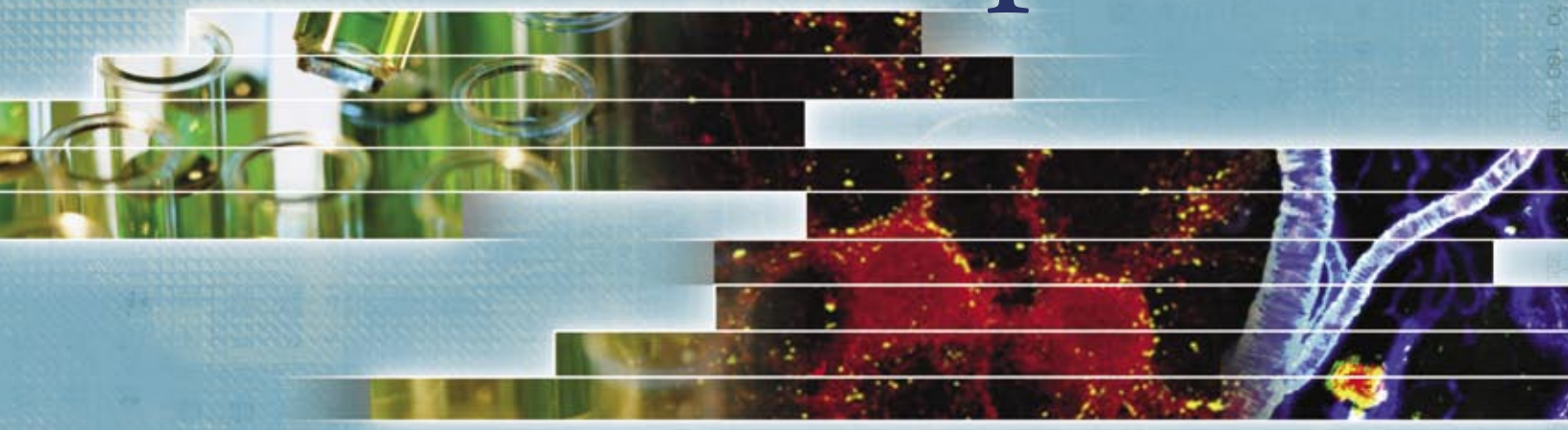
2007 PROGRESS REPORT *on* ALZHEIMER'S DISEASE

Discovery *and* Hope



U.S. Department of
Health and Human Services

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

The National Institute on Aging (NIA), part of the Federal Government's National Institutes of Health (NIH) at the U.S. Department of Health and Human Services, has primary responsibility for basic, clinical, behavioral, and social research in Alzheimer's disease (AD) as well as research aimed at finding ways to prevent and treat AD. The Institute's AD research program is integral to one of its main goals, which is to enhance the quality of life of older people by expanding knowledge about the aging brain and nervous system. This *2007 Progress Report on Alzheimer's Disease* summarizes recent AD research conducted or supported by NIA and other components of NIH, including:

- National Center for Research Resources (pages 16, 21)
- National Heart, Lung, and Blood Institute (pages 20, 21, 25, 26, 29, 36)
- National Human Genome Research Institute (page 21)
- National Institute of Biomedical Imaging and Bioengineering (page 13)
- National Institute of Diabetes and Digestive and Kidney Diseases (pages 16, 25)
- National Institute of Mental Health (pages 15, 20, 22, 25, 37, 38, 39)
- National Institute of Neurological Disorders and Stroke (pages 11, 12, 13, 14, 25, 27, 29)
- National Institute of Nursing Research (pages 18, 37, 38)

Modest AD research efforts also are supported by the National Cancer Institute, National Center for Complementary and Alternative Medicine, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Environmental Health Sciences, and John E. Fogarty International Center.

In Remembrance

The *2007 Progress Report on Alzheimer's Disease* is dedicated to Robert Katzman, M.D. (1925–2008), an internationally known AD research pioneer who fundamentally changed the way scientists and clinicians thought about the brain disorder we now know as Alzheimer's disease, and the first to detail its prevalence and severity, in 1976. Dr. Katzman was founding director of the NIA-funded AD Research Center at the University of California San Diego, one of the original members of NIA's National Advisory Council on Aging, and a founder of the Alzheimer's Association.

Table *of* Contents

INTRODUCTION 4

An Urgent National Health Priority 6

About This Report 6

A Brief Primer on Alzheimer's Disease 8

PROGRESS IN AD RESEARCH CONTINUES 10

1 Improving Our Basic Understanding of AD 10

2 Learning About Cognitive Aging 17

3 Normal Cognitive Aging, Cognitive Decline, and AD: What's the Difference? 19

4 Accelerating the Search for Genetic Causes and Risk Factors 19

5 Attention to Nongenetic Risk and Protective Factors Pays Off 22

6 Exploring All Possibilities to Improve AD Diagnosis 28

7 Making the Most of Translational Research 30

8 Supporting the Gold Standard: AD Clinical Trials 32

9 Helping Caregivers Cope 37

OUTLOOK FOR THE FUTURE 40

Improving Basic Understanding 40

Identifying Genetic Causes and Risk Factors 40

Understanding Disease Progression 41

Making the Most of Translational Research and Clinical Trials 41

Cultivating Research Infrastructure and Resources 41

CONCLUSION 42

REFERENCES 43

Introduction

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

The course of AD varies from person to person, as does the rate of decline. In most people, symptoms first appear after age 60. AD and other dementing disorders are caused by diseases that affect the brain, although age-related brain and body changes also can affect the development of dementia.

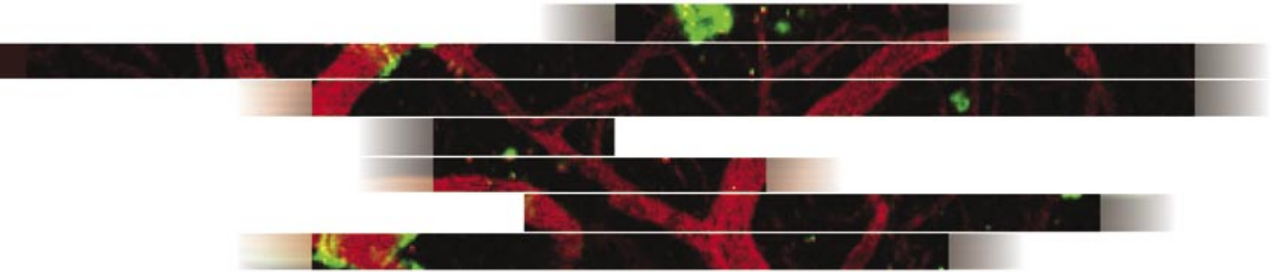
Dr. Alois Alzheimer, a German psychiatrist and neuropathologist, first described what we now know as AD when he reported the case of 51-year-old Auguste D. in 1906. He described the unusual features of her brain tissue—the numerous globs of sticky proteins in the spaces between neurons (what we now call beta-amyloid plaques) and tangled bundles of fibrils within neurons (what we now call neurofibrillary tangles). However, it was not until the 1960s and 1970s that scientists began to recognize AD as a pathology associated with aging (Katzman, 1976).

The public AD research enterprise began in earnest in the 1970s. Initially, investigators focused on understanding the manifestations and natural progression of the disease. Findings from these studies, combined with advances in many scientific areas—diagnostic imaging, genetic analysis, molecular and cellular biology, and the development of animal models, to name just a few—have led to an explosion of knowledge about AD.

Today, some 30 years later, the maturing field of AD research encourages the creativity and insights of individual investigators and targets special areas for emphasis. Enormous progress has been made, and many promising avenues lie ahead. However, if one theme predominates today, it is the growing appreciation of the pathological and clinical complexity of AD. It is clear that AD has no single cause but develops from multiple factors that interact over many years. A variety of scientific disciplines must collaborate if we are to understand the genetic and environmental influences, including lifestyle and health factors, that may increase or decrease an individual's risk of developing cognitive decline, amnestic mild cognitive impairment, or AD. (Amnestic mild cognitive impairment, or aMCI, is a condition of greater-than-normal memory problems but no impairment in multiple cognitive domains.)

The National Institutes of Health's (NIH's) broad program of AD research taps into those varied disciplines, with a growing emphasis on bringing what scientists learn in the laboratory to the clinical arena as rapidly as possible.

It is clear that AD has no single cause but develops from multiple factors that interact over many years.



An Urgent National Health Priority

The urgency of the AD research task cannot be underestimated. AD is the most common form of dementia. Its impact on the Nation is illustrated by studies estimating its prevalence (the number of people with the disease at any one time). For example, recent estimates from a nationally representative sample in the Aging, Demographics, and Memory Study (part of the ongoing NIA-supported Health and Retirement Study), suggest that among Americans age 72 and older, one in seven has dementia and about 2.4 million have AD (Plassman et al., 2007). Other investigators, using projections from community-based studies, estimate that the number of Americans aged 65 or older with AD will be 5.1 million in 2010 (Evans et al., 1990; Hebert et al., 2003). (See page 7 for more information about why prevalence estimates vary.)

Despite the differing methodologies and results of their studies, experts agree that the number of people with AD will increase significantly if current U.S. population trends continue and no prevention methods emerge (Hebert et al., 2003).

Our aging society makes AD an especially critical issue because 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 population age 65 and older is expected to double to about 72 million people in the next 25 years. Moreover, the 85-and-older age group is now the fastest growing segment of the U.S. population.

About This Report

The *2007 Progress Report on Alzheimer's Disease* describes NIH's important AD research effort. It begins with a brief primer on AD that reviews the main features of the disease, discusses the causes, and describes how AD is diagnosed and treated. The next section, "Progress in AD Research Continues," highlights recent advances in nine major areas. The *Progress Report* concludes with an outline of the diverse ways in which NIH is building on the momentum of 3 decades of groundbreaking AD research.

How Many People Have AD?

Published estimates of the prevalence of AD vary. That's because investigators use different methods for counting, and each method has its own strengths and weaknesses.

NIA continues its research interest in studies to estimate AD prevalence because having an as-accurate-as-possible number indicates the scope of AD as a public health problem. This helps scientists, policy makers, health care providers, and health care insurers determine the costs of AD to the Nation and develop appropriate services and resources to address the problem.

Equally important, the ability to reliably track trends in AD prevalence and incidence (the number of new cases in a specified time period) helps investigators correlate these trends with changes in environmental and biological factors. Results from these correlations may provide insights into potential risk and protective factors and help inform the design of prevention and treatment interventions.

Some scientists have obtained a prevalence count by using a random sample of older adults that reflects characteristics of the overall U.S. population. Sample findings are then extrapolated to the entire population. Other scientists calculate a national estimate by projecting results from one or more studies of particular communities within the United States. No matter which method scientists use, getting a complete and accurate count of people with AD is a daunting challenge.

Measuring AD in a population requires a different approach than diagnosing the disease in an individual at, for example, a major AD clinical center. In populations, researchers try to identify all the people in a selected group with AD, ruling out those who do not have the condition. There is no simple test to do this, and the count can be further compromised if individuals or their caregivers decline to participate in a study.

To make population assessments easier and more cost-efficient to conduct, investigators often use screening tests and abbreviated cognitive test batteries. These study instruments may help, but they risk overlooking milder cases of AD or diagnosing AD in individuals who have another type of dementia. Further, prevalence studies generally test people at only one point in time, and the tests may not be able to pick up the disease in its early stages. Better diagnostic tools are needed to capture cognitive impairment and AD at their earliest stages, both in population studies and studies conducted in major AD clinical centers, so that we can get a better measure of the scope of the problem.

One of the toughest issues is who to include in the count, a decision that can be driven by budget and staff limitations as well as by study design considerations. For example, including only people older than 65 will miss younger people who may have the disease. If scientists exclude people in nursing homes and assisted living facilities, then they also are likely to end up with an underestimate. Also, many people choose not to participate in these kinds of studies because they don't want to find out if they have AD or because participation is inconvenient.

