. Research into the genetics of early-onset AD has revealed much about the biological basis of the disease, the interrelationship of genetic and environmental factors in causing it, and molecular pathways that might be targeted to prevent or treat both early- and late-onset AD. As medical science moves toward individualized medicine based on a person’s unique genetic makeup, identification of other genes contributing to the development and progression of AD—including those that may be involved in sporadic, late-onset disease, the most common form of AD—may help determine which preventive and treatment strategies are best suited to particular individuals.

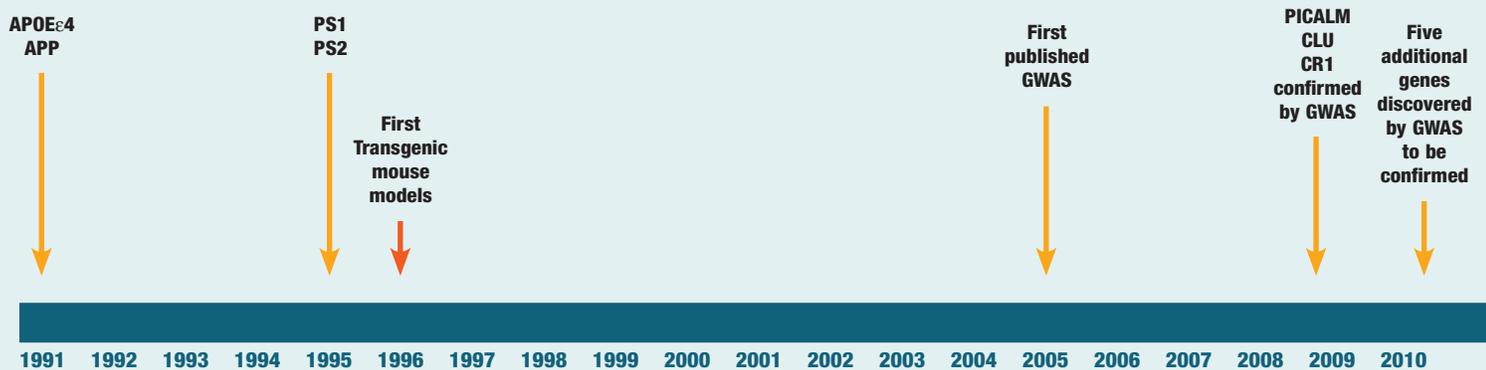
The Search for New Genes

Four genes affecting the development of AD have been known for many years. Mutations in three of them—the 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. The AD-associated mutations in each of these genes promote the breakdown of the large APP protein along a pathway that generates more harmful forms of beta-amyloid.

The fourth gene, apolipoprotein E (APOE), found on chromosome 19, is linked to late-onset AD. Late-onset AD is not “inherited” in the same sense that the early-onset mutations actually cause AD, but genes involved in late-onset AD can affect the risk of developing it. APOE was the first gene to be identified as influencing late-onset AD. APOE has three forms, or alleles: ε2, ε3, and ε4. The ε2 form may provide some protection against AD, and ε3 is thought to play a neutral role. The ε4 form can increase a person’s risk of developing AD.

Research shows that additional genes likely influence the development of late-onset AD, either as risk factors or protective factors. Geneticists worldwide are searching for these genes.

AD Gene Discovery Timeline



“Normal” Functions of AD Genes

If the genes involved in AD are so troublesome, then why do humans have them in the first place? Usually, genes remain in human or animal populations only if they have a useful biological function and confer a survival advantage. For example, there is evidence that the presenilins, particularly PS1, play a role in the earliest stages of the development of the nervous system. Better understanding the normal or “good” biological functions of the proteins encoded by AD genes could shed light on how mutations or variations in these genes lead to disease.

■ Several findings, including those from investigators at Georgetown University in Washington, DC, supported by NIA and NINDS, and Baylor College in Houston, TX, supported by NIA and NICHD, indicate a role for APP in the development of synaptic connections between nerve cells (Hoe et al., 2009a; Wang Z. et al., 2009). In particular, APP appears to promote the growth of dendrites, the branch-like structures through which neurons receive input from the axons of other neurons. APP is also necessary for neurons to form orderly synaptic contacts with other neurons or muscle cells. In both cases, APP seems to act in part by promoting cell-to-cell adhesion, a process in which certain proteins on the membrane of one cell bind to proteins on a neighboring cell and help “glue” the two cells together.

■ The presenilins have long been recognized as important to the development of neurons. New evidence suggests they also regulate the strength and flexibility of synaptic connections in the hippocampus. Researchers at Harvard University supported by NINDS found that inactivating the presenilin genes in mice reduced the process of hippocampal long-term potentiation (LTP) (Zhang C. et al., 2009). Another research group at NIA’s Laboratory of Neurosciences in Baltimore, MD, found that, instead of PS1s enhancing the use of an important chemical

neurotransmitter acetylcholine on hippocampal LTP, the PS1 mutation impaired synaptic connections. (Wang Y. et al., 2009).

■ Recent work from the Nathan S. Kline Institute in Orangeburg, NY, indicates yet another role for normal PS1 in neuronal function. It seems to participate in a process called “macroautophagy,” in which cells dispose of internal debris. Many cellular proteins and structures wear out with time and cease to function properly. Most cells have the capacity to target their worn-out components and break them down into smaller pieces, which are either reused or discarded. This process involves lysosomes, parts of cells containing enzymes that digest cellular debris. Mutations in PS1 that cause early-onset AD disrupt metabolism in the lysosomes, so that they can no longer digest cellular debris. This debris then accumulates and may contribute to neuronal death (Lee et al., 2010).

■ Like APP, the ApoE protein promotes the growth of dendrites and their spines. However, a genetic study in human ApoE model mice from Georgetown University in Washington, DC, suggests that the $\epsilon 4$ form of APOE, which is associated with higher AD risk in humans, is less effective in promoting dendrite and spine growth than the other forms of APOE (Dumanis et al., 2009). This finding may help explain how the APOE $\epsilon 4$ allele increases risk of AD. ■

Additional advances in understanding AD genes:

- Hoe et al. (2009b) The effects of amyloid precursor protein on postsynaptic composition and activity. Georgetown University. Supported by NIA and NINDS.
- Maji et al. (2009) Functional amyloids as natural storage of peptide hormones in pituitary secretory granules. Zurich, Switzerland. Supported by NIDDK.

New human AD genes identified

Genetics research has helped to reveal much about the basis of AD, the interrelationship of genetic and environmental factors in causing AD, and pathways amenable to prevention or treatment. Complicating the study of AD genetics is the fact that the risk of late-onset AD is probably influenced by many genetic risk factors, each likely contributing a small risk distributed across different genes affecting a variety of biochemical pathways. These genetic factors may influence the age at onset, the risk of getting the disease, or disease progression.

Technological developments in genetic analysis over the last few years have played a huge role in pushing this area of research forward. Genome-wide association study (GWAS) technologies let scientists use sophisticated software and hours of computing time to find links between individual gene variations and observable traits, such as the presence of AD. For just a few hundred dollars, scientists can now rapidly test 500,000 to a million sites in an individual's DNA using a gene chip the size of a postage stamp.

This year, a large GWAS search “struck gold” with the discovery of two new late-onset AD genes, CLU and PICALM. Variants of these genes that correlated with the development of late-onset AD were identified in a collaborative study led by researchers at Cardiff University, Wales (Harold et al., 2009). The group analyzed more than 16,000 samples collected by dozens of laboratories across Europe and the United States, including several funded by NIA and other NIH Institutes.

Sometimes newly discovered disease genes are mysterious entities of unknown biological function. Fortunately, a substantial body of knowledge is already available about CLU and PICALM because the proteins encoded by these genes have roles in well-studied cellular pathways. CLU (ApoJ/clusterin) is another apolipoprotein and, like ApoE, may play a role in clearing beta-amyloid out of the brain and into the blood (see *Clearing out beta-amyloid*, page 37). PICALM (phosphatidylinositol-binding clathrin assembly protein) appears to be involved in recycling of cell membrane proteins at synapses. Identification of these two new genes should help researchers home in on novel specific biological processes that are disrupted in AD.

A third gene, CR1 (complement receptor 1), identified by the Cardiff University investigators, was confirmed as a “hit” in a smaller collaborative GWAS led by French investigators (Lambert et al., 2009). CR1 is an immune system protein involved in inflammation responses and like CLU, may be involved in clearing beta-amyloid from the brain. The French study also identified CLU, confirming its potential role in AD.

A recently published analysis in an independent data set has confirmed that CR1, CLU, and PICALM are AD susceptibility genes in another population of European ancestry (Jun et al., 2010).

Investigators at Massachusetts General Hospital supported by NIMH identified a fourth potential AD gene, ADAM10. They discovered two rare mutations in this gene in individuals from seven different late-onset AD families. ADAM10 is an alpha-secretase, an enzyme that cleaves APP in a way that eliminates its potential to form beta-amyloid. A mutation could disrupt this cleavage and add to AD risk (Kim M. et al., 2009).

Research in animal models as well as humans can suggest potential human AD genes. An international team of researchers, supported by NIA and NINDS and led by the Burnham Institute in La Jolla, CA, and Xiamen University, China, identified a new gene in mice—Rps23r1—that reduces levels of both beta-amyloid and phosphorylated tau (another major hallmark of AD) when it is turned on either in AD model mice or in human cells in tissue culture (Zhang Y.W. et al., 2009). This gene may protect mice against the development of AD-like changes in the brain. If this gene or one like it is present in humans, therapeutics might be designed to mimic its protective effects.

How are people affected by knowing their risk for AD?

As new genetic risk factors for AD are discovered, measures to assess individual risk will be developed. Currently, APOE ε4 is the most robust risk marker available for late-onset AD, and requests for APOE genotyping are increasingly common. The REVEAL study group led by researchers at Boston University with support from NHGRI and NIA studied the psychological consequences of disclosure of APOE genotype test results in a group of 162 symptom-free adults who had a parent with AD. This study found that people who had

the highest genetic risk for AD and were told their test results did not suffer significantly greater anxiety or depression during the weeks or months after the test than did people who either tested negative or who did not learn their test results (Green et al., 2009).

Additional advance in effects of genetic susceptibility testing:

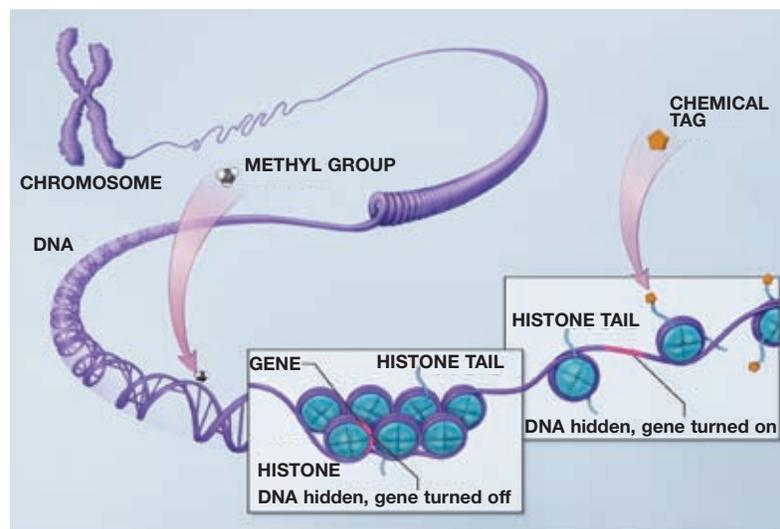
- Ashida et al. (2009) Disclosing the disclosure: factors associated with communicating the results of genetic susceptibility testing for Alzheimer's disease. NHGRI Intramural Program.

Epigenetics: Nature Meets Nurture

Until recently, scientists believed that genes and environmental factors acted independently to influence an individual's biological makeup, including a person's predisposition to different diseases. Now we realize that "nature and nurture" are not so easily untangled. Genes can be affected by environmental factors, such as diet or smoking, which a person may be exposed to, even in the womb.

The study of these interactions is called *epigenetics*, and it is emerging as a new frontier of science. Diet and exposure to environmental chemicals, among other factors, throughout all stages of human development can cause epigenetic changes that may turn on or turn off certain genes. Changes in the regulation of genes could make people more or less susceptible to developing a disease, such as AD, later in life.

Unlike gene mutations, epigenetic modifications of genes do not involve changes to the genetic code. They involve chemical alterations that make genes more or less accessible to interactions with enzymes responsible for "reading" each gene's code and cranking out the protein for which it codes. Environmental factors leave their mark on the genome by altering the epigenetic signature of genes. Like gene mutations, epigenetic changes can be passed from one cell to its daughter cells during cell division, and so can persist for an individual's lifetime. If the cells involved are egg or sperm cells, the changes can also be passed to the next generation. (The old phrase "You are what you eat" now could be revised to say, "You are what you eat and what your mother ate.")



The epigenome can mark DNA in two ways, both of which play a role in turning genes off or on. The first occurs when certain chemical tags called methyl groups attach to the backbone of a DNA molecule. The second occurs when a variety of chemical tags attach to the tails of histones, which are spool-like proteins that package DNA neatly into chromosomes. This action affects how tightly DNA is wound around the histones. (Source: NHGRI, www.genome.gov)

There is some evidence that epigenetic mechanisms contribute to AD. That may help explain why one individual in a family develops AD while another does not. One study, by scientists at the Sun Health Research Institute in Sun City, AZ, looked at certain chemical modifications in brain tissue samples from deceased identical twins. The comparison examined levels of DNA methylation, a chemical modification that can reduce the level at which a gene is expressed. One twin had developed AD at age 60 and deteriorated until his death at age 76; the other died cognitively intact at age 79. Methylated DNA levels were significantly lower in the brain tissue from the twin who had AD than in that of his brother (Mastroeni et al., 2009). The twin with AD had experienced extensive pesticide exposure during his lifetime as result of his profession. Pesticides are one environmental factor believed to cause epigenetic changes, although it is not known if they were a causative factor in this case.