A Brief Primer on Alzheimer's Disease

The healthy human brain is made up of billions of different kinds of neurons that are connected through chemical and electrical signals. A typical neuron has a nucleus in a cell body, an axon, and many dendrites. Neuronal function is supported by other kinds of cells called glial cells.

As with all cells, the nucleus of a neuron contains the cell's genetic blueprint and helps regulate the cell's activities in response to signals from outside and inside the cell. The axon transmits messages to other neurons. Dendrites receive messages from axons of other nerve cells or from specialized sense organs. The survival of neurons depends on the healthy functioning of several interdependent processes:

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

How Does AD Affect the Brain?

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

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

What Are the Main Characteristics of the Brain in AD?

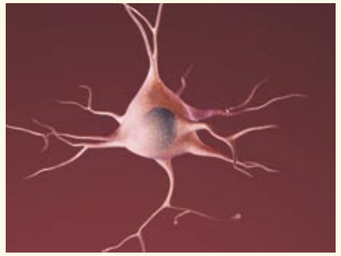
Many changes take place in the brain of a person with AD. The three major characteristics that reflect the pathology, or damage, caused by the disease are:

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

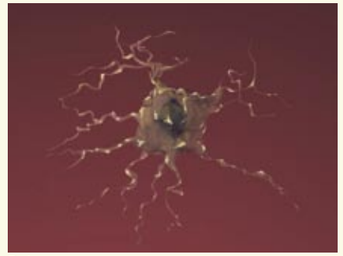
Visit the NIA Alzheimer's Disease Education and Referral (ADEAR) Center website at *www.nia.nih.gov/Alzheimers/ADvideo* to view a short video about AD and the brain.

What Causes AD?

Very rarely, people develop AD in their 30s, 40s, and 50s. In many of these cases, the disease runs in families and is caused by a mutation in one of three genes that a person has inherited from a parent. This form of the disease is called "early-onset" AD. Other early-onset cases are not caused by such mutations.



Healthy neuron



Dying neuron

More than 90 percent of AD cases develop in people older than 60. The development and pathology of this form of AD, called "late-onset" AD, are very similar to those of early-onset AD. We don't yet completely understand the causes of late-onset AD, but they probably include genetic, environmental, and lifestyle factors. The importance of these factors in increasing or decreasing the risk of developing AD differs from person to person. Scientists hope that what they learn about early-onset AD also can be applied to the late-onset form of the disease.

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

How Is AD Diagnosed?

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

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

How Is AD Treated?

A variety of treatments address behavioral and psychiatric problems that occur as AD progresses. Only a few medications have been approved by the U.S. Food and Drug Administration (FDA) to help control the cognitive loss that characterizes AD. Donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®, formerly known as Reminyl®) 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 activities of daily living and may maintain some thinking, memory, or speaking skills. They also may help with certain behavioral symptoms. However, they do not stop or reverse AD and appear to help patients only for months to a few years.

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

In addition to these medications, physicians use 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.

Progress in AD Research Continues

In 2007, scientists supported by NIH made advances in a number of areas important to AD:

- Basic research on AD
- Normal cognitive aging
- The interface between healthy cognitive aging and AD
- Genetic causes and risk factors for AD
- Nongenetic risk and protective factors for AD
- Diagnosis
- Translational research
- AD clinical trials
- Caregiver support

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

1 Improving Our Basic Understanding of AD

From the beginning, studies at the cellular and molecular levels have focused on understanding the wide range of processes that interfere with, or enhance, the function and survival of neurons and their connections. The aim is to identify targets that can be translated and developed into AD therapies. Such therapies may avoid or reduce the cell dysfunction and cell death that occur as the disease progresses and also may keep memory intact.

Interest in mechanisms at the basic level is ongoing, and the potential roles of different forms of beta-amyloid and abnormal *tau* in neuronal toxicity continue to be a source of intense investigation.

Beta-amyloid

Scientists now know a fair amount about the metabolism of amyloid precursor protein (APP), a large protein associated with the cell membrane that is the starting point for the beta-amyloid that forms plaques. Scientists also know the basic steps of beta-amyloid and plaque formation. They know that three different enzymes—alpha-secretase, beta-secretase, and gamma-secretase—are involved in cleaving APP into discrete fragments, the functions of which are still not completely understood. Depending on which enzymes are involved and where the cleaving occurs, APP processing can follow one of two pathways—a pathway that is helpful to neurons or one that is harmful because it leads to the formation of beta-amyloid and plaques.

Studies in this area have evolved to the point that investigators have begun initial testing in humans of potential therapies aimed at halting the synthesis of beta-amyloid, reducing its levels, or degrading early aggregates before harmful complexes have formed. At the same time, basic science investigators are still probing the mysteries of plaque formation and seeking to understand the potentially toxic effects that beta-amyloid exerts on neurons.

▶ Because gamma-secretase is involved in the production of harmful beta-amyloid, scientists have hypothesized that it could be a useful therapeutic target. However, gamma-secretase also is involved in the helpful APP processing pathway and in the cleavage of other developmentally important proteins, so actions to strongly inhibit its activity could have negative side effects. Johns Hopkins University School of Medicine researchers supported by the National Institute of Neurological Disorders and Stroke (NINDS) and NIA demonstrated that genetically reducing gamma-secretase activity in mice by as little as about 30 percent is enough to reduce beta-amyloid formation but leave sufficiently high gamma-secretase levels for the enzyme's other essential reactions (Li et al., 2007). These findings may have identified a possible anti-amyloid therapeutic strategy—gamma-secretase inhibitors—as well as a way to preclude potentially harmful effects from the inhibitors.

A key focus of beta-amyloid research has always been to understand how this protein peptide actually damages neurons. Recent research suggests that early, small, and soluble aggregates of amyloid, called beta-amyloid-derived diffusible ligands (ADDLs), or oligomers, may be the main culprits in harming neurons. Much evidence also suggests that synapses, the tiny gaps between neurons that are essential for neuronal communication, are oligomers' prime targets. Several recent studies have examined the pathways that lead from beta-amyloid to eventual synaptic dysfunction or neuron death and studied how beta-amyloid oligomers target specific synaptic connections between neurons, causing them to deteriorate.

▶ A research group at Northwestern University examined the ability of ADDLs to affect the composition, structure, and abundance of synapses (Lacor et al., 2007). In this test tube study of neurons situated in the hippocampus, the researchers found that ADDLs bound to synapses of a specific subset of hippocampal neurons, promoting a detrimental change in the composition, structure, and abundance of those synapses. Continued exposure to ADDLs also damaged the neurons' dendritic spines (the structures that receive messages from other neurons), affecting their ability to function properly.

▶ A study in mice by scientists at the Salk Institute for Biological Studies in La Jolla, California, provides evidence that the APP cleavage at a site known as D664 may be necessary for the synaptic dysfunction characteristic of AD to occur (Saganich et al., 2006). The research team, supported by NINDS and NIA, found that synaptic loss and behavioral abnormalities were completely prevented by a mutation at D664, even in mice that had high levels of beta-amyloid and many plaques. Uncovering the mechanism by which the D664 cleavage contributes to dysfunction may ultimately help researchers understand synaptic loss in AD and develop treatment strategies.

Another continuing line of research focuses on the possibility of harnessing an immunization response in people with AD that involves antibodies to beta-amyloid. Immunizing people against disease has been a cornerstone of medical practice for decades, and investigators have pursued the idea that it might be possible to immunize people against AD by injecting them with a beta-amyloid-related immunogen (a substance designed to elicit an immune response). This kind of injection would cause a person's immune system to make antibodies that, in turn, would lower the levels of brain amyloid.

This technique, called active immunization, has been tested in AD transgenic mice that were actively immunized with a beta-amyloid immunogen. (Transgenic animals are those that have been specially bred to develop AD-like features, such as beta-amyloid plaques.) The mice had fewer plaques and improved performance on memory tests. This finding led to a clinical trial in humans to test the safety and effectiveness of active immunization with the beta-amyloid immunogen. However, about 6 percent of participants in the trial developed brain inflammation in response to the treatment, so the trial was stopped. Despite this setback, interest in developing an AD vaccine remains high.

Research into new ways of shaping the antibody response continues in the laboratory, and more refined antibody approaches are being tested in clinical trials.

▶ Using several strains of mice, including transgenic and normal mice, Harvard Medical School investigators tested four different partial fragments of beta-amyloid as potential immunogens (Maier et al., 2006). The researchers found that the immunogens evoked the desired immune response in both sets of mice, reducing plaque levels in their brains without an accompanying inflammatory reaction. The transgenic mice also showed slight improvements in memory tests.

In a second approach to protecting against AD, called passive immunization, antibodies are produced or manufactured outside the body. For example, humanized antibodies to beta-amyloid have been made in cell cultures using recombinant DNA techniques. The antibodies can then be isolated and administered to subjects. Scientists presume that passive immunotherapy produces less of an inflammatory response than active immunotherapy, and a number of investigators are pursuing this approach.

▶ Cerebral amyloid angiopathy (CAA) is the accumulation of beta-amyloid in the walls of arteries in the brain. Because CAA is commonly found in AD, many scientists are interested in how beta-amyloid deposits in blood vessels and neurons may generate human disease and whether they can be treated by immunotherapy. Researchers at Massachusetts General Hospital, supported by NIA and the National Institute of Biomedical Imaging and Bioengineering, used microscopy at different time intervals to monitor CAA in a mouse model of AD to evaluate the effects of anti-beta-amyloid passive immunotherapy (Prada et al., 2007). The investigators saw clearance of CAA deposits within 1 week after a single administration of antibody directly to the brain, but the effect was short-lived. Chronic administration of antibody over 2 weeks led to better clearance without evidence of hemorrhage or other destructive changes. This imaging study directly demonstrated that CAA in a transgenic mouse model can be cleared with an enhanced immunotherapy regimen.

Additional insights about beta-amyloid have come from studies of neuronal networks. These studies show how beta-amyloid may damage normal electrical activity of hippocampal neurons, thereby diminishing the cells' ability to communicate with each other.

▶ A research group at the Gladstone Institute of Neurological Research in San Francisco discovered that, compared with normal mice, transgenic mice show anatomical and biochemical alterations in certain brain regions as well as abnormal excitatory electrical activity (Palop et al., 2007). The study focused on the hippocampus (a region of the brain that is key to learning and memory). These findings are important because they suggest another damaging effect of beta-amyloid—namely, that beta-amyloid presumably triggers abnormal electrical activity throughout the brain. This abnormal activity in turn triggers compensatory inhibitory activity, perhaps contributing to AD-related network dysfunction.

Other aspects of beta-amyloid also are yielding their secrets to AD researchers.

▶ Scientists at the Buck Institute for Age Research in Novato, California, bred transgenic mice to develop features of AD and to overproduce neuroglobin, a protein expressed predominantly in neurons that is closely related to hemoglobin, the oxygen-carrying protein in the blood. Neuroglobin is abundant in the brains of vertebrates. The function of this globin family protein is largely unknown, but the expression of neuroglobin can be induced when oxygen levels in the brain are lowered, as in a stroke. The transgenic mice performed significantly better on memory tasks and had fewer beta-amyloid plaques than did transgenic mice that only developed AD features (Khan et al., 2007). The researchers, supported by NINDS, speculate that increasing neuroglobin levels may merit additional research as a therapeutic target, not only for cerebrovascular disease but also for beta-amyloid toxicity.

Tau

Tau is a leading player in AD pathology and is generating new excitement as an area of study. The focus on *tau* was spurred by the finding that a mutant form of this protein is responsible for frontotemporal dementia and parkinsonism linked to chromosome 17, another neurodegenerative disorder that shares some features with AD. That finding indicated that abnormalities in *tau* can cause dementia.