Recent scientific evidence also points to the involvement of epigenetic mechanisms in memory formation and maintenance. One such mechanism involves enzymes that chemically modify histones (proteins

around which DNA is wrapped inside chromosomes) and results in the remodeling of chromosomes, the individual coils of DNA and protein storing genetic information inside cells. Two papers from the Massachusetts Institute of Technology in Boston and Columbia University in New York, NY, supported by NINDS, suggest an involvement of histone-modifying enzymes in memory formation and AD and point to these enzymes as possible targets for therapeutic development (Guan et al., 2009; Francis et al., 2009).

Additional 2009 advance in epigenetics:

- DeBette et al. (2009) Association of parental dementia with cognitive and brain MRI measures in middle-aged adults. Boston University. Supported by NIA, NINDS, NHLBI.

Looking to the Future: Epigenetics

In 2008, NIH announced funding for a new Roadmap Epigenomics Program (<http://commonfund.nih.gov/epigenomics/index.asp>), committing more than \$190 million during the next 5 years to accelerate this emerging field of biomedical research. The rationale behind this trans-NIH program is to promote understanding of how and when epigenetic processes control genes during different stages of development and throughout life. Scientists hope the effort will lead to more effective ways to prevent and treat disease.

NIA has played a very active role in the development and implementation of the Roadmap Epigenomics Program. In 2009, the Program funded 22 projects focused on exploring the epigenomic basis of various aspects of human health and disease. Four of these projects focus on establishing the epigenomic landscape of AD and testing whether epigenetic dysregulation is related to the initiation and progression of AD.

In 2010, NIA held a workshop “An Integrated Genetic-Epigenetic Approach to Alzheimer’s Disease,” which reviewed emerging epigenetic approaches to AD, explored synergies between genetic and epigenetic approaches, and spurred interactions between leading experts in AD genetics and epigenetics. ■

4 Preventing AD and Promoting Healthy Brain Aging

Genetic factors cannot fully account for why some people develop AD and others do not. There is mounting evidence that a number of nongenetic factors, such as diet, lifestyle, and exposure to certain environmental agents, may increase or reduce one’s risk of developing AD. Understanding these nongenetic risk factors will point the way to potential therapies or lifestyle changes that can help prevent AD.

Potential AD Risk Factors

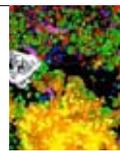
Advancing age and serious head injury are well-established risk factors for developing AD. Scientists are exploring a wide range of other possible factors.

Estrogen

The hormone estrogen has important effects on the brain, many of which are potentially relevant to cognitive aging and AD. For example, animal studies have shown that estrogen protects neurons against a wide spectrum of toxic insults, some of which are linked to AD. Estrogen can also reduce formation of beta-amyloid and can counteract some of the effects of normal aging on cognition when administered to nonhuman primates.

In humans, some large observational studies have suggested a possible protective effect of estrogen for women. Clinical trials and studies have attempted to assess whether estrogen therapy can protect women against age-associated cognitive decline. In the largest trial to date, reported in 2003, data from the Women’s Health Initiative Memory Study (WHIMS) showed that prolonged treatment with a common type of hormone therapy (conjugated equine estrogens) increased the risk of dementia and adversely affected cognition in women age 65 and older.

However, in the WHI trial, postmenopausal hormone therapy was usually started many years after normal reproductive cycles had stopped and involved synthetic hormones. Further, hormone treatment also increased the risk of stroke, suggesting that impaired cerebrovascular function may have been a factor in participants’ cognitive decline.



A number of nongenetic factors, such as diet, lifestyle, and exposure to certain environmental agents, may increase or reduce one's risk of developing AD.

To try to understand why hormone therapy impaired cognitive function in the WHIMS study, researchers at Wake Forest University and NIA's Laboratory of Personality and Cognition in Baltimore, MD, used MRI to look for brain degeneration in a group of women, ages 79 to 89, who had participated in the 2003 WHI trial. The women who had received hormone therapy showed more shrinkage of the hippocampus and frontal cortex than those who did not. (These brain regions are important for memory and planning, and also show shrinkage in AD.) Many of the women who received hormone therapy also showed evidence of varying degrees of brain damage due to cerebrovascular disease, but the extent of that damage was not significantly higher compared with women who had received a placebo (Coker et al., 2009). This finding suggests that the adverse effects of hormone therapy on cognition were not due to an increase in cerebrovascular disease (Resnick et al., 2009).

The human clinical data highlight the substantial gaps in our understanding of ovarian hormone influences on neurocognitive aging, as recently summarized from an NIA-sponsored workshop convened to address these issues (Asthana et al., 2009). One of these questions is about timing. Animal studies have shown that estrogen has positive effects on the brain, but only if administered during or immediately after withdrawal of ovarian steroids. Thus, estrogen may protect cognition in humans only if administered at a particular age or for a specific amount of time after menopause. Two NIA-funded clinical trials in progress will compare the effects of early and late hormone therapy on cognition, and other endpoints: the Kronos Early Estrogen Prevention–Cognitive and Affective Study (KEEPS–CA) and the Early versus Late Intervention Trial with Estrogen (ELITE) (see *AD Clinical Trials*, page 38).

General anesthetics

An estimated 200 million patients worldwide have surgery with anesthesia each year. Several studies have linked general anesthesia in surgery with an increased risk of AD later in life. Researchers at Massachusetts General Hospital and Harvard University in Boston, supported by NIGMS, NIA, and NINDS, looked at the most commonly used inhalation anesthetic (sevoflurane) and found increases in beta-amyloid levels and cell death when it was applied to a glial tumor cell line in culture. In addition, mice anesthetized for 2 hours showed increased beta-amyloid deposition in the frontal cortex (Dong et al., 2009). It is important to note that no evidence to date with this or any other inhalation anesthetic shows similar results in humans, but further study of effects of anesthetics on development of brain pathology may be warranted.

Lead

A pilot study of 47 healthy subjects, 55 to 67 years old, provided additional support for previous research suggesting a link between lead exposure and memory impairment. Investigators at the University of Rochester, NY, supported by NIEHS, found that higher lead levels in bone, which indicate accumulated lead exposure over time, were associated with impaired performance on two memory tests used to detect MCI (van Wijngaarden et al., 2009).

Additional advance related to AD risk factors:

- de la Monte et al. (2009) Mechanisms of nitrosamine-mediated neurodegeneration: potential relevance to sporadic Alzheimer's disease. Rhode Island Hospital/Brown University. Supported by NIAAA.

Lifestyle and Successful Cognitive Aging

Many individuals stay mentally sharp to age 90 and beyond, and there has been increasing research emphasis on finding out why. Epidemiological–observational–studies such as those described below are important to identify associations between certain lifestyle factors and the risk of developing AD. However, even if substantial evidence is found for a potential association, observational studies alone cannot establish a cause-and-effect relationship. To be useful in the clinic, associations between some factor and AD risk must be able to yield an intervention that can be randomly assigned to individuals in a clinical trial, as randomized trials remain the gold standard for identifying successful treatments (see *AD Clinical Trials*, page 38).

Researchers for the Health ABC Study at the University of California, San Francisco, and the NIA Intramural Research Program identified several factors associated with continued cognitive health. In a group of 2,509 older people who were functioning well when they entered the study (at ages 70 to 79), factors contributing to enhanced or intact cognitive function included at least a high school level of education, not smoking, and engaging in moderate to vigorous exercise on a weekly basis (Yaffe et al., 2009). Similar associations have been found in a variety of studies.

Social interaction

A number of studies have found that social interaction, whether through work, volunteering, or living with someone, is associated with maintaining cognitive health. It has not been clear, though, whether this correlation is due to the increased intellectual stimulation and physical activity that generally accompany social interaction or whether it was the social interaction itself that was beneficial. Researchers at the Rush University Alzheimer's Disease Center in Chicago, IL, addressed this question in a large study of nondemented older

people (average age, 80). Consistent with previous studies, they found that better cognitive function was correlated with more frequent participation in social activities, as well as with the subjects' own perception of being well-supported socially. This correlation was significant even after accounting for higher levels of intellectual and physical activity (Krueger et al., 2009).

Exercise

Building evidence from epidemiological studies and several small clinical trials in healthy adults have shown that aerobic exercise may help prevent age-associated cognitive decline, at least in the short term. Studies in animals suggest that exercise may strengthen cognition in part by supporting the hippocampus, a brain structure critical for learning and memory that is one of the first to deteriorate during both normal brain aging and in AD. A report from investigators at the University of Pittsburgh, PA, and the University of Illinois, Urbana-Champaign, suggests that exercise supports hippocampal function in humans as well. They assessed cardiorespiratory fitness in 165 older adults using a treadmill test, and found that higher fitness levels were associated not only with better performance on a spatial memory test but also with greater hippocampal volumes (Erickson et al., 2009).

Work by researchers at Washington University, St. Louis, MO, supported by NIA and NIMH, suggests some forms of exercise are more beneficial than others, at least in one animal model. In AD model mice, voluntary exercise was superior to forced exercise in reducing plaque deposition and improving memory (Yuede et al., 2009). Another study, supported by NIA and NIAMS, from the University of California, Irvine, on AD model mice bearing different forms of the APOE gene suggested that exercise is especially beneficial for cognitive function in mice with the APOE ε4 form (Nichol et al., 2009).

Additional advance related to exercise and AD risk:

- McAuley et al. (2009) Trajectory of declines in physical activity in community-dwelling older women: social cognitive influences. University of Illinois, Urbana-Champaign. Supported by NIA.

Interactions Between AD and Vascular Disease

The brain has one of the richest supplies of blood vessels of any organ. Cognitive health depends very much on the health of the brain's blood vessels. Aging is often accompanied by problems in cardiovascular and/or cerebrovascular function. Two of the most common are high blood pressure and clogging of blood vessels that supply the brain, which can cause stroke. Vascular disease, in turn, can cause cognitive impairment.

It has become clear in recent years that AD and vascular disease-associated cognitive impairment are closely intertwined. For example, a large proportion of people diagnosed with AD also have brain damage due to vascular disease (see *Links with Other Diseases*, page 14). In addition, two analyses of data from NIA's Baltimore Longitudinal Study of Aging and the Honolulu-Asia Aging Study found that many of the major risk factors for vascular disease may also be risk factors for AD. These findings suggest common cellular mechanisms for the two diseases (Wendell et al., 2009; Stewart et al., 2009)

The overlap between vascular disease and AD may be important because drugs and lifestyle modifications known to be effective in preventing vascular disease may also help prevent AD. In 2009, the following epidemiological and animal studies found that some factors known to reduce vascular disease are also associated with reduced risk of AD.

Controlling high blood pressure. A postmortem study of brains of people who had hypertension while living, from Mount Sinai School of Medicine, New York, NY, found significantly fewer plaques and tangles in those who had taken medication to control their blood pressure than in those who had not (Hoffman et al., 2009).

Mediterranean diet. A large study by Columbia University

researchers in a multiethnic New York community showed that people who maintained a Mediterranean diet had a 28 percent lower risk of developing MCI and a 48 percent lower risk of progressing from MCI to AD. A Mediterranean diet includes vegetables, legumes, fruits, cereals, fish, monounsaturated fats such as olive oil, mild to moderate amounts of alcohol, and low intake of saturated fats, dairy products, meat, and poultry (Scarmeas et al., 2009a).

Physical activity. Another Columbia University study in the same multiethnic New York population showed that people who reported regular engagement in "some" physical activity had a 29 to 41 percent lower risk of developing AD, compared to participants who said they were not physically active. Engaging in "much" physical activity was associated with a 37 to 50 percent lower risk (Scarmeas et al., 2009b).

Cholesterol-reducing drugs. Investigators at the University of Alabama, Birmingham, supported by NIA and NHLBI, treated AD model mice with a drug that mimics apolipoprotein A-1 (the major protein in high density lipoprotein, or HDL, the "good" form of cholesterol) together with a statin for controlling cholesterol. The mice treated with this combination of drugs showed improved cognitive function, reduced amyloid, and reduced inflammation compared with untreated AD model mice (Handattu et al., 2009). ■

Additional 2009 advance related to vascular disease and AD:

- Schuff et al. (2009a) Cerebral blood flow in ischemic vascular dementia and Alzheimer's disease, measured by arterial spin-labeling magnetic resonance imaging. University of California, San Francisco/VA Medical Center. Supported by NIA.

Looking to the Future: Preventing AD and Age-Related Cognitive Decline

Mounting epidemiological and animal-study findings point to interesting possibilities for preventing AD and cognitive decline. What can scientists say definitively now about what works to prevent Alzheimer's and age-related cognitive decline? To examine this critical question, the NIH Office of Medical Applications of Research and NIA convened a State-of-the-Science Conference, held April 26-28, 2010, with co-sponsorship from NICHD, NCCAM, NIMH, NINDS, NINR, and the Office of Dietary Supplements.

An independent, 15-member panel was convened to review questions and evidence. Panel members were not currently involved in Alzheimer's research and represented the fields of preventive medicine, geriatrics, internal medicine, neurology, neurological surgery, psychiatry, mental health, human nutrition, pharmacology, genetic medicine, nursing, health economics, health services research, and family caregiving.

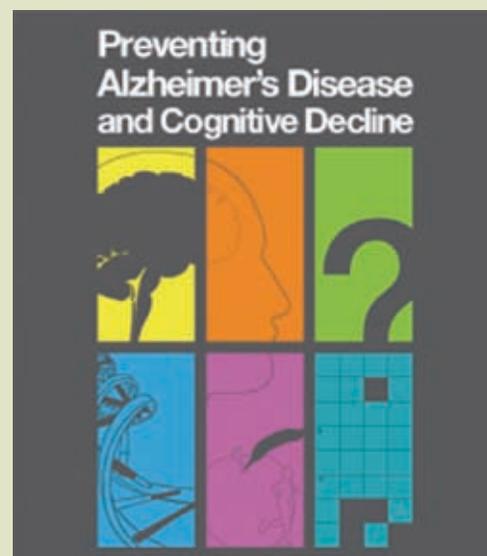
Experts from pertinent fields were invited to present data to the panel and conference audience. The panel also received a systematic evidence review from the Evidence-based Practice Center at Duke University's Clinical Research Institute, prepared under contract with the Agency for Healthcare Research and Quality. Conference participants also provided oral and written comments in response to the conference questions. The panel considered all of this evidence

when preparing its consensus statement.

The panel concluded that cognitive decline and AD are major causes of morbidity and mortality worldwide and are substantially burdensome to the people affected, their caregivers, and society in general. Extensive research during the past 20 years has provided important insights on the nature and extent of AD and cognitive decline. Currently, however, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or AD. Further, evidence is insufficient to support the use of any pharmaceutical agent or dietary supplement to prevent cognitive decline or AD.

However, promising research is underway, the panel noted. These efforts need to be increased and added to by new insights and innovations. For example, the panel indicated that ongoing studies, including those of antihypertensive medications, omega-3 fatty acids, physical activity, and cognitive engagement, may provide new avenues for the prevention or delay of cognitive decline or AD.

NIA's ongoing research programs are actively investigating and testing a variety of strategies to prevent or delay AD and cognitive decline. Research includes clinical trials investigating exercise, statins and blood pressure and diabetes medications, hormones, antioxidants, cognitive training, and other interventions (see *AD Clinical Trials*, page 38).



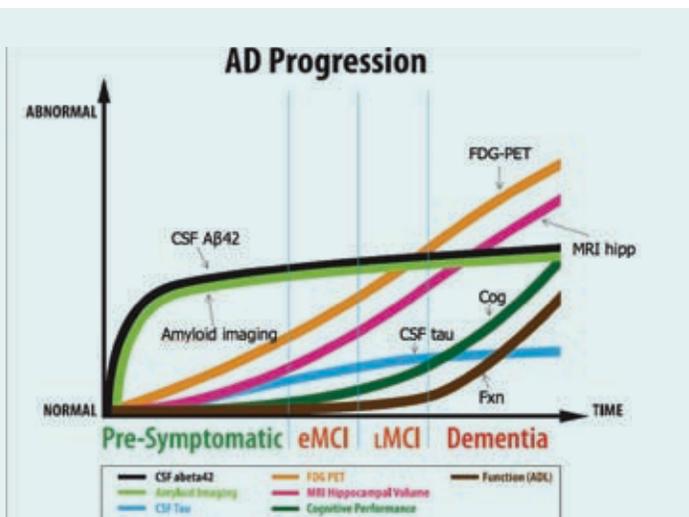
Further large-scale population-based studies and randomized clinical trials are needed to investigate strategies to maintain cognitive function in individuals at risk for decline, to identify factors that may delay the onset of AD in people at risk, and to identify factors that may slow the progression of AD in people already diagnosed.

As this research continues, there are very good reasons for adults to adopt or maintain lifestyle choices and treatments known to promote healthy aging and reduce the risk of diseases like diabetes or cardiovascular disease.

For more information on the State-of-the-Science Conference and consensus statement, go to <http://consensus.nih.gov/2010/alz.htm>. ■

5 Detecting Disease Earlier

Many researchers believe that therapeutic interventions for AD are more likely to be effective if initiated early in the disease process. Since we now know that the brain damage caused by AD can begin long before cognitive impairment becomes evident, intensive effort has been aimed at developing methods to detect this damage at its earliest stages.



This diagram illustrates current thinking about how Alzheimer's changes in the brain contribute to disease progression, from a presymptomatic stage through early and late mild cognitive impairment to Alzheimer's dementia. The curves on the diagram represent specific markers as they appear sequentially over time as the disease progresses.

Scientists are currently exploring three main approaches to early diagnosis: cognitive testing, brain imaging, and measurement of biomarkers in CSF. In addition, there is a growing body of research on other early symptoms and changes that may signal the onset of AD.

Cognitive Testing

Extensive cognitive testing has been a key diagnostic tool in AD, refined over many years. Many existing tests were designed to diagnose relatively later stages of the disease—for example, in people who come to the doctor's office already complaining of memory problems. What is currently lacking are tests that can detect and track the earliest, most subtle stages of the disease and tests that can identify who is at risk of eventually developing the disease. Research efforts now concentrate on the development of a new generation of cognitive tests that are more sensitive to changes in cognition and more reliably discriminate between normal aging, early stages of AD, and cognitive impairment due to other diseases, such as cerebrovascular disease or Lewy body disease. Progress toward establishing a detailed account of normal neurocognitive aging will importantly inform this effort.

■ MCI is often a transitional stage between normal aging and AD. Sensitive, accurate diagnostic tests for MCI are critical to identify people at risk of developing AD and to predict the likely progression of symptoms. There has been considerable variability in assessing how common MCI is in the population and the rate at which people with MCI progress to AD, due in part to the use of different criteria for diagnosing MCI. Researchers at the University of California, Los Angeles Alzheimer's Disease Center assessed 115 people with amnesic or nonamnesic MCI using a battery of tests for different neuropsychological functions, such as memory, attention, and visuospatial processing, then followed their progress for 16 months. (In amnesic MCI, memory is the dominant problem; in nonamnesic MCI, other cognitive impairments dominate, such as problems with language, visuospatial processing, and attention. People with amnesic MCI are more likely to progress to AD than those with nonamnesic MCI.) In both the amnesic and nonamnesic groups, the percentage of people who had performance deficits differed significantly for different tests. However, the people who were most impaired on memory tests at the beginning of the study were also the most likely to have persistent memory deficits over the long term (Teng et al., 2009).

■ The Mini Mental State Examination (MMSE) was designed in 1975 and remains the most widely used screening test for dementia. The MMSE is not sensitive to mild cognitive changes, nor is it very useful for distinguishing between AD and other forms of dementia. It has remained in use in part because it is simple, quick to administer, and can be used in any doctor's office. Most clinical trials use MMSE scores to help determine who is eligible to participate. A number of new tests are under development that retain those virtues but provide more sensitive and accurate diagnoses. For example, researchers at Mount Sinai Medical Center in Miami, FL, reported on the Florida Brief Memory Screen, which shows high sensitivity for detection of MCI and takes only 3 to 4 minutes to administer. The test is available in Spanish and English, an important feature, as linguistic issues can compromise test performance (Loewenstein et al., 2009).

■ Several computer-based tests have also been developed, most of which can be used with a standard personal computer. Most of these tests have to be administered and scored by a clinician, as is also true for pen and paper-based tests like the MMSE. University of Pittsburgh researchers reported on a new computer-based test, Computer Assessment of Mild Cognitive Impairment (CAMCI), that is both self-administered and automatically scored. The researchers reported a good sensitivity for detection of MCI (Saxton et al., 2009).

Additional 2009 advance related to cognitive testing:

- Schneider LS et al. (2009) Characteristics and performance of a modified version of the ADCS-CGIC CIBIC+ for mild cognitive impairment trials. University of Southern California. Supported by NIA, NCRR.

Ethnicity and AD diagnosis

Several reports have suggested racial and ethnic differences in the prevalence of AD. Studies seeking to explain these differences have found that cultural factors and variations in education quality, for example, can affect performance on standardized cognitive tests.

Another source of diagnostic information, used in conjunction with cognitive tests, is reports from family members and other caregivers about how well a person is functioning in day-to-day life. However, these informant reports, too, may be affected by ethnic and cultural differences. Investigators from Duke University in Durham, NC, found that family member/caregiver reports were less likely to predict cognitive impairment without dementia in African Americans than in whites (Potter et al., 2009). These results are consistent with previous studies suggesting that African Americans are less likely than whites to report cognitive changes in family members. This difference may reflect different cultural perceptions of "normal" aging. For example, a research team at the University of Michigan and Boston University Alzheimer's Disease Centers studied a group of 301 people in the Boston area, most of whom had personal experience with AD as a caregiver and/or relative. Significantly more of the African American than white participants believed that memory impairment is an expected part of aging (Connell et al., 2009).

Looking to the Future: Cognitive Testing

The AD field is moving toward much earlier diagnosis. More sensitive measures that assess different cognitive domains in more diverse populations are needed. To explore these issues, NIA held a workshop in spring 2010, "Assessment of Cognition in Early Dementia." The purpose was to review a range of computerized cognitive assessments to determine gaps and opportunities for further development, evaluate novel assessment methods and cognitive domains (e.g., spatial orientation, prospective memory), and determine the best ways to assess cognition in diverse populations. Information from this meeting will be used in the near future to decide which cognitive measures will be incorporated into particular research studies. ■

Other Early Signs and Symptoms

The clinical picture of AD is changing considerably. For many years since AD was first described in 1906, clinicians believed that it was a rare disease affecting middle-aged adults. In the 1960s, at about the same time larger numbers of people were living past age 65, it became evident that a similar disease occurred in older adults. At the time, the clinical description of AD focused on the symptom of memory loss, specifically, loss of the ability to form and recall memories of recent events. Now there is growing recognition that, even in its earliest stages, AD can affect other cognitive skills and disrupt mood and behavior, sometimes even before memory is affected. Scientists are also increasingly aware that the symptoms and course of AD can vary considerably from person to person, depending in part on whether an individual has other common diseases and conditions of old age, such as vascular disease or diabetes.

Sensory Changes

Cognitive changes in the early stages of AD may include deficits in the ability to process sensory information. NIA-supported research published in 2008 showed that some people with AD begin losing their sense of smell early in the course of the disease (see *2008 Progress Report on Alzheimer's Disease*; also additional references below). Research reported in 2009 suggests that visuospatial skills also may falter early on.

Visuospatial skills allow us to perceive objects and the spatial relationships among them and to judge how close or far away we are from objects in our environment. These skills are crucial for navigating city streets, our own homes, or an assisted living facility. Researchers at the Washington University Alzheimer's Disease Center in St. Louis, MO, studied 444 older people, all of whom were cognitively normal at the start of the study. About 30 percent of them subsequently developed AD. In this group, performance on tests of visuospatial skill began to decline 3 years earlier on average than performance on memory tests (Johnson et al., 2009).

Investigators at the University of Rochester, NY, provided further evidence that visuospatial skills can decline while memory remains relatively intact (Duffy, 2009). The team studied navigational problems associated with AD, specifically, the question of why people with AD tend to get lost in familiar environments. They found that the brain's electrical responses to navigation are reduced in people with early AD, and that this ability can be impaired even in people with no measurable memory deficits.

Another report this year from the University of Alabama, Birmingham Alzheimer's Disease Center found that in everyday life, people with MCI have worse driving performance than their cognitively normal peers (Wadley et al., 2009). The MCI group did not have worse visual acuity (sharpness of vision) than the control group. Thus, it is possible that the MCI group's impaired driving performance reflected deficits in cortical visuospatial processing, similar to the navigation deficits observed by the Rochester researchers. On the other hand, this impaired level of driving performance could reflect changes in executive function (e.g., the ability to rapidly choose the appropriate action once you have detected a potentially dangerous situation), given the complexity of driving.

Additional advances in sensory changes:

- Murphy et al. (2009) Olfaction in aging and Alzheimer's disease: event-related potentials to a cross-modal odor-recognition memory task discriminate ApoE epsilon4+ and ApoE epsilon4- individuals. San Diego State University. Supported by NIA and NIDCD.
- Wilson et al. (2009b) Olfactory impairment in presymptomatic Alzheimer's disease. Rush University Alzheimer's Disease Center. Supported by NIA.

Looking to the Future: Sensory and Motor Changes

These studies and others suggest that examining sensory and motor changes in the context of AD may offer fresh perspectives regarding the course, early detection, assessment, and treatment of AD. To further explore these new avenues for research, NIA held an exploratory workshop in August 2010, "Sensory and Motor Dysfunctions in Aging and Alzheimer's Disease (AD)," focusing on recent findings in sensory and motor changes occurring early in the course of AD, gaps in knowledge, and strategies for advancing this area of research. Participants included experts from the fields of AD as well as leading researchers in the relevant sensory and motor fields. ■

Behavioral and Mood Problems

Many people with AD experience behavioral and mood disturbances, including depression, irritability, and disinhibition (displays of socially inappropriate behavior). Indeed, such “neuropsychiatric” symptoms are the primary reason caregivers consider moving family members with AD to nursing homes.

Behavioral and mood disturbances also appear to be associated with more rapid progression from MCI to dementia. Researchers at the Instituto Universitario CEMIC in Buenos Aires, Argentina, in collaboration with Johns Hopkins University Alzheimer’s Disease Center scientists, studied 239 people with MCI, of whom 36 percent had persistent neuropsychiatric symptoms in addition to cognitive symptoms. They also progressed more rapidly to dementia. During the period of the study, 44 percent of the people with both MCI and neuropsychiatric symptoms converted to AD, and 18 percent converted to frontotemporal dementia (FTD), a degenerative dementia affecting the frontal and temporal lobes of the brain and causing changes in personality, behavior, language, and movement. In contrast, only 18 percent of the people who had MCI without neuropsychiatric symptoms converted to AD, and none to FTD (Taragano et al., 2009).

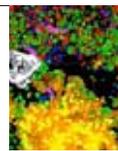
Biomarkers and ADNI

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) was launched in 2004 to determine which imaging methods and fluid biomarkers can best track and predict clinical change over time (*more information on ADNI*, page 54). As of fall 2010, ADNI scientists had collected 3 years of longitudinal data from more than 800 participants (about 200 normal, 400 with MCI, and 200 with AD) at 59 U.S. and Canadian sites. In 2009, ADNI helped identify a number of precisely measurable, clinically relevant biomarkers that will enable more accurate diagnosis and prediction of disease course and also speed and cut the cost of clinical trials.