Recent research has provided other new insights. For example, some studies have suggested that *tau*'s influence on cell death may have more to do with its interference in the normal cell cycle process than with its involvement in the formation of neurofibrillary tangles. Other studies suggest that, like beta-amyloid, early soluble forms of abnormal *tau* (not the final neurofibrillary tangle) may be the trigger for cell death.

Transgenic mouse models have played a big role in pushing forward *tau* research because they can be studied methodically for clues to human diseases. For example, the "triple transgenic" mouse forms plaques and tangles similar to those in human AD over time in brain regions. Another new transgenic mouse model, which contains only human *tau*, forms clumps of damaging *tau* filaments in a region-specific fashion similar to that seen in humans with AD.

▶ A research group from the Gladstone Institute of Neurological Research supported by NIA and NINDS explored the possibility that a treatment aimed at *tau* could block the cognitive impairments that result from beta-amyloid accumulation (Roberson et al., 2007). In this study with AD transgenic mice that normally are cognitively impaired, the scientists eliminated the animals' *tau* gene. The resulting lower levels of *tau* produced by the mice prevented behavioral problems that usually occur when too much beta-amyloid is produced, even though beta-amyloid levels remained high. This surprising result suggested that reducing *tau* levels may present another target for future AD treatments.

Transgenic mouse models have played a big role in pushing forward *tau* research.

AD and Other Neurodegenerative Diseases

Studies of brain abnormalities resulting from common mechanisms in a number of neurodegenerative diseases are providing important insights into AD. Diseases such as AD, Lewy body disease, Huntington's disease, frontotemporal dementia, amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), Parkinson's disease, and Creutzfeldt-Jacob disease have similar clinical symptoms, including memory loss, movement problems, and sleep-wake disorders.

People with any of these disorders also exhibit the same pathological hallmark—misfolded and mutant proteins in the brain. Under normal conditions, most misfolded proteins are either repaired or degraded, but when too many of these proteins are produced over a long period of time, the body's repair and clearance process may be overwhelmed. The toxic misfolded proteins accumulate and lead to the age-related neurodegenerative disorder.

In 2007, several studies provided valuable insights into how this process may occur and why some neurodegenerative diseases have overlapping features.

▶ Scientists at the University of Pennsylvania School of Medicine identified, for the first time, a protein called TDP-43 as a component of the protein aggregates that form in ALS and in some forms of frontotemporal dementia (Neumann et al., 2006). Finding the same molecular signature in the two diseases suggests that they may represent different facets of the same neurodegenerative disorder. It may be that a number of neurodegenerative diseases that affect different groups of neurons have similar disease processes. If that is true, then developing therapies for these disorders and other similar diseases may be simplified.

▶ Another research team, working at Northwestern University, explored how the expression of a single protein that is prone to abnormal aggregation can lead to the disruption of many cellular pathways. These researchers also examined whether one general mechanism might explain the many common features of protein misfolding diseases (Gidalevitz et al., 2006). The investigators used the worm *C. elegans* as a model to test whether expression of a pathogenic protein known as a "polyQ protein" (similar to the abnormal huntingtin protein that causes Huntington's disease) could affect the folding or degradation of other proteins.

Worms with the polyQ protein were crossed with worms that expressed other mutant proteins in either muscle or brain cells. The researchers found that the offspring of those worms showed chronic expression of the aggregation-prone polyQ protein, which caused the other proteins to become toxic under conditions where they were normally innocuous. Moreover, the toxic action was reciprocal in that the other mutant proteins, which had no adverse effect under normal physiological conditions, could enhance the aggregation of polyQ proteins. These clues about the interactions between abnormal proteins and their effects on neurons may provide a valuable boost to efforts to target potential treatments for various age-related neurodegenerative diseases.

▶ Researchers at the University of Texas Southwestern Medical Center used transgenic mice to explore relationships between AD and Parkinson's disease. This study, supported by the National Institute of Mental Health (NIMH), showed that in the spinal cords of mice made to overexpress human normal and mutant alpha-synuclein (a protein implicated in Parkinson's disease) a change occurred in the ubiquitin/proteasome system. This is a cellular system that degrades misfolded proteins (Gallardo et al., 2008). Curiously, the mice also exhibited a fourfold increase in levels of the ApoE protein (ApoE is a genetic risk factor implicated in AD; see page 19 for more on ApoE). This overexpression produced marked increases in aggregates of alpha-synuclein and insoluble beta-amyloid. Deleting the APOE gene, which makes ApoE, had a number of positive effects in the transgenic mice—alpha-synuclein-induced neurodegeneration was delayed, survival increased, accumulation of alpha-synuclein aggregates decreased, and accumulation of beta-amyloid was suppressed. These findings suggest that ApoE is involved in the response to alpha-synuclein toxicity, and that AD and Parkinson's disease may share a molecular link through the ubiquitin/proteasome system. This insight may have important implications for preventing and treating these devastating diseases.

AD and Aging

Another set of insights about AD derives from an apparent risk factor common to a number of neurodegenerative diseases: aging itself. Age-related changes, such as inflammation, changes in expression of certain proteins, and the generation of free radicals, may precede, follow, or exacerbate the neuronal damage that occurs in AD. In addition, age-related changes in one or more of the hundreds of varieties of proteins could result in inefficient functioning of certain synapses, predisposing neurons to failed communication and death. Scientists are investigating all of these possibilities.

▶ In a study using the *C. elegans* worm, scientists at the Salk Institute for Biological Studies introduced a gene that increased the lifespan of the worms and a gene that made beta-amyloid (Cohen et al., 2006). The investigators found that the worms containing the increased-lifespan gene also suppressed the aggregation-related toxicity of beta-amyloid. These findings suggest that aging itself plays a role in the rate at which beta-amyloid aggregates, and investigators identified two genes essential for this process.

▶ An intramural research group at NIA identified disease-specific changes in gene expression in different regions of brain tissue from people with AD, people with other types of dementia, and cognitively healthy people (Weeraratna et al., 2007). The analysis revealed that genes that differed in expression the most between the groups were related to nervous system development and function and neurological disease, followed by genes involved in inflammation and immunological signaling. A specific group of genes associated with beta-amyloid accumulation and clearance was found to be significantly altered in the AD group. The most significantly down-regulated gene in this dataset was one containing the genetic information necessary to make an enzyme implicated in beta-amyloid clearance. Together, these findings open up new avenues of investigation and possible therapeutic strategies targeting inflammation and enzymes associated with amyloid clearance in AD patients.

▶ Scientists at the University of North Dakota School of Medicine and Health Sciences supported by the National Center for Research Resources (NCRR) have been investigating cytokines, substances produced by immune system cells. These substances are secreted by cells during the body's response to inflammation. The investigators found that a cytokine called tumor necrosis factor alpha, which is present in the brain during an inflammatory response, can begin a process in nerve cells that ultimately leads to cell death (Jara et al., 2007). This finding may help explain one mechanism leading to cell death in AD and related diseases.

▶ Free radicals—oxygen or nitrogen molecules that combine easily with other molecules—are important in the aging process and may be important in AD as well. Free radicals can help cells in some ways, but overproduction of these highly reactive molecules can damage neurons in a process called oxidative stress. A substance called 4-hydroxy nonenal (4-HNE), formed as a result of oxidative stress, is increased in AD. 4-HNE also is found in AD plaques. Scripps Research Institute scientists, supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), found that 4-HNE modifies beta-amyloid fragments, triggering the formation of toxic beta-amyloid oligomers (Siegel et al., 2007). These findings provide impetus for additional research on whether, or to what extent, oxidative stress is a risk factor or a consequence of AD.

New Insights into New Neurons

Until recently, scientists believed that neurons in mammals were formed only during the fetal period and for a short time after birth. The belief was that once a mammal had reached a certain level of maturity early in life, neurons could only be lost. The notion that new neurons could develop later in life was radical. Finding that this was, in fact, true was revolutionary.

This shift in thinking over the past few years was based on studies showing that neurogenesis (the formation of new neurons) takes place in the adult brain, at least in a limited number of brain regions, such as the hippocampus. Neurogenesis declines during aging but can be stimulated by environmental influences, including physical activity and learning tasks.

This evidence raises a big question: Do these new neurons actually help brain regions function or are they merely a reservoir to replace dying neurons? Several recent studies, conducted by scientists from Johns Hopkins University, the Chicago Medical School of the Rosalind Franklin University of Medicine and Science, and the University of Arizona, have helped answer this question.

In studies with mice and rats, investigators showed that new neurons produced in the adult hippocampus are better able to adapt (an attribute called "plasticity") and to mature (Ge et al., 2007). In fact, they found that because of their enhanced "excitability," new neurons may help process information and form memories in the hippocampus (Ramirez-Amaya et al., 2006). The researchers also found that certain types of stress disrupted neurogenesis by decreasing the survival of the new neurons (Thomas et al., 2007).

These and other similar findings may help researchers develop future interventions that maintain or enhance the formation of new neurons, thereby helping to slow age-related cognitive decline.

2 Learning About Cognitive Aging

Improvements in public health, medical care, nutrition, and living standards mean that we are now living longer than ever. Many older adults enjoy active, productive lives, but they also face the risk of cognitive and memory problems.

This challenge has provided a major impetus for research into healthy cognitive aging. Scientists want to know how and why some people remain cognitively healthy all their lives while others do not. Answers to these questions also can help researchers understand what goes wrong in AD and other neurodegenerative diseases and can point the way to interventions that might maintain successful brain and cognitive aging.

▶ Working memory is an important kind of short-term memory that maintains information in a temporary "buffer" that can be continually updated as needed. This type of memory is important for cognitive and emotional function, allowing us to inhibit inappropriate actions and plan future actions. Working memory appears to depend on recurring activity in networks

involving neurons in the front part of the brain (the prefrontal cortex). This activity allows neurons to continue firing during periods of delay when the stimulus or event to be remembered is not present in the environment, thus maintaining a representation of the information over time, even in the face of distracting stimuli or information. With increasing age, working-memory deficits become a consistent feature of declines in cognitive performance.

Investigators at the Yale University School of Medicine conducted an extensive series of experiments in rats and nonhuman primates and found that stimulating neuronal receptors in the prefrontal cortex improved working memory (Wang et al., 2007). They also found that weakened connections within neuronal networks in this brain region may underlie some of the cognitive deficits seen in older adults.

▶ A research team at the University of Kentucky and Memory Pharmaceuticals Corporation in Montvale, New Jersey, took another approach to studying cognitive aging (Rowe WB et al., 2007). This study in rats combined analyses of changes in expression of many genes with behavioral testing to determine gene changes that are selectively associated with age-related cognitive dysfunction in the hippocampus. Results showed clear differences in expression of genes that occurred in the brain between the cognitively impaired and cognitively healthy rats, suggesting a model for age-related cognitive impairment. In this model, if decreases in expression of genes important for the use of glucose and in energy production by cells that support neuronal function were coupled with deficiencies in neuronal energy production, neurons would be unable to trigger activity that enables plasticity and memory formation in response to learning tasks. In this model, these deficiencies also might generate signals that activate harmful pathways, further disrupting cognitive processes.

Scientists want to know how and why some people remain cognitively healthy all their lives while others do not.

▶ The multi-site Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) clinical trial, funded by NIA and the National Institute of Nursing Research (NINR), is designed to test the effects of brief cognitive training in older adults. In one component, researchers at the Indiana University School of Medicine examined the effects of cognitive training on participants who exhibited declines in cognitive function (Unverzagt et al., 2007). Participants received training in memory, reasoning, or speed of processing of visual information.