Structural MRI

During the course of AD, certain regions of the brain shrink due to the degeneration of synapses and death of neurons. Researchers have been using brain scans to try to detect such changes very early, before people have significant cognitive impairment. A collaborative team of investigators from the University of Pennsylvania in Philadelphia and NIA’s Laboratory of Personality and Cognition in Baltimore, MD, developed a pattern detection program to analyze MRI scans obtained from ADNI participants. The program compared patterns of brain area loss over time in people with AD with those of cognitively normal people the same age. Based on differences in these patterns, the program generated a kind of “search image” for AD-like changes, called the “spatial patterns of abnormality for recognition of early AD (SPARE-AD).” The researchers then used the program to analyze people enrolled in NIA’s Baltimore Longitudinal Study of Aging neuroimaging study. In that investigation, people who had either MCI or memory decline with otherwise normal cognition had the highest SPARE-AD scores (Davatzikos et al., 2009). The study suggests that sophisticated pattern detection methods with MRI imaging may help identify cognitively normal individuals who are likely to show cognitive decline.

A 1-year structural MRI study of 449 participants by ADNI investigators at the University of California, San Francisco, found that people with AD and MCI lost volume in the hippocampus more quickly than did cognitively normal people. The losses were associated with deteriorating scores on cognitive assessments. In people with AD, higher rates of loss in hippocampal volume also



In 2009, ADNI helped identify a number of precisely measurable, clinically relevant biomarkers.

correlated with the presence of the ApoE $\epsilon 4$ gene, a risk factor for Alzheimer's. In people with MCI, higher rates of hippocampal loss were associated with lower levels of the peptide beta-amyloid 1-42 (A β 1-42) in CSF. The finding of accelerating hippocampal loss is important for understanding the natural history of the disease and emphasizes the need for early diagnosis and therapeutic intervention, the study report noted (Schuff et al., 2009b).

Other ADNI studies, including one published by researchers at the Mayo Clinic in Rochester, MN, have shown that PET imaging holds potential for a different use: the identification of people with AD pathology who have not yet developed dementia. Detection of brain beta-amyloid could potentially be used as a risk factor to predict future decline to AD (Jack et al., 2009).

Cerebrospinal fluid

Researchers took a major step forward in developing a test to diagnose early-stage AD by measuring two biomarkers—tau and beta-amyloid proteins—in CSF. Previous imaging studies had shown that AD-like changes can occur in the brain years before any cognitive symptoms appear. However, CSF testing costs less than brain imaging, so researchers have sought CSF biomarker changes correlated with the development and progression of AD. A report from the ADNI Biomarker Core at the University of Pennsylvania School of Medicine in Philadelphia provided strong evidence that changes in CSF tau and beta-amyloid signal the onset of mild AD. Researchers also established a method for standardized testing for these biomarkers (Shaw et al., 2009). These results may open the door to the discovery of an entire panel of CSF biomarkers that will predict who is at risk of developing AD and how the disease

responds to therapies. Like all ADNI results, these findings have been posted to a publicly accessible database available to qualified researchers worldwide.

Additional advances in neuroimaging:

- Dickerson et al. (2009) The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to moderate AD dementia and is detectable in asymptomatic amyloid-positive individuals. Massachusetts General, Harvard University. Supported by NIA, NINDS, and NCRR.
- Fennema-Notestine et al. (2009) Structural MRI biomarkers for preclinical and mild Alzheimer's disease. University of California, San Diego (ADNI).
- McEvoy et al. (2009) Alzheimer disease: quantitative structural neuroimaging for detection and prediction of clinical and structural changes in mild cognitive impairment. University of California, San Diego. Supported by NIA (ADNI).

Additional advances in biomarkers:

- Fagan et al. (2009a) Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease. Washington University. Supported by NIA, NINDS, and NCRR.
- Fagan et al. (2009b) Decreased cerebrospinal fluid Abeta(42) correlates with brain atrophy in cognitively normal elderly. Washington University. Supported by NIA, NINDS, and NCRR.
- Jagust et al. (2009) Relationships between biomarkers in aging and dementia. University of California, Berkeley (ADNI).
- Okereke et al. (2009) Ten-year change in plasma amyloid beta levels and late-life cognitive decline. Harvard University. Supported by NIA and NCCAM.

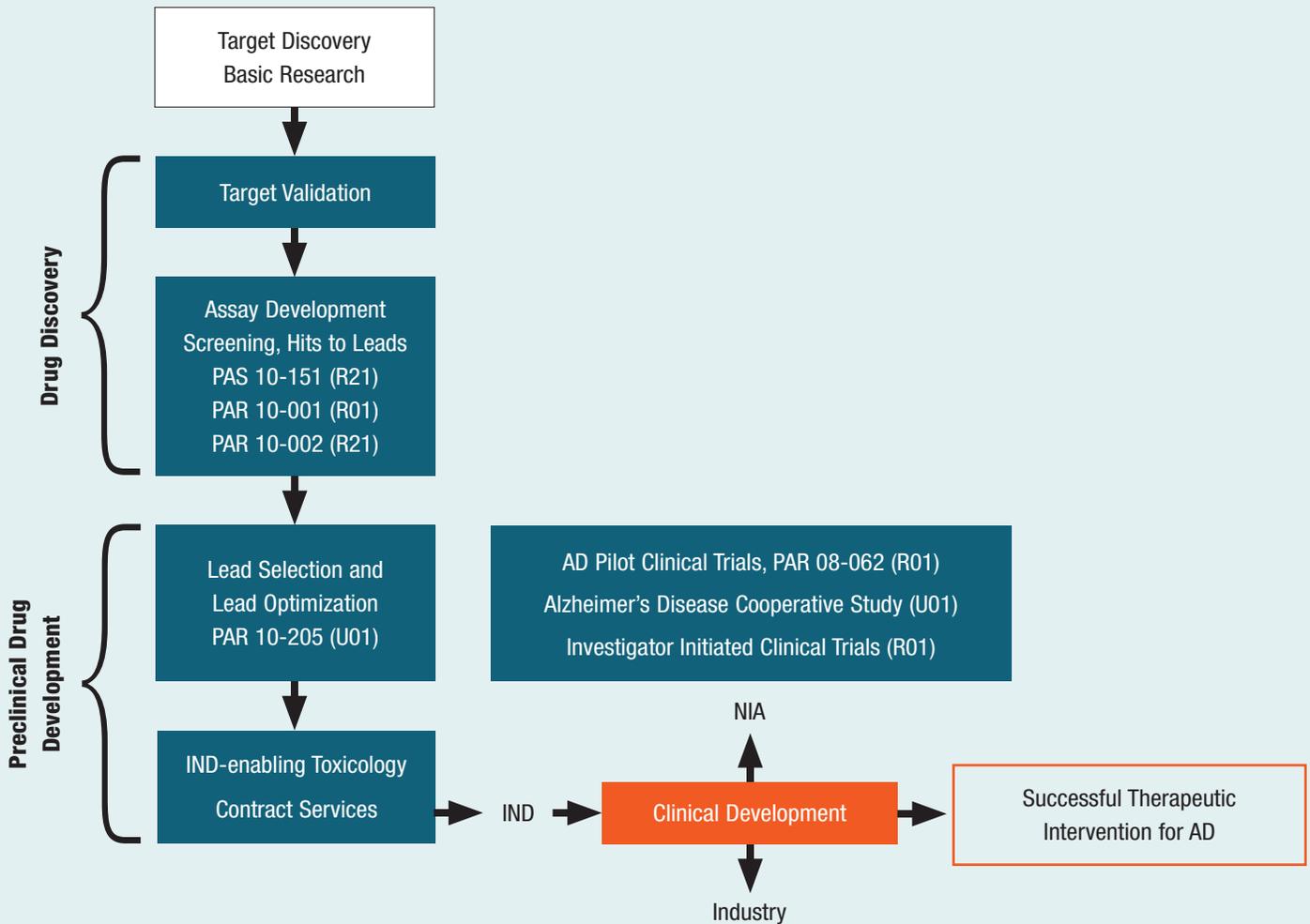
6 Developing Novel Therapeutic Approaches

Translational research is a multidisciplinary effort that enables the transfer of information between basic-science laboratory studies and clinical research for the purpose of developing novel therapies. The discovery and development of new drugs for neurological disorders is extremely challenging and very expensive. On average, it takes more than 13 years and costs \$1.78 billion from

the discovery of a new therapeutic target to the time a new drug receives FDA approval for use in the general patient population (Paul et al., 2010). At each step of the translational process, there is a very high failure rate.

In recognition of the difficulties in moving basic scientific knowledge toward drug development, NIA's Division of Neuroscience instituted a series of funding initiatives aimed at creating a robust AD translational research program. The aim is to increase the number of investigational new drugs that can then be tested in humans.

NIA's Alzheimer's Disease Translational Research Program



During the last 5 years, NIA launched a series of funding initiatives to support early drug discovery and preclinical therapy development for AD. The funding opportunity PAS 10-151 supports exploratory drug discovery research using the R21 grant mechanism, and the funding opportunity PA 10-205 supports the preclinical development of promising candidate therapeutics through a cooperative agreement mechanism (U01). In addition, NIA participates in drug discovery funding opportunities initiated by other Institutes (PAR

10-001 and PAR 10-002). The U01 program in conjunction with toxicology services provided through an NIA contract enable researchers involved in preclinical development of candidate therapeutics to secure an Investigational New Drug (IND) status from the FDA. Once a compound has received an IND status, the multiple steps of testing in humans (clinical development) can be pursued either by the pharmaceutical industry or through NIA's clinical trial funding opportunities or clinical trial consortium (ADCS).

Drug Discovery and Preclinical Development

NIA support provides critical investments in the riskiest early steps of AD drug discovery and preclinical drug development, which the pharmaceutical industry is unlikely to pursue. The NIA Translational Research Program funds a diverse portfolio of more than 60 projects, ranging from early drug discovery to preclinical development of novel therapeutic compounds aimed at a variety of targets (see *Petanceska et al.*, 2009, for a detailed summary).

To date, this Program includes more than a dozen preclinical drug development projects focused on 1) preclinical optimization of novel therapeutic candidates, 2) repurposing and/or reformulation of drugs currently in use to treat other disease conditions, and 3) preclinical development of naturally occurring compounds. Following are examples of new candidate therapeutics for each of these three areas.

Novel compounds

Tau aggregation inhibitors. One of the hallmarks of AD is the abnormal clustering of the tau protein into neurofibrillary tangles (see *A Brief Primer on AD and the Brain*, page 11). Tau has emerged as an attractive therapeutic target for AD and other neurodegenerative diseases, commonly known as tauopathies. A multidisciplinary team from the University of Pennsylvania in Philadelphia reported the discovery in mice of two candidate compounds that are effective inhibitors of tau aggregation and can penetrate the blood brain barrier after being orally administered (Ballatore et al., 2010). The Translational Research Program is supporting the further preclinical optimization of these compounds.

Hsp90 inhibitors. Heat shock protein 90 (Hsp90) is a member of a large family of molecules that help regulate the transformation of healthy cells to diseased ones. Until recently, Hsp90 was mostly known for its involvement in malignant transformation in cancer. But several laboratories have now provided evidence that Hsp90 plays a role in maintaining the stability of abnormally folded neuronal proteins, allowing the accumulation of toxic aggregates (Luo et al., 2010). Previous research has shown that

agents that inhibit Hsp90 can protect neurons against beta-amyloid toxicity as well as *tau* aggregation. A drug discovery research team from the University of Kansas in Lawrence involved in the design of novel Hsp90 inhibitors for AD reported that three new analogues of the Hsp90 inhibitor novobiocin provide excellent neuroprotection, with little, if any, toxicity in a cell culture model of beta-amyloid (Lu Y et al., 2009).

Old drug, new purpose

Memory is governed by long-term changes in nerve cell firing patterns, which in turn require changes in the expression of certain neuronal genes. Regulation of gene expression is the business of proteins called “transcription factors.” The activity of one such factor, CREB (which seems to be particularly important in memory formation) can be increased using the drug sildenafil (Viagra®). When scientists at Columbia University in New York, supported by NIA and NINDS, applied sildenafil to hippocampal cells from AD model mice in tissue culture, they saw immediate and long-lasting improvements in synaptic function. In addition, short-term (2- to 3-week) administration of sildenafil to living AD model mice significantly improved their performance in memory tests up to 3 months later. Interestingly, the drug also reduced beta-amyloid levels in these mice, perhaps through its effects on gene expression (Puzzo et al., 2009).

Nature to the rescue

Data from epidemiological studies and laboratory experiments suggest that gonadal steroid hormones (sex steroids) and their metabolites can promote neuronal health, while their decline or absence is associated with higher risk of neurodegenerative disease, including Alzheimer’s (see *Estrogen*, page 25). One of the steroids that declines in the aged brain, and in AD brains in particular, is allopregnanolone. Previous experimental evidence demonstrated the ability of this neurosteroid to stimulate the production of neuronal progenitor cells (cells that ultimately develop into functional neuronal cells in the brain) in rodent models. A multidisciplinary team from the University of Southern California in Los Angeles initiated a translational project focused on the preclinical development of allopregnanolone as a regenerative AD therapeutic. The team reported that allopregnanolone can rescue the loss of neurogenic potential in a

transgenic mouse model of AD and reverse associated cognitive decline (Wang JM et al., 2010). The USC team is currently identifying a formulation and dosing regimen for allopregnanolone that will result in an optimal efficacy and safety profile for testing in future clinical trials in humans.

Additional advances in drug discovery and preclinical drug development:

- Cohen AD et al. (2009a) Anti-amyloid effects of small molecule Abeta-binding agents in PS1/APP mice. University of Pittsburgh. Supported by NIA.
- Ma QL et al. (2009) Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. University of California, Los Angeles. Supported by NIA and NCCAM.

New Therapeutic Targets

As scientists continue to learn more about the complexity of the processes and mechanisms of AD, they are also discovering potential new targets for attacking the disease and new approaches for treating it. These basic research findings are the stepping stones for translational research efforts that ultimately may lead to new, effective drug therapies.

Nourishing the brain with its own growth factor

Brain-derived neurotrophic factor (BDNF), a growth factor produced by neurons, is essential for early brain development and healthy brain function in adulthood. Among other actions, BDNF supports nerve cell growth and survival and promotes synaptic outgrowth and plasticity. In people with AD, BDNF levels are abnormally low in certain brain regions where neurons are dying. To test the possible therapeutic effects of BDNF, researchers at the University of California, San Diego used a gene therapy approach in several animal models of AD and aging. They found that BDNF had beneficial effects in all of the models. In AD model mice, it induced recovery of synapses and synaptic signaling markers and improved spatial memory. In rats, BDNF prevented the death of cortical nerve cells that were exposed to beta-amyloid in tissue culture. BDNF gene therapy also had positive effects on spatial learning and memory in the aged rats, as well as in nonhuman primates (Nagahara et al., 2009).

These findings indicate that BDNF has multiple protective effects on the neuronal systems that deteriorate during AD and suggest that therapeutic delivery of BDNF or other means of stimulating BDNF activity holds promise as a therapeutic approach for the disease.

Stem cell therapy for AD

Neural stem cells—cells present in both embryonic and adult neural tissue that have the capacity to develop into neurons—have received less consideration as therapy for AD than for other neurodegenerative disorders like Parkinson's disease and stroke. Because AD affects a wide variety of cell types across widespread regions of the brain, it seemed implausible that many different cells could be replaced using stem cells. Recently, however, scientists have realized that stem cells can improve brain function not only by replacing lost cells, but also by promoting the survival and function of remaining cells.

Researchers at the University of California, Irvine, supported by NIA and NIAMS, took neural stem cells from newborn normal mice and transplanted them into the hippocampal regions of aged AD model mice with widespread plaques and tangles. The transplanted neural stem cells reversed spatial learning and memory deficits in the older mice. They did so not by reducing plaques or tangles in their brains, but by promoting the growth of new synapses in surrounding brain tissue. The beneficial effect of these stem cells turned out to be due to their secretion of the growth factor BDNF (Blurton-Jones et al., 2009). This study is important because it suggests the potential of neural stem cell therapy in AD and shows its beneficial effects in old transgenic mice with substantial AD-like pathology in their brains.

Clearing out beta-amyloid

A number of potential new therapeutic targets are emerging from studies of the multiple mechanisms by which beta-amyloid is removed or cleared from the brain. Beta-amyloid clearance is accomplished by proteins on brain blood vessels that bind beta-amyloid and transport it out of the brain and into the blood. A research team at Washington University in St. Louis, supported by NIA and the NIH Neuroscience Blueprint, showed that by experimentally increasing levels of the beta-amyloid transport protein LRP-1 in the mouse brain, it was possible to dramatically enhance beta-amyloid clearance and reduce its accumulation (Kim J et al., 2009).

Work by another team of investigators at the University of Rochester, NY, supported by NIA,

NINDS, and NHLBI, raised the possibility that beta-amyloid clearance by the same transport protein is disrupted in some forms of AD. They found that LRP-1 production is suppressed by two gene regulatory proteins (SRF and myocardin) present in abnormally high levels in the brain blood vessels of some people with AD. Levels of these regulatory proteins in turn are stimulated by low blood oxygen levels, a condition associated with AD (Bell et al., 2009).

Additional advances related to translational research and beta-amyloid clearance:

- Lakshmana et al. (2009) Novel role of RanBP9 in BACE1 processing of amyloid precursor protein and amyloid beta peptide generation. University of California, San Diego. Supported by NIA.
- Lakshmana et al. (2010) A fragment of the scaffolding protein RanBP9 is increased in Alzheimer's disease brains and strongly potentiates beta-amyloid peptide generation. University of California, San Diego. Supported by NIA.
- Oddo et al. (2009) Genetically altering Abeta distribution from the brain to the vasculature ameliorates tau pathology. University of California, Irvine. Supported by NIA.
- Persaud-Sawin et al. (2009) Raft aggregation with specific receptor recruitment is required for microglial phagocytosis of Abeta42. NIEHS Intramural Program.

Looking to the Future: Translational Research

Although NIA's AD Translational Research Program has built significant momentum, much remains to be done. To this end, NIA held an advisory panel workshop on "Alzheimer's Disease Preclinical Therapy Development" in October 2010. This meeting convened leading therapy development experts from academia, biotechnology and pharmaceutical companies, and disease-focused foundations to develop recommendations for continued improvements in translational research efforts. ■

7 Testing Therapies for Prevention and Treatment

AD Clinical Trials

Clinical trials, which compare a potential new treatment with a standard treatment or a placebo (an inactive substance), are the only way to demonstrate whether a drug or other type of treatment is safe and effective in humans. The first stage of human trials, Phase I, involves testing a new treatment in a small group of healthy people to evaluate safety and tolerability. In Phase II, the treatment is given to a larger group of people with the disease to see if it is effective and to further evaluate safety. In Phase III, the last stage before a treatment is approved by the FDA, the treatment is given to a large group of people with the disease to confirm its effectiveness and monitor safety. Phase III trials are complex and expensive, involving hundreds or even thousands of people and often conducted over long periods of time.

In AD, some clinical trials focus on treatment—strategies to preserve cognitive function for as long as possible and alleviate behavioral or psychiatric problems. Other trials aim to delay progression from MCI to AD (secondary prevention). Still others focus on primary prevention—strategies to help cognitively healthy people reduce the risk of developing AD in the future.

NIA provides both infrastructure and funding opportunities for clinical development of AD therapeutics. The major clinical trial programs are the Alzheimer's Disease Cooperative Study (ADCS) and the AD Pilot Clinical Trials Initiative (see *additional information*, pages 53 and 56). These programs are in addition to continued support of investigator-initiated clinical trials for AD, MCI, and age-related cognitive decline.

Results from completed AD clinical trials

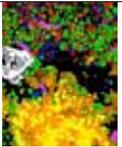
Two trials published in 2009 support the notion that AD progression can be slowed by targeting symptoms other than memory loss (for example, depression or sleep apnea, in the trials reported here). A third study argues against the popular belief that ginkgo biloba is effective in preventing cognitive decline. Eleven additional clinical trials reached completion this year; the results are still being analyzed and/or awaiting publication (see *Recently Completed Trials*, page 40).

Slowing progression to AD among people with MCI and depression

People with MCI are at higher risk for progressing to AD if they also have neuropsychiatric symptoms such as depression, apathy, or anxiety. The Alzheimer's Disease Cooperative Study (ADCS) examined the effects of depression on progression from amnesic MCI to AD in 208 people who had depression and 548 who did not. Symptoms of depression were assessed as a secondary outcome measure as part of the ADCS trial of donepezil (Aricept®), vitamin E, and placebo in participants with MCI. Study investigators reported that depressed patients were more likely to progress from MCI to AD than nondepressed patients. Also, the proportion of depressed patients progressing to AD was significantly lower for the donepezil group than for the combined vitamin E/placebo group for a little more than 2 years and remained marginally lower for up to 2.7 years. Nondepressed MCI patients who received donepezil initially exhibited a slower rate of progression compared to the vitamin E and placebo groups, but by 2 years there was no difference between the groups. These findings demonstrate that donepezil can reduce the increased risk of progression to AD in MCI patients with depressive symptoms (Lu PH et al., 2009).

Treatment of sleep apnea may slow cognitive decline

Obstructive sleep apnea is common among people with AD. The condition reduces brain oxygen levels and disrupts normal sleep patterns and thus may exacerbate cognitive and behavioral problems in people with AD. Researchers at the University of California, San Diego, supported by NIA and NCCR, evaluated the long-term effects of continuous positive airway pressure (CPAP) treatment in a small sample of 10 people who had participated in a larger 6-week randomized controlled trial of CPAP in AD patients with obstructive sleep apnea. Five of the participants had continued CPAP use for a little more than a year after the larger trial ended, and the other five had not. Those who continued CPAP use showed less cognitive decline and daytime sleepiness, greater stabilization of depressive symptoms, and better sleep quality than



Two trials found that AD progression can be slowed by targeting symptoms other than memory loss, such as depression or sleep apnea.

those who discontinued CPAP use. Importantly, caregivers of people in the CPAP group reported that their sleep was better and that the patients' behavioral disturbances improved (Cooke et al., 2009). The results of this small study suggest that long-term CPAP treatment for patients with AD and obstructive sleep apnea may slow cognitive decline and produce lasting improvements in sleep and mood. Larger randomized controlled trials are needed to test these findings. (See also *Amyloid and Sleep*, page 17.)

Ginkgo not effective in reducing risk of AD or cognitive decline

Ginkgo biloba is a widely marketed supplement used by people hoping to improve their cognitive health. The largest double-blind, randomized controlled trial to date, the Ginkgo Evaluation of Memory (GEM) study, included 3,069 community-dwelling older adults aged 72 to 96 years who had either normal cognition or MCI. The study, funded by NCCAM, NIA, and NHLBI, was conducted in six academic medical centers in the United States between 2000 and 2008. The primary analysis demonstrated that ginkgo was not effective in reducing risk of either AD or dementia overall. To learn if ginkgo has more subtle effects on cognitive health, GEM investigators analyzed additional data from this trial. They found no significant effect on cognitive decline or on more specific measures of memory, attention, visuospatial skill, language, and executive functioning (Snitz et al., 2009).

Recently Completed Trials

The following clinical trials supported by NIA were recently completed and are undergoing data analysis:

■ **ACCORD–MIND** (Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes)—NIA-funded primary prevention add-on trial to NHLBI's ACCORD trial
Principal Investigator (PI): Lenore Launer, NIA Intramural Research Program

■ **ESPRIT** (Evaluating Simvastatin's Potential Role in Therapy)
PI: Cynthia Carlsson, University of Wisconsin

■ **RECALL** (Rosiglitazone Effects on Cognition for Adults in Later Life)
PI: Suzanne Craft, University of Washington/VA Medical Center

■ **SNIFF 120** (Study of Insulin to Fight Forgetfulness, 120 Days)

PI: Suzanne Craft, University of Washington/VA Medical Center

■ **SHARP-P** (Seniors Health and Activity Research Program Pilot)

PI: Mark Espeland, Wake Forest University

■ **Transdermal Nicotine Treatment of MCI**

PI: Paul Newhouse, University of Vermont

Investigators are preparing and submitting results for publication from the following completed clinical trials supported by NIA:

■ **Huperzine A in Alzheimer's Disease**—ADCS

PI: Paul Aisen, University of California, San Diego

■ **VALID** (Valproate in Dementia)—ADCS

PI: Pierre Tariot, Banner Alzheimer's Institute

■ **CLASP** (Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease Study)—ADCS

PI: Mary Sano, Mount Sinai

■ **Antioxidant Trial** (Vitamins E and C, alpha lipoic acid, coenzyme Q)—ADCS

PI: Douglas Galasko, University of California, San Diego

■ **PREPARE** (Prevention of Postmenopausal Alzheimer Disease and Cognitive Loss with Replacement Estrogen)

PI: Mary Sano, Mount Sinai ■

Observational studies on treatments

There has been increasing interest in combination therapy for AD—simultaneous administration of two or more drugs or behavioral interventions. Investigators at the University of Pittsburgh Alzheimer's Disease Research Center looked at the effects of combined treatment with drugs from each of the two major classes currently approved to treat AD, cholinesterase inhibitors and an NMDA receptor blocker (memantine). They studied data from 943 probable AD patients at the Center from April 1983 to December 2004 who had been treated with a cholinesterase inhibitor alone, a cholinesterase inhibitor plus memantine, or no medication. The researchers found that those treated with two drugs delayed admission to a nursing home significantly longer than those who took just one drug (Lopez et al., 2009).

Cholinesterase inhibitors may ameliorate some types of behavioral symptoms in AD patients, but what happens when those drugs are stopped? Researchers at Brown University in Providence, RI, found that discontinuation of cholinesterase medications in nursing home residents with dementia who had been treated for 3 to 9 months was associated with some worsening behavioral changes and less time engaged in leisure-related activities compared to residents who received longer-term treatment (greater than 9 months) (Daiello et al., 2009).

Ongoing clinical trials

Alzheimer's Disease Cooperative Study

The ADCS, a large clinical trials consortium with sites throughout the United States and Canada, is a major initiative for AD clinical trials in the Federal Government. It addresses treatments for cognitive and behavioral symptoms (see *additional information* on page 53). The ADCS mission is to advance research in the development of clinical trial designs, instruments, and interventions that might be useful for treating patients with AD, particularly interventions that might not be developed by industry.

The most recent round of new ADCS studies, funded in October 2006, explore a variety of approaches:

■ **Docosahexaenoic acid (DHA)**. This completed trial examined whether treatment with DHA, an omega-3 fatty acid found in fish, would slow cognitive decline in people with AD. Observational studies associate high fish consumption with reduced risk of AD in people, and studies in mouse models of AD show that dietary DHA reduces

brain levels of beta-amyloid, oxidative damage associated with beta-amyloid, and neurotoxicity. The manuscript of the results has been accepted for publication in the *Journal of the American Medical Association (JAMA)*.

■ **Intravenous immunoglobulin (IVIg).** IVIg, a blood product that is administered intravenously, contains naturally occurring antibodies against beta-amyloid. Preliminary studies have shown that IVIg may improve cognition, and research has demonstrated that IVIg increases levels of anti-beta-amyloid antibodies in plasma and promotes clearance of beta-amyloid from CSF. This ongoing Phase III, double-blind randomized controlled trial will demonstrate whether IVIg is effective in treating AD.

■ **Home-based assessment.** This ongoing study, conducted in people aged 75 and older, will examine the development and use of three types of home-based assessments: 1) a low-technology telephone assessment, 2) a high-technology automated telephone assessment, and 3) a high-technology computer assessment. Cognition, daily functioning, mood, and other factors will be evaluated in each of the methods. These innovative assessment and data collection tools will be compared to traditional in-person measures. The findings from this study will provide information on how home-based assessments might be used in prevention trials. Such methods could significantly reduce the cost and increase the feasibility of participation in long-term clinical trials.