Compared with a control group that received no training, the participants who received the memory training and had normal memory at the start of the study showed significant improvement in memorization skills. Among participants with pre-existing declines in memory function, however, those in the memory training group showed no benefit. Those who received the reasoning or the speed-of-processing training showed improvement comparable to participants with normal memory.

These findings suggest that older adults with pre-existing mild memory impairment may not benefit from memory training as much as those with normal memory function, but they benefit just as much from certain forms of cognitive training that do not rely on memorization. This training may be able to improve the ability of older adults to maintain skills that allow them to carry out daily tasks and lead a higher quality of life.

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

As knowledge grows about normal cognitive aging, AD, and the stages in between, it is increasingly evident that there is no clear line between a completely healthy brain and a diseased brain. Evidence shows that most people develop some plaques and tangles in their brains as they get older, but not everyone develops cognitive problems, amnestic MCI, or AD. At what point does an age-related process become a disease-causing process? Several recent studies have explored this question.

▶ Evidence from the Religious Orders Study and the Memory and Aging Project—two community-based epidemiologic studies conducted by Rush University Medical Center scientists—indicated that about one-third of individuals between the ages of 82 to 85 who did not have clinical dementia or aMCI when they died still met the neuropathologic criteria for intermediate or high likelihood of AD (Bennett et al., 2006a). In earlier tests of memory and other cognitive functions, those who met the AD neuropathologic criteria scored a little lower on tests of episodic memory (the ability to place information in long-term storage for later retrieval) than other study participants but showed no differences on other cognitive domains.

▶ The development of Pittsburgh Compound-B (PiB) has allowed scientists to take huge steps forward in their understanding of normal and abnormal age-related changes in the brain (Klunk et al., 2004). PiB is a radiolabeled compound that binds to beta-amyloid plaques in the brain and can be imaged in living people using positron emission tomography (PET) scans. Two recent studies conducted by researchers at Washington University School of Medicine and the Centre for PET in Victoria, Australia, showed that approximately 20 percent of 66- to 86-year-olds with normal cognition showed positive PiB binding, indicating an abundance of beta-amyloid in the brain (Mintun et al., 2006; Rowe CC et al., 2007).

These and other findings show that studies to explore further the interface between a pathological process (formation of beta-amyloid plaques) and the aging process are both feasible and necessary. Future studies will clarify the relationship between AD brain pathology and the eventual diagnosis of aMCI and AD, as well as when the diagnosis can be made with certainty.

4 Accelerating the Search for Genetic Causes and Risk Factors

Until recently, only four of the approximately 30,000 genes in the human genome were conclusively shown to affect the development of AD. Mutations in three genes—the APP gene found on chromosome 21, the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1—are linked to the rare early-onset form of familial AD. The APP gene is responsible for making APP, the precursor to beta-amyloid. The presenilin genes contain the information necessary to make the proteins that are part of one of the enzymes that help to cleave APP to form beta-amyloid. Mutations in each of these genes promote the breakdown of APP in a way that leads to increased production of harmful beta-amyloid.

The fourth gene, APOE, found on chromosome 19, contains the information necessary to make a protein called apolipoprotein E (ApoE). ApoE carries lipids in the bloodstream and is important in clearing lipids from the blood. APOE has three common 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 is a known risk-factor gene for the common late-onset form of AD, and many studies are underway to clarify its impact.

▶ Boston University School of Medicine scientists supported by the National Heart, Lung, and Blood Institute (NHLBI) and NIA examined whether APOE ε4 affects the relationship between brain volume and cognitive performance in 1,477 participants in the Framingham Study population (see page 25 for more information about the Framingham Study) (Palumbo et al., 2007). Those with an APOE ε4 allele and smaller brain volume did less well on tests of visual memory, new learning, and executive function than those without APOE ε4, who also had smaller brain volumes. It may be that having APOE ε4 not only increases the risk of AD, but also leads to poorer outcomes in those who do not yet have symptoms of the disease.

▶ People who have two copies of the APOE ε4 allele may be at high risk of developing AD at an earlier age of onset and for experiencing far more rapid declines in memory performance, compared with people without this allele and people with only one copy. Such memory declines, even within a normal range of performance, could be early markers of disease, detectable before the individual experiences clear symptoms of the disorder. Investigators supported by NIMH and NIA examined how performance on neuropsychological tests by a sample of healthy adults in their 50s and 60s related to their APOE ε4 status (Caselli et al., 2007). The investigators, with the Mayo Clinic in Scottsdale, Arizona, and the University of Arizona, found that even before a diagnosis of aMCI, individuals with two copies of APOE ε4 showed higher rates of cognitive decline than those at lower genetic risk for AD.

These findings support the notion of a presymptomatic state of disease, the identification of which might aid in early detection and diagnosis of AD among people at increased genetic risk. Further prospective studies are needed to examine how rates of cognitive decline relate to rates of AD disease progression and conversion to a final diagnosis of AD. Results from these studies may suggest new targets for possible interventions to delay onset or progression of AD.

▶ Though scientists know that APOE ε4 is a risk factor for cognitive decline that eventually leads to AD, they have yet to understand the steps in that process. Many think that it involves an interaction between genetic and environmental factors. One study, supported by NIMH and conducted by a research team at the University of California San Diego, examined the role of one such environmental factor, prolonged psychological stress (Peavy et al., 2007). Stress generally involves elevations in the hormone cortisol, which have been linked to hippocampal atrophy and to memory and learning impairments. This study assessed APOE status, stress levels, salivary cortisol, and memory performance of 91 older adults without dementia.

The researchers found that having either one or two APOE ε4 alleles and high stress were associated with reduced memory performance. In addition, the investigators found significant interactions between stress and APOE ε4; participants with high levels of stress and the APOE ε4 allele consistently manifested worse memory and higher cortisol concentrations than other participants. These findings point the way to future studies that could follow individuals over time to determine whether stress levels and APOE status in combination could be used to predict future development of cognitive decline leading to clinically diagnosable dementia.

Most experts believe that in addition to APOE ε4, at least half a dozen more genes may influence the development of late-onset AD in some way. Geneticists around the world are searching for these genes.

▶ In 2007, a worldwide collaboration of scientists supported by NIA, the National Human Genome Research Institute, NCRR, the Canadian Institutes of Health Research, and private foundations in the United States, Canada, and Japan unveiled their discovery of a new AD risk-factor gene called SORL1 (Rogaeva et al., 2007). This gene is involved in recycling APP from the surface of cells, and its association with AD was identified and confirmed in three separate studies (Lee JH et al., 2008; Lee JH et al., 2007; Meng et al., 2007). The researchers found that when SORL1 is expressed at low levels or in a variant form, harmful beta-amyloid levels increase, perhaps by moving APP away from its normal pathways and toward cellular compartments that generate beta-amyloid.

Studies are ongoing to clarify SORL1's role in the AD process. For example, NHLBI-supported scientists at Boston University School of Medicine conducted a genome-wide association study on Framingham Study participants using cognitive data collected in an NIA-funded add-on study (Seshadri et al., 2007). A genome-wide association study tests for linkage between genes and a particular disease across all the genes in a specific population of individuals. The researchers found that the SORL1 gene was associated with measures of abstract reasoning and that another gene, CDH4, was related to total cerebral brain volume. This association of an AD risk-factor gene with cognitive function suggests there may be a common pathway in the brain aging process and in AD.

NIA's Alzheimer's Disease Genetics Initiative (ADGI) provides critical support to all of this work. Launched in 2003, this study aims to identify at least 1,000 families with members who have late-onset AD and members who do not have the disease. Investigators are collecting blood samples and other clinical data from participating volunteers. These biological specimens allow investigators to create and maintain "immortalized" cell lines—cells that are continuously regenerated in the laboratory.

Most experts believe that in addition to APOE ε4, at least a half a dozen more genes may influence the development of late-onset AD in some way.

The cell lines will be used in DNA analyses to further understand SORL1 and to identify additional AD risk-factor genes, a critical task even if individual risk-factor genes may have relatively small effects on AD development. More than 4,000 new cell lines are now available for researchers to study risk-factor genes for late-onset AD.

A second investigator-led initiative, the Alzheimer's Disease Genetics Consortium, was launched in 2007 to accelerate the application of genetics technologies to late-onset AD through collaborations among leading researchers in AD genetics. The ultimate goal of this effort is to obtain genetic material from 10,000 people with AD and 10,000 cognitively healthy people and then to scan the entire genome for the remaining AD risk-factor genes, as well as genes for age-related cognitive decline. Some of the genetic material will be drawn from existing samples of blood and tissue that are mostly held at Alzheimer's Disease Centers. Other genetic material will be collected from new participants.

With such efforts, the search for the genetic underpinnings of late-onset AD is intensifying, allowing investigators to identify who is at high risk of developing AD, understand the mechanisms at work, and focus on new pathways amenable to prevention or treatment.

Other Genetics Initiatives Are Key to Successful AD Research

Rapid advances in AD genetics research are fostered though several other essential initiatives funded by NIA and NIH.

National Cell Repository for Alzheimer's Disease (NCRAD)

www.ncrad.org

This research resource, located at Indiana University, is the central repository for the AD Genetics Initiative and provides the cell lines and DNA needed for genetic analyses.

Genetics of Alzheimer's Disease Data Storage Site

www.niageneticsdata.org

Scientists who use NCRAD samples and other NIA-funded AD geneticists are required by NIA to submit their published data to this site, which was established in 2006 at Washington University in St. Louis. The data then undergo additional analysis by AD genetics experts.

Database of Genotype and Phenotype (dbGaP)

www.ncbi.nlm.nih.gov/entrez/query/Gap/gap_tmpl/about.html

This NIH collaboration was developed to archive and distribute the results of large-scale genome-wide association studies, gene sequencing studies, and analyses of the association between genotype and genetic traits. Datasets from multiple studies done using different types of analysis can then be merged. This process allows data from thousands of study participants to be analyzed together, with increased probability of gene discovery.

National Institute of Mental Health Genetics Dataset

www.nimh.nih.gov

NIMH has established a national resource of demographic, clinical, and genetic data from 1,411 individuals from families with AD. Housed at Washington University, the NIMH AD Genetics Dataset offers researchers clinical and genetics data from both NIMH and NIA.

5 Attention to Nongenetic Risk and Protective Factors Pays Off

Epidemiologic studies, animal studies, and clinical trials are all important in identifying potential factors that may contribute to or protect people from AD risk—separately or interactively with genetics. In the past several years, two areas of focus have emerged: lifestyle factors and the management of health conditions. Scientists also have continued their research interest in looking at estrogen and AD.

Lifestyle Factors and AD

Several elements of a healthy lifestyle, including a nutritious diet, regular physical activity, not smoking, and strong social networks, can help people stay healthy as they grow older. An important reason for this benefit is that lifestyle choices strongly affect the risk of several chronic diseases, including heart disease, diabetes, and stroke, that commonly affect people as they age. Evidence is emerging that AD may share some of these risk factors. Findings from epidemiologic research, basic studies in animals, and limited clinical trials suggest that an array of lifestyle factors may influence the risk of developing age-related cognitive decline, aMCI, or even AD.

▶ As part of a large longitudinal study of older women, researchers at the San Francisco Coordinating Center and California Pacific Medical Center Research Institute examined the relationship between quality of sleep and cognitive function (Blackwell et al., 2006). The investigators found that disruptions to sleep, rather than the total amount of sleep, were consistently related to reductions in cognitive function. Another study of cognitively healthy women living in the community found a similar association between cognitive decline and sleep quality but not total sleep time (Yaffe et al., 2007).

▶ It is well recognized that the damage of AD often adds to and interacts with other changes in the brain to cause cognitive impairment. Two studies from the Memory and Aging Project provide supporting evidence for this observation. In one analysis of more than 600 cognitively healthy people, investigators found that chronic psychological distress was associated with a nearly threefold increased risk of AD; change in a global measure of cognition; and change in episodic memory, the clinical hallmark of AD (Wilson et al., 2006). In a separate study, researchers found that social engagement might also modify the severity of dementia (Bennett et al., 2006b). Although individuals with larger social networks did not have fewer plaques or tangles than more isolated individuals in the study, AD pathology had a smaller effect on the cognition of the more socially connected individuals. This correlation was similar to the protective effect provided by years of formal education.

▶ Investigators with the Group Health Cooperative in Seattle, Washington, have been following 1,740 older adults in the Adult Changes in Thought Study (Larson et al., 2006). Every 2 years, participants undergo physical and cognitive tests, answer questions about their lifestyles, and are assessed for dementia. After 6 years, the investigators found that the risk of AD in people who exercised three or more times per week, at least 15 minutes per day, was 31 percent lower than in those who exercised fewer than three times per week. This result suggests that regular exercise is associated with a delay in the onset of AD.

Epidemiologic studies correlate lifestyle factors with altered cognitive function. Epidemiology cannot, however, establish a cause-and-effect relationship. To directly examine cause and effect, NIA is sponsoring several clinical trials to test the questions raised by observational and animal studies and to specifically look at the effects of one lifestyle factor—physical activity and exercise—on cognitive function in older adults.

▶ Researchers from the University of Illinois at Urbana-Champaign conducted functional magnetic resonance imaging tests on older adults before and after a 6-month program of brisk walking (Erickson et al., 2007). Results showed that neuronal activity in the frontal cortex increased with increases in participants' cardiovascular fitness. A similar trial conducted by University of Illinois investigators showed that brain volume increased as a result of a walking program (Colcombe et al., 2006). These findings suggest a strong biological basis for the role of aerobic fitness in helping to maintain the health and cognitive functioning of adults as they age, at least in the short term.

▶ A small-scale clinical trial is looking at the effects of 1 year of aerobic fitness training on cognition and brain activity and structure in older adults. Other small trials are examining the role of aerobic exercise on electrocortical and behavioral measures in older adults and assessing the effects of a short aerobic conditioning program on cognitive function in older adults with aMCI.

▶ A 3-year trial of a group exercise and health education intervention in people with aMCI is examining a variety of issues, such as whether the exercise intervention will slow the progression from aMCI to dementia. More recently, researchers at Wake Forest University started a pilot study to assess whether an intervention involving physical activity and cognitive training reduces significant cognitive decline in memory-impaired older individuals. The Seniors Health and Activity Research Program-Pilot (SHARP-P) will compare the outcomes of physical activity, cognitive training, and combined physical activity and cognitive training with those of health education.

Advising the Public Before All the Scientific Results Come In

Although the evidence to date suggests that physical activity and other lifestyle choices, such as mentally stimulating activity, a healthy diet, and social engagement, have positive effects on brain function and may reduce risks of cognitive decline and AD, results from definitive clinical trials will not be available for several years.

Even so, experts can recommend that older adults (and other age groups) participate in these activities. These low-risk, low-cost interventions have many proven benefits for overall healthy aging. For example, regular physical activity and a healthy diet help reduce the risk of age-related diseases and conditions, such as heart disease and type 2 diabetes. Social activities with friends and family and the pursuit of mentally stimulating activities help people feel engaged.

Additional clinical trials are critical to discern whether physical activity and exercise can, in fact, prevent or delay long-term cognitive decline or AD and, if so, to determine the type and amount of physical activity necessary.

Health Conditions and AD

A growing body of evidence suggests that the metabolic changes that occur in a variety of age-related chronic diseases, such as heart disease, stroke, high blood pressure, and type 2 diabetes, may contribute to the development of AD, affect the severity of AD, or cause vascular dementia (a loss of thinking and reasoning abilities caused by stroke or other forms of brain injury related to damage to the brain's blood vessels). However, these relationships are complex. Several studies in the past year have attempted to untangle them.

▶ Investigators with the Memory and Aging Project examined the brain tissue of deceased participants who had donated their brains to the study (Schneider et al., 2007). Results showed that about one-third of the participants had evidence of strokes, which increased the odds of having AD-related reductions in memory function.

▶ At least four long-term studies have linked diabetes with a decline in cognitive function. In one of these studies, a Columbia University research team examined whether diabetes is related to an increased risk of aMCI (Luchsinger et al., 2007). Working with a large multiethnic population with a high prevalence of diabetes, the researchers found that diabetes was associated with a significantly increased risk of aMCI as well as other types of MCI.

▶ Evidence increasingly suggests that overweight and obesity may increase AD risk. Two studies explored this issue by examining the relationship of obesity or overweight at midlife and cognitive performance or AD in later life. In the first study, conducted at the Kaiser Permanente Division of Research in Oakland, California, and supported by NIDDK, investigators found that participants who were obese (a body mass index of 30 or more) during midlife had a threefold increase in AD risk (Whitmer et al., 2007). Those who were overweight (a body mass index of 25 to 29) had a twofold increase in AD risk.

In the second study, Boston University School of Medicine researchers used data from 1,814 Framingham Study participants to examine whether obesity at midlife affected the impact of hypertension (a key risk factor for heart disease) on cognitive abilities (Wolf et al., 2007). The study, supported by NIA, NHLBI, and NINDS, found that participants with a high measure of abdominal obesity and hypertension did worse on tests of executive function and visuomotor skills than did those who weighed less and had normal blood pressure. Furthermore, hypertensive participants who were most obese did less well on the tests compared with those who were not as obese. This finding suggests that obesity may have exacerbated the impact of hypertension on the brain. The researchers concluded that controlling abdominal obesity and blood pressure in midlife may help reduce the risk of cognitive problems and dementia in later life.

Framingham Study Data Provide Insights into the Lifetime Risk of Stroke and Dementia

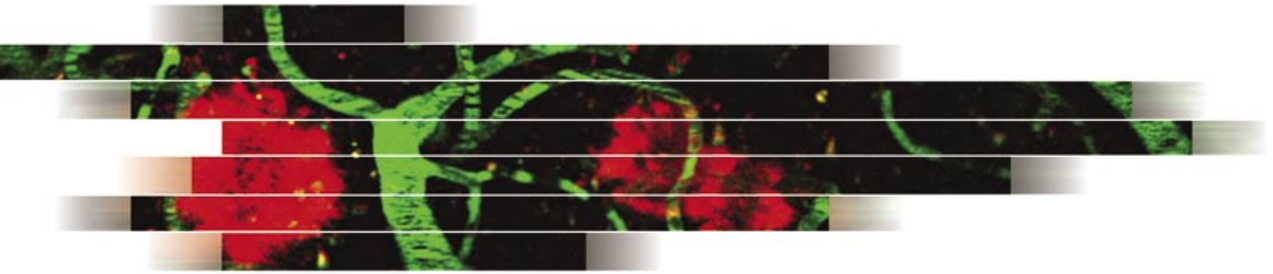
The Framingham Heart Study, begun in 1948, is a long-term investigation of physical and environmental factors that influence the development of cardiovascular disease in healthy individuals. The study, funded by NHLBI, is still following the remaining members of the original study group, as well as the remaining members of a group of 5,000 people who were recruited in 1971 into the Framingham Offspring Study. Investigators are now working with the third generation of volunteers in this landmark epidemiologic study.

One of the distinguishing elements of the study has been "add-on" components funded by other NIH institutes, including NIA and NIMH. These add-on components have provided a cost-effective opportunity for scientists to examine additional issues using existing study populations.

The Framingham Study's rich harvest of data has allowed researchers to explore many dimensions of the relationship between cardiovascular risk factors, cognitive health, and AD. The fact that it has been going on for so many years also gives scientists a unique opportunity to study certain aspects of an issue. For example, in describing the burden of any disease, scientists often refer to incidence, or the number of people who may develop the disease in a given time period, usually a year. However, some investigators have argued that "lifetime risk," or the risk of developing a disease across the remaining estimated lifespan, may provide a more accurate measure of the possible burden to a population than does incidence. They note that lifetime risk reflects risk across a longer period of time rather than risk over a single year.

Framingham investigators at the Boston University School of Medicine conducted a lifetime risk analysis using many years of follow-up data from the original group of Framingham participants. This analysis, which was supported by NHLBI, NIA, and NINDS, focused on the lifetime risk of stroke and AD, two conditions of enormous public health concern.

Using 51 years of follow-up data, the analysis showed that the lifetime risk of stroke was 1 in 5 for a middle-aged woman and 1 in 6 for a middle-aged man. For AD, using 29 years of follow-up data, lifetime risk was 1 in 5 for a middle-aged woman but only 1 in 10 for a middle-aged man. The authors concluded that measures of age- and sex-specific lifetime risk indicate that a middle-aged person has a 1 in 3 chance of having a stroke or becoming demented. These rates have serious implications for the provision and cost of future health care services.



As noted earlier, epidemiologic studies cannot determine cause-and-effect relationships even though they provide valuable information about associations between chronic diseases and aMCI or AD. As a result, NIA is supporting several clinical trials to see whether managing these conditions might reduce the risk of cognitive decline and dementia.

Clinical trials have examined whether two treatments—simvastatin (a cholesterol-lowering drug) and vitamin supplements that reduce homocysteine (an amino acid linked to heart disease and AD)—could slow the rate of cognitive decline in older adults with AD. These trials were recently completed, and the data are being analyzed.

Other clinical trials are underway to examine whether diabetes-related interventions can prevent or delay the progression of cognitive decline or AD:

- **ACCORD-MIND (ACCORD-Memory in Diabetes)**. This NIA-funded trial is nested within NHLBI's Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which is evaluating whether intensive glucose, blood pressure, and lipid management can reduce cardiovascular disease in people with type 2 diabetes. ACCORD-MIND will test whether these interventions also can reduce the rates of cognitive decline and structural brain change in 2,800 of the ACCORD study participants over a 4-year period. Participants will undergo periodic cognitive testing and MRI scans to assess change over time (Williamson et al., 2007).
- **RECALL**. In this 18-month multi-center trial, researchers from the University of Washington will test the effects of the drug rosiglitazone on attention and memory skills in older adults with aMCI. Rosiglitazone has anti-inflammatory properties and improves the body's ability to use insulin. This trial will examine the medication's effects on brain structures that support memory and other cognitive abilities, as well as on biological markers associated with inflammation, insulin resistance, and cardiovascular disease. As with most clinical trials, participants will be divided into two groups—one will receive rosiglitazone, the other a placebo (an inactive substance). Participants also will have MRIs before and at the end of treatment to determine whether rosiglitazone slows the rate of atrophy in brain structures that support memory. The RECALL trial will provide valuable data about the effects of improved insulin sensitivity, reduced insulin levels in the body, and reduced inflammation on cognitive function and biological markers in aMCI.
- **SNIFF 120**. This 4-month clinical trial will examine the effects of a nasal-spray form of insulin on cognitive function, ability to carry out daily activities, glucose metabolism in the brain, and levels of beta-amyloid in people with aMCI or AD. AD is associated with reduced levels of insulin in cerebrospinal fluid, and treatment with insulin has been shown to improve memory performance. Insulin injections can be problematic because they can result in hypoglycemia (low blood sugar). A nasal spray delivers insulin directly to the brain. Preliminary data on this way to administer insulin show that people with AD improved their verbal memory and did not develop hypoglycemia. This clinical trial will provide useful data on the safety, feasibility, and potential efficacy of this innovative treatment approach, which investigators may use to plan future large-scale clinical trials.
- **Metformin**. This NIA-funded clinical trial's primary aim is to determine whether metformin, a drug used safely and effectively to treat diabetes, reduces the risk of cognitive decline. Very high blood insulin levels have surfaced as a potential risk factor for AD. Half of the population 60 years and older may have such high insulin levels, and the prevalence is increasing with the epidemic of overweight and obesity. The research team at Columbia University hypothesized that metformin could prevent cognitive decline by reducing insulin levels in overweight and obese people who do not have diabetes but who do have aMCI. In this new, 12-month pilot trial, 60 people with aMCI will receive either metformin (1,000 mg twice a day) or a placebo. The investigators also want to determine whether metformin prevents the decrease in brain metabolism that is characteristic of the transition from aMCI to AD.
- **POEM (Pioglitazone or Exercise)**. Metabolic syndrome is an increasingly prevalent medical condition that raises a person's risk of developing diabetes and heart disease. Its cardinal features are insulin resistance (a condition in which muscle, fat, and liver cells are not able to use insulin properly), physical inactivity, and abdominal obesity. Recently, several large studies have linked metabolic syndrome to the development of cognitive impairment. In a new NIA-funded pilot trial, investigators at the University of Colorado, Denver, will examine whether treatments for metabolic syndrome in older people with aMCI can improve, stabilize, or lessen the decline in cognitive function compared with a no-treatment group. Investigators plan to test the diabetes drug pioglitazone and endurance exercise training, both of which have been shown to ameliorate many components of metabolic syndrome, including insulin resistance, and to have positive effects on cognition. This pilot trial also will evaluate how the interventions affect cognition and inflammatory biomarkers.