■ **Resveratrol.** This Phase II, double-blind randomized controlled trial, scheduled to begin in 2011, will evaluate the impact of resveratrol treatment on AD biomarkers and clinical outcomes in patients with mild to moderate AD. Resveratrol, a compound found in grapes and wine, has been shown in animal studies to be neuroprotective, and observational studies have shown that moderate consumption of red wine is associated with a lower incidence of AD.

NIH currently supports 37 active clinical trials, including pilot and large-scale trials, of a wide range of interventions to prevent, slow, or treat AD and/or MCI (see *Table 1* and *Table 2*). In particular, the NIA is currently funding seven primary prevention and six secondary prevention trials (*Table 1*). Of the primary prevention

trials, two are NIA-funded cognitive/AD measure add-ons to large NIH primary prevention trials that address a variety of other primary outcomes. One such trial is NHLBI's Systolic Blood Pressure Intervention Trial (SPRINT), which will evaluate the health effects of lowering systolic blood pressure from 140 mmHg to 120 mmHg. The add-on study, SPRINT-MIND, funded by NIA and NINDS, will assess the effect of lowering systolic blood pressure on cognitive decline and development of MCI and AD. The study will also use brain imaging to measure treatment effects on brain structure, including white matter lesions typical of vascular disease.

A number of the prevention trials are focusing on lifestyle interventions, including exercise, cognitive training, and a combination of the two. Other prevention trials examine how treatments for diabetes might reduce risk of AD. Diabetes is associated with the development of AD, and insulin regulation has been shown to be disrupted in AD. Two trials are examining the effect of the diabetes medications metformin and pioglitazone on cognition and progression to AD in MCI subjects who are also obese. The trial using pioglitazone compares the effects of the medication and exercise (endurance training) as well as a placebo.

Another recently completed diabetes-related trial (SNIFF-120) examined the effects of intranasal insulin in people with MCI or early AD. The idea is that restoring normal insulin function in the brain may provide cognitive benefit and slow disease progression. Administering insulin through the nose does not result in increased peripheral insulin levels, and the drug enters the brain within 15 minutes. Data analysis is ongoing for this trial.

Table 2 summarizes treatment trials to delay the progression of AD and to treat the behavioral disturbances typical of the disease. It also summarizes several trials that are testing biomarkers and performing feasibility studies. Taken together, the trials test a wide range of potential therapies. Several are due to be completed in the next 2 years; other longer trials will not finish data collection until 2014 or later. It is important to note that the year the trial is completed does not include the additional time necessary for analysis of data and publication of findings.

TABLE 1. Ongoing AD/MCI Prevention Clinical Trials Funded by NIA

Trial Name	Principal Investigator/ Institution	Intervention	Population	Type of Trial	Anticipated Completion Date
Antioxidants					
PREADVISE (Prevention of Alzheimer's Disease by Vitamin E and Selenium)*	Frederick Schmitt, Univ. of Kentucky	Vitamin E, Selenium, Vitamin E + Selenium	Men age 60-90	Primary Prevention	2014
Vitamin E in Aging Persons with Down Syndrome	Arthur Dalton, NY State Inst. for Basic Research in Developmental Disabilities	Vitamin E	People age 50+ with Down syndrome, at high risk of developing AD	Primary Prevention	2012
Omega-3 Fatty Acids and Antioxidants					
AREDS2 (Age-Related Eye Disease Study 2)†	John Paul San Giovanni (Study Director), NEI	Macular xanthophylls (lutein and zeaxanthin) and/or omega-3 fatty acids (DHA and EPA)	People age 50-85 with age-related macular degeneration (AMD) in both eyes or advanced AMD in one eye	Primary Prevention	2015
Cardiovascular					
ASPREE (Aspirin in Reducing Events in the Elderly)	Richard Grimm, Berman Center for Outcomes & Clinical Research; John McNeil, Monash Univ.	Aspirin	Healthy adults age 70+	Primary Prevention	2017
SPRINT-MIND (Systolic Blood Pressure Intervention Trial-MIND)*	David Reboussin, Wake Forest Univ.	Blood pressure lowering to <140 mmHg versus <120 mmHg	Adults age 55+ with systolic blood pressure of 130 mmHg or higher, history of cardiovascular disease, high risk for heart disease	Primary Prevention	2017
Hormones					
ELITE (Early Versus Late Intervention with Estradiol)	Howard Hodis, Univ. of Southern California	17 β -estradiol	Healthy early (less than 6 years) or late (10 years+) menopausal women	Primary Prevention	2014
SMART (Somatotrophics, Memory, and Aging Research Trial)	Michael Vitiello, Univ. of Washington	Growth hormone releasing hormone (GHRH)	People with MCI and healthy older adults age 55-80	Secondary Prevention	2011
Testosterone Supplementation in Men with MCI	Monique Cherrier, Univ. of Washington	Testosterone	Older men with MCI and low testosterone	Secondary Prevention	2011

Trial Name	Principal Investigator/ Institution	Intervention	Population	Type of Trial	Anticipated Completion Date
Diabetes					
Metformin in Amnestic MCI	Jose Luchsinger, Columbia Univ.	Metformin	Overweight/obese older adults with MCI	Secondary Prevention	2012
Pioglitazone & Exercise Effects on Older Adults with MCI and Metabolic Syndrome	Robert Schwartz, Univ. of Colorado, Denver	Pioglitazone	Overweight/obese older adults with MCI	Secondary Prevention	2012
Exercise, Cognitive Training					
Exercise Versus Cognitive Interventions for Elders at Risk for Dementia	David Loewenstein, Mount Sinai Medical Center, Miami	Cognitive training, aerobic exercise training, cognitive training + aerobic exercise training	People with MCI	Secondary Prevention	2012
Lifestyle Interventions and Independence for Elders (LIFE)	Marco Pahor, Univ. of Florida	Aerobic exercise, resistance, and flexibility exercises	Adults age 70+	Primary Prevention	2015
Memory Training Intervention in Mild Cognitive Impairment	Miriam Mintzer, Johns Hopkins Univ.	Repetition lag training procedure (RLTP)	People with MCI	Secondary Prevention	2014
<p>Note: For information on new and currently recruiting trials, visit: www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials or www.ClinicalTrials.gov.</p> <p>* NIA-funded primary prevention add-on trials: PREADVISE (add-on to National Cancer Institute's SELECT trial); SPRINT-MIND (add-on to National Heart, Lung, and Blood Institute's and National Institute of Diabetes and Digestive and Kidney Diseases' SPRINT trial; co-funded with the National Institute of Neurological Disorders and Stroke).</p> <p>† Co-funded primary prevention trial: AREDS2 (National Eye Institute, lead institute).</p>					

TABLE 2. Ongoing AD/MCI Treatment, Biomarker, and Feasibility Clinical Trials Funded by NIA

Trial Name	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Cardiovascular				
Effects of Simvastatin on CSF AD Biomarkers in Cognitively Normal Subjects	Gail Li, Univ. of Washington	Simvastatin	Cognitively normal adults age 45-64	2013
Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for AD	Cynthia Carlsson, Univ. of Wisconsin, Madison	Simvastatin	Adults at high risk of AD (family history, APOE4) age 45-65	2013
Hormones				
Alzheimer's Disease: Potential Benefit of Isoflavones	Carey Gleason, Univ. of Wisconsin, Madison	Novasoy (soy isoflavones–phytoestrogens)	People with AD	2010
Estrogen Receptor-beta phytoSERMs for Management	Lon Schneider, Univ. of Southern California	ER2-selective phytoestrogens (phytoSERMs–selective estrogen receptor modulators)	Postmenopausal women age 50-59	2014
Raloxifene for Women with Alzheimer's Disease	Victor Henderson, Stanford Univ.	Raloxifene	Older women with AD	2012
Exercise, Cognitive Training				
Aerobic Fitness in Slowing the Progression of AD	Jeffrey Burns, Univ. of Kansas	Aerobic exercise training	People with AD	2014
Conversational Engagement as a Means to Delay AD Onset	Hiroko Dodge, Oregon Health & Science Univ.	Internet-based conversational engagement	Adults age 75+	2014
Effects of Standardized Aerobic Exercise Training on Neurocognition and Neurodegeneration	Thomas Obisesan, Howard Univ.	Aerobic exercise training	African Americans with AD	2012
MCI: Cerebrovascular Dysfunction and Exercise Training	Rong Zhang & Hanzhang Lu, Univ. of Texas Southwestern	Endurance exercise training	People with MCI	2014
Neural Effects of Exercise, Cognitive, or Combined Training in AD At-Risk Elders	Stephen Rao, Cleveland Clinic	Cognitive training, aerobic exercise training, cognitive training + aerobic exercise training	Healthy adults age 65-85	2012

Trial Name	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Other Interventions				
AAV-NGF Gene Delivery in Alzheimer's Disease	Paul Aisen, Univ. of California, San Diego	Nerve growth factor (NGF) gene delivery	People with AD	2014
ADMIT (Alzheimer's Disease Multiple Intervention Trial)	Chris Callahan, Indiana Univ.	Home-based occupational therapy	People with AD	2016
fMRI Activation in Mild Cognitive Impairment	Michela Gallagher, Johns Hopkins Univ.	Levetiracetam	People with MCI	2012
Glucose Regulation and Memory in Alzheimer's Disease	Suzanne Craft, Univ. of Washington	Improved insulin resistance, 3 studies: diet, triglyceride emulsion, rosiglitazone	People with AD and age-matched healthy older adults	2016
Intravenous Immunoglobulin (IVIg) for Treatment of AD (passive immunization)*	Norman Relkin, Weill Medical College, Cornell Univ.	IVIg	People with AD	2013
Lipoic Acid and Omega-3 Fatty Acids in AD	Lynne Shinto, Oregon Health & Science Univ.	Lipoic acid and/or omega-3 fatty acids (DHA and EPA)	People with AD	2014
Thalidomide as BACE1 Inhibitor in AD	Marwan Sabbagh, Banner Sun Health Research Inst.	Thalidomide	People with AD	2012
Therapeutic Effects of Cataract Removal in AD	Grover Cleveland Gilmore, Case Western Reserve Univ.	Cataract removal surgery	People with AD	2014
Behavioral Disturbance Interventions				
ADMET (Apathy in Alzheimer's Disease Methylphenidate Trial)	Jacobo Mintzer, Medical Univ. of South Carolina; Krista Lanctot, Sunnybrook Health Sciences Center; Paul Rosenberg, Johns Hopkins Univ.	Methylphenidate	People with AD	2012
Antipsychotic Discontinuation in AD	Davangere Devanand, NYSPI/Columbia Univ.	Risperidone	People with AD	2011
CITAD (Citalopram Treatment for Agitation in Alzheimer Dementia)	Constantine Lyketsos, Johns Hopkins Univ.	Citalopram	People with AD	2014
Light Treatment for Sleep/Wake Disturbances in AD	Jerome Yesavage, Stanford Univ.	Light treatment	People with AD and their caregivers	2010
Prazosin Treatment for Disruptive Agitation in Alzheimer's Disease	Elaine Peskind, Univ. of Washington	Prazosin	People with AD	2013
TREA (Treatment Routes for Exploring Agitation)	Jiska Cohen-Mansfield, Research Inst. on Aging	TREA-systematic approach to individualizing nonpharmacological interventions for persons with dementia	Nursing home residents with AD/dementia	2012

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

*Alzheimer's Disease Cooperative Study trial

Looking to the Future: Biomarkers and AD Clinical Trials

AD clinical trials have progressed from a focus on symptomatic treatment to disease modification to halting the progression from MCI to AD (secondary prevention) to preventing MCI/AD (primary prevention). Many researchers believe that prevention trials that are started before AD pathology has taken hold have the best chance of a positive result. However, the conduct of prevention trials needs to become more efficient by reducing the time and/or number of subjects involved, each of which would reduce the cost. It is clear from completed AD prevention trials, such as ADAPT (AD Anti-Inflammatory

Prevention Trial) and GEMS (Ginkgo Evaluation of Memory Study), that using as endpoints the progression from normal cognition to a clinical diagnosis of MCI/AD or changes in cognition takes 8 to 10 years and costs tens of millions of dollars.

Based on the results of ADNI and similar imaging and fluid biomarker studies, the AD clinical trials community is starting to consider the use of biomarkers as potential endpoints in prevention trials. Biomarkers such as structural MRI, amyloid PET imaging, FDG PET, and CSF protein concentrations may ultimately provide a window into the course of the

disease in the living brain. Their use in clinical trials may show whether a particular intervention affects underlying brain pathology more quickly than traditional clinical/neuropsychological outcome measures would. These biomarkers could also be used as selection factors to determine which normal subjects, for example, have significant beta-amyloid loads in their brains and may be at higher risk of progression to MCI/AD in a clinical trial. Discussions about the feasibility and cost of such biomarker prevention trials are ongoing, but this is certainly an area of research that will be much more prominent in the near future. ■

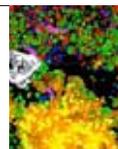
Clinical Trials to Maintain or Improve Cognitive Function with Age

As the population ages, there is growing interest not only in preventing AD but in maintaining general good cognitive function and health throughout life. Although modest in comparison with AD, cognitive decline associated with normal aging significantly compromises quality of life and independent living. Terms like “use it or lose it” refer to mental fitness and perhaps how exercise or diet might keep cognitive decline at bay. NIA is testing a number of interventions to see if they might directly benefit cognitive health. As these tests move forward, NIH encourages the adoption of healthy lifestyle practices, as some, like exercise and social engagement, are known to reduce risk of other diseases or are otherwise important as people age.