Estrogen and AD

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

Clinical trials have shown that estrogen does not slow the progression of already-diagnosed AD and does not effectively treat or prevent the disease if treatment begins in later life. However, questions remain as to whether some forms of estrogen might help if started somewhat earlier than the older ages already tested. These questions are now being investigated.

▶ NINDS-supported investigators at the Mayo Clinic College of Medicine have found that women who had one or both ovaries removed before menopause had an increased risk of cognitive impairment or dementia compared with a control population (Rocca et al., 2007). They also found that ovary removal at a young age (younger than age 45) further increased the risk of dementia. This risk was significantly diminished when women were treated with estrogen until the age of natural menopause. These findings underscore the relationship between estrogen and cognition and open additional avenues of investigation into estrogen's full therapeutic effects.

6 Exploring All Possibilities to Improve AD Diagnosis

AD pathology begins to develop long before clinical symptoms are readily apparent. However, AD diagnosis currently depends on assessing a range of cognitive and behavioral changes over time. Finding a way to detect the disease at the earliest point possible will allow clinicians to treat it as early as possible. One active area of AD research focuses on the development of sensitive screening instruments and neuropsychological tests to diagnose cognitive decline, aMCI, and AD as early as possible.

Ambitious efforts also are underway to find new ways to measure changes in the structure and function of the brain and in other biomarkers, such as substances in cerebrospinal fluid (CSF), and blood. These biomarkers may hint at pathological changes that occur before clinical signs of aMCI or AD are evident or when they emerge. Improvements in brain imaging and new findings about CSF biomarkers are already yielding results. For example, the development of PiB has enabled scientists to visualize beta-amyloid plaques in the living brain (see page 19 for more on PiB). Advances like this may lead to very early diagnosis of AD and will help researchers and clinicians develop new treatments and monitor their effectiveness.

▶ Clinicians need practical tools to help them differentiate memory and thinking changes that come with normal aging from those of very mild dementia. Existing cognitive tests may not be sensitive enough to detect problems in highly educated individuals or may falsely identify people with poor lifelong cognitive functioning as demented. Other tests are not practical for general clinical use.

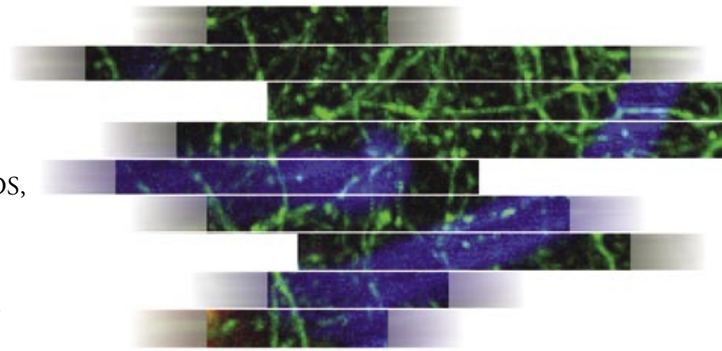
Investigators at the Washington University School of Medicine developed a new tool, the AD8, which takes advantage of the knowledge that family and close friends have of a person with memory or cognitive problems. The AD8 asks about changes in the way a person remembers or acts in various circumstances, such as forgetting appointments or having difficulty handling financial affairs. Since the AD8 was published in 2005, two studies (Galvin et al., 2006; Galvin et al., 2007) have demonstrated its reliability, validity, and flexibility. The tool can be used in face-to-face encounters or over the phone, and it can even be completed by a person with memory problems. These studies suggest that a tool like the AD8 could improve dementia diagnoses in primary care, where dementia often goes undetected. This tool also may be valuable in screening for clinical trials, community surveys, and epidemiologic studies.

▶ Because AD is a progressive disease, investigators want to be able to predict the progression from normal cognition to aMCI to AD. Two studies used neuropsychological tests to explore this area. The first study, by scientists at Harvard Medical School, indicated that the risk of progressing from normal cognition to aMCI was greater in individuals with relatively low scores on tests of episodic memory, and that the risk of progressing from aMCI to AD was increased in people with relatively low scores on tests of both episodic memory and executive function (Blacker et al., 2007). In the second study, conducted within the Alzheimer's Disease Cooperative Study (ADCS), investigators found that the best predictor of progression from aMCI to AD over the 36-month trial period was a combination of four easily administered cognitive measures (Fleisher et al., 2007) (see page 32 for more about the ADCS). The results of these studies not only may help in diagnosing aMCI and AD, but also will be important in evaluating the efficacy of interventions to modify the progression of the disease.

▶ Investigators at the Washington University School of Medicine assessed the ability of biomarkers found in CSF to identify people who were likely to get AD (as defined by clinical criteria or the presence of beta-amyloid as shown with PiB on PET scans) within a group of nondemented older people (Fagan et al., 2007). Previous work has shown that levels of beta-amyloid in CSF typically decrease in AD, but that levels of *tau* in CSF increase. This study had three main findings. First, people with very mild symptoms of AD showed the same CSF biomarker profile as those in more advanced stages of the disease, suggesting that it may be possible to diagnose AD accurately at an early stage. Second, combining CSF amyloid measures with amyloid imaging in the PET scans revealed that low CSF amyloid levels can predict whether individuals have amyloid deposits in the brain, regardless of the presence of dementia. Information about CSF amyloid levels may therefore be a useful preclinical biomarker of AD. Third, the investigators found the same relative ratio of beta-amyloid and *tau* as earlier studies have done, suggesting that this ratio may have promise as a biomarker to predict future dementia in cognitively normal older adults.

▶ In recent years, scientists have become increasingly interested in the role of inflammation in AD. A research team at Beth Israel Deaconess Medical Center, Harvard Medical School, and Boston University conducted a study, supported by NIA, NHLBI, and NINDS, to assess whether the presence of markers of inflammation was linked to increased risk of AD (Tan et al., 2007). From 1990 to 1994, the researchers measured several inflammatory markers, including CRP, IL-6, IL-1, TNF-α, and IL-1-RA, in 691 original participants in the Framingham Study. The participants were then followed for 7 years to see whether they developed AD. Participants who produced the most of two markers, IL-1 or TNF-α, showed a greater risk of developing AD than those who produced the least. The researchers concluded that high levels of some inflammatory substances may be an early risk marker of AD, and that inflammation may play a role in AD development.

▶ Although people with aMCI are at high risk of developing AD, not everyone with aMCI goes on to develop AD. Researchers want to develop diagnostic markers that can predict whether someone with aMCI will eventually progress to AD. Two studies, by researchers at the University of California Davis and at Columbia University, used MRIs to monitor the extent of atrophy (shrinkage) in critical brain regions (DeCarli et al., 2007; Devanand et al., 2007). Both studies showed that atrophy of structures in the brain's medial temporal lobe, including the hippocampus and entorhinal cortex (two structures heavily damaged by AD), could predict development of AD and the rate of progression from aMCI to AD. These results suggest that combining MRI tests with standard clinical tests during an evaluation of aMCI could help to identify which people with this condition are more likely to develop AD.



To advance this area of diagnosis research, NIA and other Federal and private-sector organizations launched the AD Neuroimaging Initiative (ADNI) in 2004. ADNI is following about 200 cognitively healthy individuals and 400 people with aMCI for 3 years, and 200 people with early AD for 2 years. Early results from ADNI suggest that the data generated will help in evaluating disease progression and may reduce the time and expense of clinical trials by improving methods and developing uniform standards for imaging and biomarker analysis. ADNI also has created a publicly accessible database containing thousands of MRI and PET scan brain images as well as clinical data that is available to qualified researchers worldwide. More than 300 researchers already have accessed ADNI data and images, and ADNI has inspired similar efforts in Europe, Japan, and Australia.

In another relatively new area of AD diagnosis research, investigators are examining other types of physical changes that may hint at AD, opening the door to other potential tools to help clinicians diagnose AD early and accurately.

▶ Researchers have studied changes in visual abilities as a possible early indicator of aMCI or AD. Scientists at the Boston University School of Medicine found that, in some people with AD, tangles and plaques develop early in the disease process in the back of the cortex, a brain region deeply involved in visual processing (McKee et al., 2006). A second group of scientists, at the University of Rochester Medical Center, used several highly sensitive tests to examine how old age and AD affect various visual abilities, including "optic flow"—the way in which the surrounding environment appears to flow past as a person moves through space (Mapstone et al., 2006). The investigators found that in visual ability tests, healthy older people did better with optic flow than with other abilities, while those with AD had trouble with optic flow as well as other visual abilities. These findings may help create objective diagnostic tests for AD.

▶ Investigators at the Rush Alzheimer's Disease Center in Chicago assessed whether impaired odor identification is related to increased risk of aMCI (Wilson et al., 2007). Consistent with previous studies, they found that, compared with people whose ability to identify odors was intact, those with impaired odor identification had a lower cognitive level and more rapid decline in certain cognitive abilities. More importantly, the researchers found that a person's score on the odor identification test was able to predict the development of aMCI.

▶ Another study, conducted at the Rush University Medical Center, found that a higher level of frailty at the beginning of the study and a more rapid increase in frailty were both associated with an increased risk of developing AD (Buchman et al., 2007).

7 Making the Most of Translational Research

Translational research is a multidisciplinary effort that creates a two-way bridge between basic science studies and clinical research. In essence, it allows valuable knowledge from the laboratory to be applied as quickly as possible to potential new tests or interventions in the clinical setting. Translational research also offers an important opportunity for collaboration between scientists concerned with the cellular, molecular, and pathologic dimensions of disease and clinicians who focus on treating people.

NIA is engaged in a variety of translational initiatives to expand possible avenues for AD therapies and, eventually, the number of clinical trials to test them in humans. For example, NIA is working to stimulate the discovery, development, and preclinical testing of various novel compounds to prevent and treat the cognitive impairment and behavioral symptoms of aMCI, AD, and age-related cognitive impairment. The Institute's Translational Research Initiative aims to increase the number of submissions of investigational new drug (IND) applications to the FDA, so that more clinical trials to test promising therapies can be started and can use a wider variety of intervention strategies.

In addition, NIA supports toxicology services for investigators and small companies that have a potentially viable drug for AD treatment but lack the resources to begin the formal drug toxicology testing process needed for an IND. Two program announcements have been issued for this initiative—one for early-phase drug discovery grants and another for later-phase cooperative agreement drug development grants. The first cooperative agreement awards under the drug development initiative were made in 2006. The first annual Investigators Meeting for Translational Research was held in September 2007.