Trial results

There is widespread popular belief that mental fitness can be increased with consistent brain exercise (e.g., crossword puzzles, Web-based games). To date, clinical trials have yielded little clear evidence to support this notion. This year, however, two clinical trials reported that different cognitive training protocols improved certain aspects of cognitive function in older adults. The Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study tested a computer-based training intervention designed to improve speed and accuracy of auditory information processing in a randomized trial with 487 cognitively normal older adults age 65 and older in San Francisco and Los Angeles, CA, and Rochester, MN.

Investigators found that training on one particular set of auditory tasks can improve a person’s performance



NIA is testing a number of different interventions to see if they might directly benefit cognitive health.

on other auditory tasks and that participants who received training later showed improved performance on not only the specific exercises they had been trained with, but other auditory memory and attention exercises as well. (Smith et al., 2009)

In another study of 66 cognitively normal adults ages 65 to 75 at Wake Forest University in Winston-Salem, NC, supported by NIA, NINDS, and NCRR, researchers observed significant benefits of an intervention aimed at improving the brain's ability to focus on one set of visual or auditory signals while resisting distraction by irrelevant ones (Mozolic et al., 2009). These trials showed training effects on highly related tasks, but leave the question unanswered as to what sort of brain exercise, or combination of exercises, could improve cognitive performance more broadly.

The Experience Corps study from Johns Hopkins University in Baltimore, MD, supports the concept that activities aimed at enriching life experience can lead to positive changes in specific brain circuits in older people. Employing an “immersion” intervention that combined physical, social, and cognitive activity simultaneously through participation in a volunteer program for young children in Baltimore City public schools, the researchers examined cognitive improvements and brain function in eight older female study participants who were already in the study compared to nine matched controls who were on the wait list to participate. The study revealed improved executive function—the ability to exercise control over cognitive function, such as switching quickly and accurately from task to task or carrying out a sequence of tasks appropriately—in the study participants that was

correlated with increased activity in prefrontal cortex relative to controls (Carlson et al., 2009). The results indicate that an intervention designed to promote better cognitive function through everyday activity may enhance plasticity in relevant brain regions. Larger studies will be necessary to validate these findings.

Additional advance in remediating age-related cognitive impairment:

- Hertzog et al. (2009) Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced?

Ongoing trials on age-related cognitive function

NIA currently supports 27 active clinical trials, including pilot and large-scale trials as well as treatment studies, to better understand the mechanisms related to cognitive decline and to better target interventions (see *Table 3*). Approaches include cognitive training, exercise, nutritional supplementation, hormone therapy, combinations of these, and pharmacological intervention. In addition, interventions to control hypertension and to regulate kidney dialysis to improve cognitive function are underway. Even though the range of interventions is wide, the trials share the common focus of trying to remediate age-related cognitive decline.

TABLE 3. Ongoing Age-Related Cognitive Decline Clinical Trials Funded by NIA

Trial Name	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Cognitive Training				
Active Interventions for the Aging Mind	Denise Park, Univ. of Texas, Dallas	Cognitive enrichment through training in digital photography or quilting	Healthy adults age 60+	2012
Brain-Based Approach to Enhancing Executive Control Functions in Healthy Aging	Mark D'Esposito, Univ. of California, Berkeley	Cognitive training	Healthy adults age 50+	2012
Expanding the Implementation of an Effective Cognitive Aging Intervention	Helga Noice, Elmhurst College	Cognitive enrichment through training in acting	Healthy adults age 65+	2010
Experience Corps Trial: Improving Health in Older Populations through Generativity	George Rebok, Johns Hopkins Univ.	Health promotion for older adults embedded within a social engagement program (volunteering in schools)	Healthy adults age 60+	2011
Senior Odyssey: A Test of the Engagement Hypothesis of Cognitive Aging	Elizabeth Stine-Morrow, Univ. of Illinois, Urbana-Champaign	Cognitive enhancement through participation in the Odyssey of the Mind program	Healthy adults age 60+	2012
Speed of Processing Modes to Prevent Cognitive Decline in Older Adults	Fredric D. Wolinsky, Univ. of Iowa	Comparison of standard versus enhanced visual processing training	Healthy adults age 50+	2011
Omega-3 Fatty Acids and Antioxidants				
Omega-3 and Blueberry Supplementation in Age-Related Cognitive Decline	Robert Krikorian, Univ. of Cincinnati	Omega-3 and blueberry supplements	Healthy adults age 62-80	2012
Cardiovascular				
Aging and the Renin-Angiotensin System in Elderly Hypertensive Individuals	Ihab Hajjar, Hebrew Rehabilitation Center for Aged	Angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, diuretic	Adults age 60+ with uncontrolled hypertension and cognitive impairment	2012

Trial Name	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Hormones				
Estrogen Effects on Cholinergic Function in Older Women	Paul Newhouse, Univ. of Vermont	Acute or chronic 17 β -estradiol + muscarinic and nicotinic cholinergic antagonist	Healthy women age 50+	2014
Estrogen Use in Protection from Cognitive Decline	Natalie Rasgon, Stanford Univ.	Continuation of or removal from postmenopausal estrogen treatment	Healthy women age 50-65	2011
Hormones and Cognitive Processing in Early Postmenopausal Women	Yolanda Smith, Univ. of Michigan	Estradiol and prometrium (progesterone)	Healthy early postmenopausal women age 45-55	2011
KEEPS-CA (Kronos Early Estrogen Prevention Study—Cognitive and Affective Study)	Sanjay Asthana, Univ. of Wisconsin, Madison	Oral conjugated equine estrogen and transdermal 17 β -estradiol	Healthy postmenopausal women age 42-58	2012
Mechanisms for Sex Steroid Effects on Cognition in Aging	Jeri Janowsky, Oregon Health & Science Univ.	Gonadotropin releasing hormone agonist, testosterone, testosterone + aromatase inhibitor	Healthy adults age 60-80 and 25-35	2009
Sex Steroids and Cognition in Postmenopausal Women	Elliot Hirshman, George Washington Univ.	Dehydroepiandrosterone (DHEA)	Healthy postmenopausal women age 55-65 and 70-80	2011
Testosterone Trial	Peter Snyder, Univ. of Pennsylvania	Testosterone gel	Older men	2015
Exercise				
Cognitive Benefits of Aerobic Exercise Across the Lifespan	Yaakov Stern & Richard Sloan, Columbia Univ.	Stretching/toning or aerobic conditioning	Healthy adults age 25-65	2015
Dose-Response Study of Exercise in Older Adults	Jeffrey Burns, Univ. of Kansas	Aerobic exercise	Healthy older adults	2012
Exercise, Age-Related Memory Decline, and Hippocampal Function	Scott Small & Richard Sloan, Columbia Univ.	Exercise training or maintenance of sedentary lifestyle	Healthy adults age 20-65	2015
Exercise, Cognitive Training				
Brain and Cognitive Changes after Reasoning or Physical Training in Cognitively Normal Seniors	Sandra Chapman, Univ. of Texas, Dallas	Cognitive training, aerobic exercise	Adults age 60-75	2011
Combined Exercise and Cognitive Training Intervention in Normal Aging	Yaakov Stern, Columbia Univ.	Aerobic exercise and cognitive training	Healthy adults age 65-75	2012

Trial Name	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Exercise, Cognitive Training (Continued)				
Combining Exercise and Cognitive Training to Improve Everyday Function	Ellen Binder & Mark McDaniel, Washington Univ.	Aerobic exercise and cognitive training	Healthy adults age 55-75	2012
Impact of Exercise and Engagement on Cognition in Older Adults	Denise Park, Univ. of Texas, Dallas	Walking, exercise regimen (aerobic tasks); quilting, photography (cognitive tasks)	Healthy adults age 60-85	2011
Improvement of Visual Processing in Older Adults	Karlene Ball, Univ. of Alabama, Birmingham	Combination of visual processing training and exercise	Healthy adults age 65+	2011
Influence of Fitness and Cognitive Training on Brain and Cognition	Arthur Kramer, Univ. of Illinois, Urbana-Champaign	Aerobic training (walking), combined aerobic training/ cognitive training (dancing)	Adults age 60-75	2015
Tai Chi and Guided Autobiography for Remediation of Age-Related Cognitive Decline	Victor Henderson, Stanford Univ.	Low-impact Tai Chi exercise and autobiographical writing	Healthy adults age 70+	2012
Other				
Guanfacine Treatment for Prefrontal Cognitive Dysfunction in Elderly Subjects	Christopher Van Dyck, Yale Univ.	Guanfacine	Healthy adults age 75+	2011
Mechanisms of Cognitive Impairment in Chronic Kidney Disease	Manjula Kurella Tamura, Stanford Univ.	Frequent hemodialysis	Adults age 55+	2012

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

8 Supporting AD Caregivers

Family members often bear much of the burden of caring for people with AD. This includes the time and energy spent on caretaking, worry about the mental and physical decline of a loved one, and frustration in trying to communicate with and help them. While caregiving can be rewarding, it can also be incredibly stressful and contribute to physical and emotional health problems for the caregiver. Understanding caregivers' needs and health risks and supporting them are critical for reducing the personal and public health burden of AD.

Starting in 1995, NIA and NINR funded two clinical trials, REACH I and REACH II, to develop and test strategies for helping dementia caregivers manage their stress and emotional burden. The interventions included education on dementia, training in specific caregiving skills, and encouragement and techniques for physical and emotional self-care. The REACH findings are now being put into practice through two Federal agencies, the Veterans Administration (VA) and the Administration on Aging (AoA).

The VA successfully used REACH strategies in a demonstration project with 19 of its home health care services and is now considering the use of REACH throughout the VA system. AoA's REACH OUT Program is beginning to implement these strategies through local social service agencies. Researchers reported on one of the AoA-funded efforts, a partnership between the Alabama Department of Senior Services and the University of Alabama. An analysis of 236 caregivers showed significant improvement in caregivers' sense of burden, social support, depression, and health, as well as care recipient behavior problems and mood (Burgio et al., 2009).

Efforts are underway to develop tests to gauge the emotional well-being of caregivers and identify areas where they may need support. One of these, the Risk Appraisal Measure (RAM), was tested on participants in the REACH II trial. The test probes six areas in which caregivers are at risk: depression, burden, self-care, health behavior, physical safety, and problem behaviors in the care recipients. RAM shows promise as a test to identify caregivers who might benefit from assistance in specific areas, for use in future research on supportive measures, and as a guide for clinicians and community health agencies (Czaja et al., 2009).

Occupational therapy

Participation in meaningful activity is known to promote well-being in older adults, and its potential to reduce symptoms of dementia is now receiving more attention. The Tailored Activity Program (TAP) is a home-based occupational therapy plan that assesses the interests and capabilities of individuals with dementia, provides a program of customized activities for each individual, and trains their families to use those activities as part of their daily care routines. A preliminary study of 57 people with dementia and their caregivers, conducted by researchers at Thomas Jefferson University in Philadelphia, PA, and funded by NIMH, found that the TAP program improved overall levels of pleasure and engagement in the demented individuals, as assessed by their caregivers. It also reduced the extent to which caregivers were upset by the behavioral symptoms of the individuals they were caring for, and improved their sense of skill and personal control in dealing with behavioral problems (Gitlin et al., 2009).

Additional advances in support for caregivers:

- Hilgeman et al. (2009) Testing a theoretical model of the stress process in Alzheimer's caregivers with race as a moderator. University of Alabama, Tuscaloosa. Supported by NIA and NINR.
- Mitchell et al. (2009) The clinical course of advanced dementia. Hebrew SeniorLife Institute for Aging Research, Boston. Supported by NIA.
- Norton et al. (2009) Caregiver-recipient closeness and symptom progression in Alzheimer disease. Utah State University. Supported by NIA.
- Skarupski et al. (2009) Race differences in emotional adaptation of family caregivers. Rush University. Supported by NIA.
- Vitaliano et al. (2009) Depressed mood mediates decline in cognitive processing speed in caregivers. University of Washington. Supported by NIDDK, NCRR, and NIMH.



Advancing the Future of AD Research: RESOURCES AND COLLABORATION

Alzheimer's researchers are gaining better understanding of AD pathology and using new insights to develop therapies more likely to be successful in clinical trials. The outpouring of AD-related applications in response to the 2009 American Recovery and Reinvestment Act (ARRA) initiative, many of which were successful in review, demonstrated the vitality of new ideas in the scientific community. Several of these ideas, now supported by ARRA and non-ARRA funds, resulted in large collaborative projects designed to address the multifaceted nature of aging and AD research. However, the profusion of good ideas combined with investment in more expensive collaborative grants has its downside, and that is that the overall success rate for grants is very low and may be difficult to improve in the current economic climate.

As planners and stewards of Federally funded science, NIA must both develop and sustain the research infrastructure necessary for productive research and at the same time phase out approaches that may have outlived their usefulness. In this endeavor, it is critical to maintain and encourage lines of research that hold promise for new therapies while reducing investment in research less crucial to the mission. The Institute keeps current and looks to the future in several ways—by convening and collaborating in forward-looking workshops in these new areas; by working within NIA to vigorously

discuss new science and opportunities for new investments; and by partnering with other NIH Institutes and Federal agencies, not-for-profit groups, and industry.

Collaboration has been key for NIA's coordinating mechanisms and initiatives. By pooling and sharing data widely, and efficiently using the well-established AD research infrastructure, NIA is advancing AD science even within the limits of existing resources.

Research Infrastructure

NIA Intramural Research Program (IRP). In addition to funding a broad portfolio of aging-related and AD research at institutions across the country, NIA supports its own laboratory and clinical research program based in Baltimore, MD. The NIA IRP focuses on understanding age-related changes in physiology and behavior, the ability to adapt to biological and environmental stresses, and developing insight about the pathophysiology of age-related diseases, including AD. Laboratory research ranges from basic science, such as neurogenetics and cellular and molecular neurosciences, to personality and cognition. The IRP also leads the Baltimore Longitudinal Study of Aging, America's longest-running scientific study of human aging, begun in 1958, along with other clinical research studies.