To date, NIA has funded more than 60 translational research grants, using various funding mechanisms, directed at discovery or development of multiple therapeutic targets, including:

- **Anti-amyloid approaches**. Researchers are conducting studies to identify compounds that can activate alpha-secretase (an enzyme that cleaves APP in such a way that harmful beta-amyloid is not formed), liver X-receptor activators, and different metal-complexing strategies.
- **Anti-*tau* approaches**. Researchers are discovering and developing drugs that stabilize microtubules, the structures that guide nutrients and other molecules from the cell body to the end of the axon.
- **Cognitive enhancer approaches**. Researchers are working to discover novel nonsteroidal anti-inflammatory drugs (NSAIDs), nitric oxide/cyclic guanosine monophosphate/CREB pathway enhancers, and dual gamma-aminobutyric acid and nicotinic receptor activators, all of which are designed to enhance cognitive processes.

In other funded translational research projects, investigators are developing a range of novel compounds and drugs that may eventually be used to treat AD.

▶ Investigators at the Center for Drug Discovery and Chemical Biology at Northwestern University have developed an innovative, safe, and water-soluble small molecule that prevents increases in selected injury-induced inflammatory proteins in the brain (Hu et al., 2007). The development of this molecule presents scientists with an opportunity to explore new approaches for potentially useful AD therapies.

▶ Because of the associations between diabetes and AD, scientists are looking at whether a class of drugs that includes rosiglitazone, which increase a person's sensitivity to insulin, may be useful in treating AD. However, the mechanisms underlying the potential beneficial effects of rosiglitazone in AD remain unclear. A study conducted by scientists at Creighton University Medical Center, in Omaha, Nebraska, demonstrates that rosiglitazone lessens learning and memory deficits in a transgenic mouse model of AD (Pederson et al., 2006). The drug's beneficial effects on learning and memory were associated with reduced accumulation of beta-amyloid in the brain. The data also suggest that these effects may be mediated by the glucocorticoid-lowering actions of the drug. A clinical trial is underway to test rosiglitazone's effects on attention and memory in adults with aMCI (see page 26 for a description of this trial).

8 Supporting the Gold Standard: AD Clinical Trials

Clinical trials, which compare a potential new treatment with a standard treatment or a placebo, are the only way to prove whether a drug or other type of treatment is effective. These complex, expensive studies can involve hundreds or even thousands of people and often are conducted over a long period of time. Some clinical trials focus on prevention strategies to help people reduce the risk of developing AD in the future. Others focus on AD treatment strategies to preserve cognitive function for as long as possible, to alleviate behavioral or psychiatric problems, or to slow disease progression.

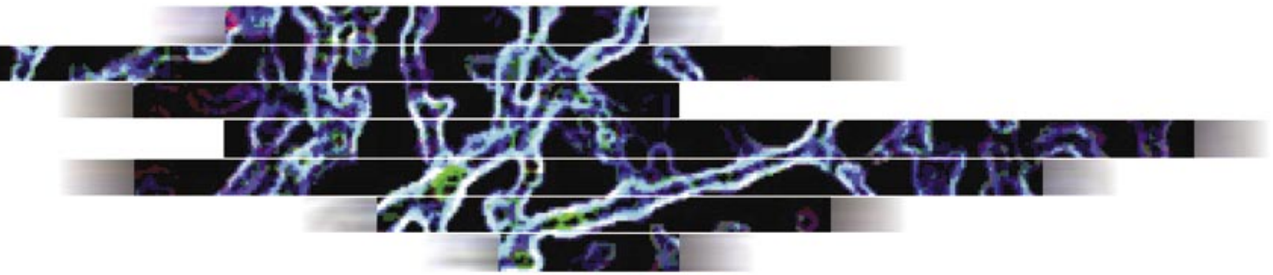
For example, a recently funded clinical trial will use gene therapy to treat AD with nerve growth factor (NGF). NGF potently prevents the death and augments the function of cholinergic neurons (neurons that produce the neurotransmitter acetylcholine) in regions of the brain that are extensively damaged in AD. This trial builds on the results of an earlier clinical trial of NGF gene delivery in early-stage AD patients. That earlier trial demonstrated robust growth responses of cholinergic neurons to NGF in the AD brain, possible effects on cognition over 22 months, and a significant increase in cortical glucose uptake in participants who received the treatment.

The new 24-month, multi-center clinical trial of NGF gene delivery in AD will test whether this therapy slows the clinical progression of AD by preventing cell loss and augmenting neuronal function. Fifty people with mild to moderate AD will be randomly assigned to receive two injections of NGF in their brains or to have a control surgical procedure with no injections of NGF. University of California San Diego investigators will conduct cognitive, clinical, and safety assessments as well as PET scans. If the preliminary results are favorable, participants who received the control surgery will be offered active NGF treatment.

Federal and non-Federal agencies and organizations are currently supporting more than 50 AD-relevant clinical trials (see the table on pages 34 to 36 that lists trials funded by NIA). A cornerstone of NIA's efforts in clinical-trials research is the Alzheimer's Disease Cooperative Study (ADCS), launched in 1991. This consortium of about 70 sites focuses on trials of compounds developed by individual investigators or small companies with limited resources for clinical trials. A recent focus has been on partnering with larger companies. In addition to testing new compounds, the ADCS is developing new methods for conducting dementia trials.

The most recent round of ADCS trials, funded in October 2006, explore a variety of topics:

- **Docosahexaenoic acid (DHA)**. This ongoing trial is examining whether treatment with DHA, an omega-3 fatty acid found in fish, will slow cognitive decline in 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 levels of beta-amyloid in the brain, oxidative damage associated with beta-amyloid, and neurotoxicity.
- **Immune globulin intravenous (IGIV)**. Interest in passive AD immunization strategies is growing (see page 13 for more on this research). IGIV, a blood product that is administered intravenously, contains naturally occurring antibodies against beta-amyloid. Preliminary studies have shown that it may improve cognition. Other research has demonstrated that IGIV increased levels of anti-beta-amyloid antibodies in plasma and promoted clearance of beta-amyloid from CSF. The new ADCS trial will study whether IGIV is useful clinically for treating AD.
- **Lithium**. The biological activity of lithium, shown in animal studies to block abnormal changes in *tau*, has created interest in this drug as a novel treatment for AD. ADCS investigators plan to undertake a pilot biomarker trial to see whether lithium can lower *tau* and beta-amyloid levels in CSF and be safely tolerated in older AD patients.
- **Home-based assessment**. In this ADCS trial, conducted in people age 75 and older, researchers at 26 sites will test three home-based methods to assess cognition, daily functioning, mood, and other factors. The first involves the use of a computer "kiosk" that combines a touch-screen monitor with a telephone handset to answer a series of questions. The second is an interactive voice-response system that prompts a person to answer questions out loud. The third involves filling out and mailing in paper forms and completing a validated cognitive assessment by telephone. Each of these methods will be compared with traditional in-person methods. The findings will provide information about the use of home-based assessments to reduce the cost and increase the feasibility of participation in long-term clinical trials.
- **Resveratrol**. Investigators conducting this trial will evaluate the impact of resveratrol treatment on AD biomarkers and clinical outcomes in people with mild to moderate AD. Resveratrol, a molecule that promotes neuronal survival, has been shown to prevent learning impairments in mouse models of neurodegenerative diseases. Participants in this trial will receive either resveratrol or a placebo in addition to existing FDA-approved AD medical management.



NIA-Funded Clinical Trials for the Prevention and Treatment of AD, aMCI, and Cognitive Decline*

Trial Name	Principal Investigator	Intervention	Population
Antioxidants			
Alzheimer's Disease in Down Syndrome: Antioxidant Trial	Ira Lott	Vitamins E and C, alpha-lipoic acid	People ages 40+ with Down syndrome and AD
Antioxidant Trial**	Douglas Galasko	Vitamins E and C, alpha lipoic acid, coenzyme Q	People with AD
GEM (Ginkgo Evaluation of Memory)†	Steven DeKosky	Ginkgo biloba	People ages 75+
PREADVISE (Prevention of Alzheimer's Disease by Vitamin E and Selenium)‡	William Markesbery	Vitamin E, selenium, Vitamin E + selenium	Men ages 60-90 participating in SELECT
Vitamin E in Aging Persons with Down Syndrome	Arthur Dalton	Vitamin E	People ages 50+ with Down syndrome, at high risk of developing AD
Cardiovascular			
ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes—Memory in Diabetes)‡	Lenore Launer	Intensive glucose, blood pressure, and lipid management	People ages 40-79 with type 2 diabetes
CLASP (Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease Study)**	Mary Sano	Simvastatin	People with AD
ESPRIT (Evaluating Simvastatin's Potential Role in Therapy)	Cynthia Carlsson	Simvastatin	People ages 35-69 at high risk of AD (family history)
Omega-3 Fatty Acids			
AREDS2 (Age-Related Eye Disease Study 2)†	Emily Chew and John Paul SanGiovanni	Macular xanthophylls (lutein and zeaxanthin) and/or omega-3 fatty acids (DHA and EPA)	People ages 50-85 with age-related macular degeneration (AMD)
DHA (Docosahexaenoic Acid), an Omega-3 Fatty Acid, in Slowing the Progression of Alzheimer's Disease**	Joseph Quinn	DHA	People with AD
Passive Immunization			
Immune Globulin Intravenous (IGIV) for Treatment of Alzheimer's Disease**	Norman Relkin	IGIV	People with AD

Trial Name	Principal Investigator	Intervention	Population
Hormones			
Alzheimer's Disease: Potential Benefit of Isoflavones	Carey Gleason	Novasoy (soy isoflavones–phytoestrogens)	People with AD
ELITE (Early Versus Late Intervention with Estradiol)	Howard Hodis	17β-estradiol	Healthy early (less than 6 years) and late (10 years+) menopausal women
KEEPS-CA (Kronos Early Estrogen Prevention Study—Cognitive and Affective Study)‡	Sanjay Asthana	Oral conjugated equine estrogen (CEE, or Premarin®) and transdermal 17β-estradiol	Healthy perimenopausal women, ages 42-58
Raloxifene for Women with Alzheimer's Disease	Victor Henderson	Raloxifene (selective estrogen receptor modulator, or SERM)	Older women with AD
SMART (Somatotrophics, Memory, and Aging Research Trial)	Michael Vitiello	Growth hormone releasing hormone (GHRH)	People with aMCI and healthy people, ages 55-80
Testosterone Supplementation in Men with MCI	Monique Cherrier	Testosterone	Older men with aMCI and low testosterone
Diabetes			
Glucose Regulation and Memory in Alzheimer's Disease	Suzanne Craft	Diet, triglyceride emulsion, rosiglitazone	People with AD (all studies), age-matched healthy older adults (diet)
Metformin in Amnestic MCI	Jose Luchsinger	Metformin	Overweight people with aMCI
RECALL (Rosiglitazone Effects on Cognition for Adults in Later Life)	Suzanne Craft	Rosiglitazone	People with aMCI
SNIFF 120 (Study of Insulin to Fight Forgetfulness, 120 Days)	Suzanne Craft	Intranasal insulin	People with aMCI and AD
Diabetes and Exercise			
POEM (Pioglitazone or Exercise to Treat Mild Cognitive Impairment)	Robert Schwartz	Pioglitazone, endurance exercise training	Older people with aMCI and metabolic syndrome
Exercise			
Exercise and Cognitive Aging	Robert Krikorian	Aerobic exercise	People with aMCI
Exercise and Health Promotion for MCI: A Controlled Trial	Linda Teri	Two exercise programs	People with aMCI and cognitively intact older people

Continued on next page

NIA-Funded Clinical Trials (continued)

Trial Name	Principal Investigator	Intervention	Population
Exercise and Cognitive Training			
SHARP-P (Seniors Health and Activity Research Program Pilot)	Mark Espeland	Physical activity, cognitive training	People at risk of aMCI, ages 70-85
Other Trials			
Antipsychotic Discontinuation in Alzheimer's Disease	Dev Devanand	Risperidone	People with AD
CITAD (Citalopram for Agitation in AD)	Constantine Lyketsos	Citalopram	People with AD
Huperzine A in Alzheimer's Disease	Paul Aisen	Huperzine A	People with AD
Phase II Trial of AAV-NGF Gene Delivery in Alzheimer's Disease	Paul Aisen	Nerve growth factor (NGF) gene delivery	People with AD
Pilot Phase II Study to Evaluate the Impact of Biomarkers of Resveratrol Treatment**	R. Scott Turner	Resveratrol	People with AD
Transdermal Nicotine Treatment of MCI	Paul Newhouse	Nicotine patch	People with aMCI
TREA (Treatment Routes for Exploring Agitation)	Jiska Cohen-Mansfield	TREA, a systematic approach to individualizing nonpharmacological interventions for people with dementia	Nursing home residents with AD/dementia
Trial to Assess Biomarker Outcomes, Safety, and Tolerability of Lithium Carbonate**	Pierre Tariot	Lithium	People with AD
VALID (Valproate in Dementia)**	Pierre Tariot	Valproate	People with AD

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

* As of October 2008.
** Alzheimer's Disease Cooperative Study trial.
† NIA co-funded trials: GEM (National Center for Complementary and Alternative Medicine, lead institute); AREDS2 (National Eye Institute, lead institute).
‡ NIA-funded add-on trials: PREADVISE (add-on to National Cancer Institute's SELECT trial); ACCORD-MIND (add-on to NHLBI's ACCORD trial); KEEPS-CA (add-on to Kronos Longevity Research Institute's KEEPS trial).