Alzheimer's Disease Centers. NIA's Alzheimer's Disease Centers (ADCs) form the backbone of the national AD research effort. These multidisciplinary centers, located

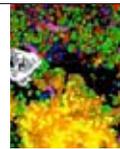
at 30 institutions nationwide, promote research, training and education, and technology transfer. With participation by the community, the Centers conduct longitudinal multicenter and collaborative studies of AD diagnosis and treatment, age-related neurodegenerative diseases, and predictors of future change in people without dementia that may indicate the initial stages of development of AD. Complementary studies, such as imaging studies and autopsy evaluations, also are conducted at ADCs. All people enrolled in the Centers receive a standard annual evaluation. Data from those evaluations are collected and stored by the National Alzheimer's Coordinating Center (NACC, see below) as the Uniform Data Set.

The ADCs serve as sites for other major studies, such as the ADCS and ADNI (see descriptions below). Recently, DNA from 10,000 individuals enrolled in the ADCs was collected for use by the Alzheimer's Disease Genetics Consortium (ADGC) for whole genome analysis.

National Alzheimer's Coordinating Center (NACC). NIA established NACC in 1999 with the goal of pooling and sharing data on participants in ADC studies. The longitudinal clinical data from living subjects and the brain material and pathological data collected at autopsy give scientists opportunities to conduct clinical-pathological studies with much larger patient samples collected from multiple centers than they could working independently. NACC helps coordinate these studies and, in some cases, provides limited funding.

By 2009, NACC had collected information on more than 90,000 ADC study participants and neuropathologic data on more than 10,000 brains from autopsied participants. Much of these data and autopsy materials are available to qualified AD researchers worldwide. Since 2000, there have been over 60 publications by external researchers using NACC data, 51 publications by NACC personnel, and 95 publications from NACC-funded collaborative ADC projects.

One such study quantitatively assessed pathological plaques and neurofibrillary tangles at autopsy in 97 nondemented participants age 60 years or older (average age 84 years) who had been enrolled in one of seven different ADCs. While all of the research subjects had been



As planners and stewards of Federally funded science, NIA must develop and sustain the infrastructure necessary for productive research.

determined not to have dementia before death, some did have mild cognitive impairment. The researchers concluded that it is likely that neuropathological processes related to AD in persons without dementia are associated with this mild cognitive decline. By age 80-85 years, many nondemented older adults had substantial AD pathology. (Price et al., 2009)

The NACC data are helping to reveal different symptom patterns in different subsets of AD patients—patterns that would not have become apparent without analyzing a dataset of this size. NACC has also been involved in coordinating other NIA efforts, such as the identification and selection of appropriate postmortem material from the individual ADCs to send to the National Cell Repository for Alzheimer's Disease for use in the ADGC GWAS studies.

Alzheimer's Disease Cooperative Study (ADCS). NIA launched the ADCS in 1991 to develop and test new interventions and treatments for AD that might not otherwise be developed by industry. Operated under a cooperative agreement with the University of California, San Diego, the large clinical trials consortium, a significant component of NIA's AD Prevention Initiative, comprises more than 75 sites throughout the United States and Canada. The ADCS focuses on testing agents that lack patent protection, patented drugs

that are marketed for other indications, and novel compounds developed by individuals, academic institutions, and small biotech companies. It also develops new evaluation instruments for clinical trials and innovative approaches to clinical trial design. The group also provides infrastructure support to other Federally funded clinical efforts, including ADNI and the Dominantly Inherited Alzheimer Network (DIAN, a study of familial AD). (See *Alzheimer's Disease Cooperative Study*, page 40, for a summary of current trials and studies conducted by the ADCS.)

The National Cell Repository for Alzheimer's Disease (NCRAD). This NIA-funded repository, located at Indiana University Medical Center in Indianapolis, provides resources that help researchers identify the genes that contribute to AD and other types of dementia. NCRAD collects and maintains biological specimens and associated data on almost 43,000 people from a variety of sources, including genetically informative, phenotypically well-characterized families with multiple individuals affected by AD, as well as people enrolled in ADNI, ADGC, and the Ginkgo Evaluation of Memory Study. Qualified research scientists may apply to NCRAD for samples and data to conduct genetic research. Since it was funded, more than 52,000 DNA samples have been requested and sent to investigators across the U.S., resulting in 204 publications.

NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS). Located at the University of Pennsylvania, NIAGADS is a Web-based data warehouse for AD genetic data. All genetic data derived from NIA-funded studies on the genetics of late-onset AD are deposited at NIAGADS, another NIA-approved site, or both. Data from GWAS that are stored at NIAGADS are also made available through the database of Genotype and Phenotype (dbGaP) at the National Library of Medicine's National Center for Biotechnology Information, which was developed to archive and

distribute the results of large-scale GWAS analyses. Through dbGaP, data sets from multiple GWAS done on different platforms can be merged, and data from thousands of study participants can be analyzed together, increasing the probability of gene discovery.

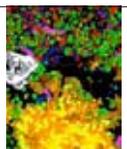
Initiatives

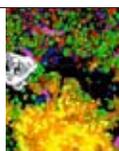
Alzheimer's Disease Neuroimaging Initiative (ADNI).

In 2004, NIA launched this groundbreaking initiative, the largest public-private partnership to date in AD research. The goal was to find neuroimaging and other biological markers that could be used to detect AD progression and measure the effectiveness of potential therapies. The study recruited 800 participants, a mix of cognitively healthy people and those with AD or MCI. To speed the pace of analysis and findings, ADNI investigators agreed to make their collected data widely available. MRI and PET scan brain images as well as clinical, genetic, and fluid biomarker data are available to qualified researchers worldwide through a Web-based database.

The first phase of ADNI has already borne remarkable fruit: more than 170 papers using ADNI data have been published from investigators around the world, and many more will come as further data are collected and analyzed. These early findings have generated excitement about using brain and fluid markers to identify people who may be at risk for developing AD or for cataloguing their pace of deterioration. Accomplishments include new findings about how changes in the structure of the hippocampus may help detect disease progression and effectiveness of potential treatments, and the establishment of biomarker and imaging measures that predict risk for cognitive decline and conversion to dementia in this clinical cohort. (See *Biomarkers and ADNI*, page 33, for descriptions of several published studies.) The success of ADNI has inspired similar efforts in Europe, Japan, and Australia. A follow-on effort, ADNI-GO, was launched with ARRA funds in 2009, and ADNI 2 was launched in fall 2010. ADNI 2 will enroll a new cohort

ADNI has already borne remarkable fruit: more than 170 papers using ADNI data have been published from investigators around the world.





*The ADGC
confirmed the likely role of
three newly discovered late-onset
AD genes and is now working
to confirm additional genes.*

of participants with very early MCI and continue to follow participants in the other ADNI cohorts, with the goal of identifying and tracking early changes in the brain before the onset of AD symptoms.

Alzheimer's Disease Genetics Initiative (ADGI) and Alzheimer's Disease Genetics Consortium (ADGC). The study of AD genetics is complicated by the likelihood that the risk of late-onset AD is influenced by many genes, each of which confers a relatively small risk. Identifying these genes requires analyzing the genomes of large numbers of people. ADGI was launched in 2003 to identify at least 1,000 families containing both members who have late-onset AD and members who do not. The ADGC was funded in 2009 to support the use of large-scale, high-throughput genetics technologies by researchers studying late-onset AD.

The ADGC confirmed the likely role of three newly discovered genes in contributing to the risk of LOAD (see *Discovering New Genetic Mechanisms*, page 21) and is now working to confirm additional genes in collaboration with research groups in Europe. In addition to providing additional insight into AD pathogenesis and suggesting therapeutic targets, these new gene discoveries may also one day help predict who is at risk for AD.

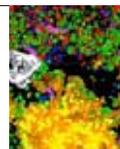
Revising AD Diagnostic Criteria. NIA and the Alzheimer's Association organized two meetings in spring 2009 to discuss new data and technologies for improving the clinical diagnosis of AD and a research agenda for diagnosis at earlier stages of the disease. The current system of AD classification has deficiencies that limit its utility for drug development, research, and practice. Existing standards for diagnosis of the dementia stage of AD, the NINCDS-ADRDA clinical criteria, are more than 25 years old and do not address very early and presymptomatic AD. They were developed without the knowledge available from more recent studies on the epidemiology of AD, clinical-pathologic correlations, and diagnostic imaging and fluid biomarkers.

Following discussion at the meetings, three working groups were set up, one to revise the NINCDS-ADRDA criteria for Alzheimer's dementia; a second to better define the stage(s) between normal and Alzheimer's dementia, often termed MCI; and a third to examine factors in older individuals with no symptoms or very minor symptoms that may predict MCI and Alzheimer's dementia.

The overall goals of this project are to better define the natural history of AD, from its asymptomatic stages to clinically diagnosed dementia, and to attempt to relate clinical symptoms as they emerge to underlying pathophysiology. An overarching goal is to stimulate research on how imaging and fluid biomarkers can contribute to the identification of people at risk for cognitive dysfunction and to better diagnose them after symptoms appear.

The groups presented their preliminary proposals at the International Conference on Alzheimer's Disease (ICAD) in July 2010. The three committees are reviewing public comments and will publish proposed guidelines in a scientific journal in 2011. The guidelines, primarily for use in research studies, will likely be revisited and revised periodically as new data emerge from imaging and biomarker research studies.

AD Translational Initiative. Launched in 2004, the AD Translational Initiative supports early drug discovery and drug development research by academic scientists and small biotechnology companies, with the goal of



The AD Translational Initiative is broadening the range of potential treatments and therapeutic targets by supporting critical research steps not traditionally supported by industry.

finding ways to treat and prevent AD, MCI, and age-related cognitive decline. This effort is broadening the range of potential treatments and therapeutic targets by supporting critical steps of translational research that are traditionally not supported by the pharmaceutical industry. In 2009, the NIA committed \$5 million to continue two funding initiatives for early drug discovery and pre-clinical drug development through 2012. (See *more about translational research*, page 35.)

AD Pilot Clinical Trials Initiative. This initiative, begun in 1999, is aimed at increasing the number and quality of preliminary clinical evaluation of interventions for AD, MCI, and age-associated cognitive decline. The goal is not to duplicate or compete with pharmaceutical companies but to encourage, complement, and accelerate the process of testing new, innovative, and effective treatments. Initially focused on drug interventions, the program has been broadened to nonpharmacologic as well as pharmacologic interventions. NCCAM and NINR also participate in this initiative. (See *AD Clinical Trials*, page 38, for summaries of pilot clinical trials.)

Research Partnership on Cognitive Aging. Through the Foundation for NIH, NIA and the McKnight Brain Research Foundation convened a Cognitive Aging Summit in 2007 focused on healthy brain aging and function. This summit helped galvanize the field and served as a catalyst for two subsequent research initiatives. The first, “Remediation of Age-Related Cognitive Decline,” is funding research on pilot interventions to reverse age-related decline or maintain successful function. The second, “Neural and Behavioral Profiles of Cognitive Aging,” is funding studies to understand neural and behavioral mechanisms involved the maintenance of cognitive health and to identify characteristics that distinguish normal age-related change from patho-

logical decline. A second Summit, held in October 2010, shared progress from funded studies and identified future research directions.

NIH Toolbox for Assessment of Neurological and Behavioral Function. Awarded in 2006, this contract is supported by the NIH Blueprint for Neuroscience Research and the NIH Opportunity Network for Basic Behavioral and Social Science Research. The goal is to develop a set of brief tests to assess cognitive, sensory, motor, and emotional function, particularly in studies with many people (such as epidemiological studies and clinical trials). The tests will be available in English and Spanish and applicable for use in individuals age 3 to 85, enabling direct comparison of cognitive and other abilities at different ages across the lifespan.

NIH Blueprint for Neuroscience Research Initiative on the Human Connectome Project. The Human Connectome Project was started in 2010 to develop and share knowledge about the structural and functional connectivity of the healthy human brain. This collaborative effort will use state-of-the-art imaging instruments, analysis tools, and informatics technologies to map the neural pathways underlying human brain function. The project will map the connectomes in 1,200 healthy adults—twin pairs and their siblings—and will study anatomical and functional connections between regions of the brain, which will be related to behavioral test data. The goal is to reveal the contributions of genes and environment in shaping brain circuitry and the variability in such connectivity. The human connectome map of the healthy adult brain will serve as a foundation to further understand how brain networks change with age and neurological diseases like Alzheimer’s.

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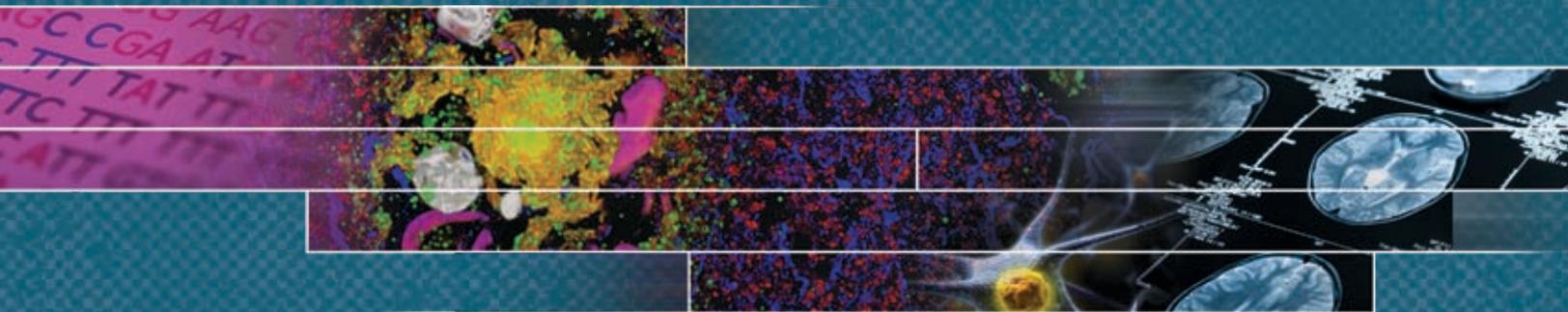
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