9 Helping Caregivers Cope

Caring for a person with AD presents unique challenges, and considerable research has explored the physical, emotional, and mental stresses on AD caregivers. This area of research is an important component of NIH's overall AD research effort. Investigators supported by NIA, NIMH, and NINR continue to study ways to understand better the effects of caring for a loved one with AD and to find improved methods of caregiving.

▶ An emerging body of findings suggests that chronic stress has a negative impact on the immune system. A study by NIA intramural investigators compared the immune cells of AD caregivers and a control group. They found strong evidence that the chronic stress of caregiving adversely affected the caregivers' immune function (Damjanovic et al., 2007). In addition, the investigators found negative effects on the regulatory processes controlling cell replication and aging.

An ultimate goal of AD research is to find ways to reduce stress and burden on caregivers. For example, agitation, psychosis, and disruptive behaviors can be difficult for caregivers to cope with. Investigators are exploring a diverse array of treatment approaches to help both the person with AD and the caregiver by reducing psychiatric and behavioral symptoms through drug therapies and other means.

▶ A clinical trial is examining whether the drug valproate can delay or prevent agitation and psychosis in people with mild to moderate AD. Researchers also are interested in seeing whether valproate's possible neuroprotective properties can slow the rate of cognitive decline.

▶ A clinical trial supported by NIMH has tested the safety and effectiveness of two medications to treat psychosis in people with dementia (Pollock et al., 2007). One group received the antidepressant citalopram and the other group received the second-generation, or "atypical," antipsychotic risperidone, which is commonly prescribed to treat agitation and psychosis in people with dementia. The trial, conducted by scientists at the Rotman Research Institute in Toronto, found that the number of patients who completed the treatment protocol did not differ between the two groups. Symptoms declined similarly in the two groups. However, the group treated with risperidone reported more side effects than the citalopram group. This trial suggests that antidepressants may be better tolerated and possibly safer than atypical antipsychotic medications in people with dementia. Before definitive conclusions can be made about treating behavioral and psychotic symptoms in people with AD, these findings need to be replicated in a larger group with a broader array of antidepressants and antipsychotic medications.

▶ Managing agitation is a major priority in AD treatment, but nondrug options have limited effectiveness. Several drug options have been explored, but findings for anticonvulsants, antipsychotics, and cholinesterase inhibitors have been disappointing or associated with questionable risk-to-benefit ratios. Better drug options are needed. Selective serotonin reuptake inhibitors show promise as a treatment for agitation in AD, based on evidence of a link between agitation and serotonin abnormalities in people with AD. Also encouraging are preliminary clinical data from a single-site trial in which the selective serotonin reuptake inhibitor citalopram proved superior to perphenazine (an antipsychotic drug) and a placebo. NIA and NIMH recently co-funded the Citalopram for Agitation in AD (CITAD) trial, which brings together investigators who have collaborated successfully in the ongoing Depression in Alzheimer's Disease Study (DIADS-2) and the completed Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE–AD). CITAD will examine the efficacy and safety of citalopram as a treatment for clinically significant agitation in 200

people with AD. The 9-week, eight-site trial also will investigate pharmacogenomic, genetic, and clinical predictors of response to citalopram therapy in outpatients and nursing-home and assisted-living residents. Using state-of-the-art clinical ratings and novel weekly caregiver telephone ratings, CITAD will examine the effects of citalopram on agitation, other neuropsychiatric symptoms, cognition, quality of life, and daily functioning.

▶ NIMH-supported investigators at the University of Southern California and the Veterans Administration Connecticut Health Care System conducted a cost-benefit analysis of the use of atypical antipsychotic drugs to treat psychosis, agitation, and aggression in people with AD (Rosenheck et al., 2007). Using data from a large clinical trial on the effectiveness of treatment with antipsychotics, the investigators found that in some instances treatment with these drugs was no more effective than "watchful waiting," which involves general medical management and support but no treatment with antipsychotics. They also found that drug treatment was significantly more expensive.

Other investigators are exploring ways of managing psychiatric and behavioral problems through interventions that do not involve drugs.

▶ An NIMH-supported study by researchers at Pennsylvania State University showed that adult day care services may help caregivers manage some behavioral and psychological symptoms, such as nighttime sleep disturbances (Femia et al., 2007).

▶ Scientists at the Research Institute on Aging of the Charles E. Smith Life Communities in Rockville, Maryland, developed and tested an algorithm for nursing home staff to use in providing individualized, non-drug interventions for residents with agitation (Cohen-Mansfield et al., 2007). The algorithm helped staff identify the type of agitation and the particular needs of the resident. It also helped them design responses that reduced the resident's agitation in a way that matched his or her cognitive, physical, and sensory abilities and lifelong habits and roles. Use of the algorithm significantly decreased agitation in the test group, and use of the individualized interventions increased residents' pleasure and interest in life.

▶ NINR supported a clinical trial, conducted by a research team at Rush University Medical Center, to test a skill-building intervention with a group of caregivers who were coping with severe behavioral symptoms in a family member with AD (Farran et al., 2007). Compared with a basic information and support intervention, the skill-building program more effectively reduced caregivers' emotional distress. The reduced stress level persisted during an 18-month period.

▶ NINR-supported researchers at the University of California San Francisco conducted a clinical trial that tested the effect of 1 hour of daily light therapy on the frequency and severity of disruptive behaviors in nursing home residents with AD (Dowling et al., 2007). Residents who received light therapy showed a small but statistically significant reduction in levels of agitation, depression, eating disorders, and abnormal motor behavior.

Many people who develop AD must eventually move from their homes or an assisted living facility to a nursing home where they can receive more intensive care. A major clinical goal is to maximize the person's ability to function independently and to continue living in the least restrictive environment for as long as possible. A number of researchers are investigating ways to achieve this goal.

▶ Placing a loved one in a nursing home may relieve some of the burden of caregiving but does not necessarily reduce caregiver stress or emotional distress. Investigators at New York University School of Medicine tested the effects of an enhanced counseling and support program on nursing home placement and caregiver health (Mittelman et al., 2006; Mittelman et al., 2007). This program for AD caregivers consisted of six sessions of individual and family counseling, support group participation, and on-demand telephone counseling. Participants showed less of a decline in how they rated their own health over time than did other caregivers who did not participate in the program. Participants also were able to delay placing their loved ones in nursing homes by about 18 months. Researchers attributed these results to improved caregiver well-being, which was demonstrated by greater tolerance for the loved one's memory and behavior problems, improved satisfaction with the support provided by family and friends, and fewer symptoms of depression.

▶ In an ongoing NIMH-supported study, investigators at Johns Hopkins University followed 198 people for 18 months to estimate the association between dementia and the length of time in an assisted living facility before death or placement in a nursing home (Lyketsos et al., 2007). Preliminary findings showed that the length of residence for people with dementia was, on average, 209 days shorter than for other residents. The researchers found that a lack of treatment for dementia and the presence of other serious medical conditions predicted the shorter stays of residents with dementia. To a lesser extent, impairments in mobility and limited participation in activities at the assisted living facility also played a role.

The ADEAR Center: Helping Caregivers Become Informed

One of the best ways caregivers can help themselves is to become well informed about AD and to learn strategies for effective and flexible caregiving. The Alzheimer's Disease Education and Referral (ADEAR) Center is an NIA service that provides the public—including caregivers, people with AD, and health professionals—with AD information and resources.

ADEAR staff members answer telephone, email, and written requests and make referrals to local and national resources. In addition, the ADEAR Center offers information and publications for families, caregivers, and professionals on diagnosis, treatment, patient care, caregiver needs, long-term care, education and training, and research related to AD.

The ADEAR website offers free, online publications in English and Spanish, email alerts, online *Connections* newsletter subscriptions, an AD clinical trials database, the AD Library database, and more.

Alzheimer's Disease Education and Referral (ADEAR) Center
800-438-4380 (toll-free)
www.nia.nih.gov/Alzheimers

Outlook *for the* Future

After 30 years of intensive study, momentum in AD research is palpable. Today, scientists are increasingly optimistic about the promise of AD research. Initially, they focused on defining the major characteristics of the disease, its course, and aspects of its etiology. Since then, they have built an enormous base of knowledge about AD and the many factors that contribute to the damage it causes to the brain and body. Researchers are now beginning to apply that knowledge to treatment and prevention strategies. To sustain this momentum, NIH is moving ahead on a number of fronts, described in the sections below.

Improving Basic Understanding

Research must continue to refine the mechanistic understanding of AD. Though we understand much about the disease, important gaps in knowledge remain. Basic research is central to the search for effective new therapies because it allows scientists to understand better the normal biology of the aging brain and what goes wrong in a disease like AD. One promising area of basic research involves studies to learn more about the molecular basis of cognition and how it changes with age. Another area of interest is how the brain adapts to injury. Researchers know that the brain is a remarkably adaptive organ, and they want to learn more about the components that are important to adaptability, the molecular basis of cognitive reserve, and whether strategies to build cognitive reserve can prevent or delay the negative consequences of AD pathology. The Cognitive Aging Summit sponsored by NIA and the McKnight Brain Research Foundation in Washington, D.C., in October 2007 helped identify topics in these areas of basic research that are most likely to bear fruit.

Identifying Genetic Causes and Risk Factors

With the establishment of the Alzheimer's Disease Genetics Initiative and the Alzheimer's Disease Genetics Consortium, scientists hope to learn considerably more about the major risk-factor genes for late-onset AD and for cognitive decline. Understanding more about the genetics of cognitive decline and AD will shed light on how much genetic risk they share. Knowing the risk-factor genes will help to pinpoint new pathways that contribute to the early development of AD and to identify people at the greatest genetic risk of cognitive decline or AD.

Understanding Disease Progression

Findings from the Alzheimer's Disease Neuroimaging Initiative reported over the next few years will likely indicate which combinations of clinical, neuropsychological, imaging, and biomarker tests best predict who will progress from aMCI to AD and how this progression occurs. Improved knowledge in this area also will help accelerate and refine the conduct of clinical trials. A greater understanding of disease progression will eventually allow clinicians to start therapies much earlier in the disease process, when changes in the brain associated with AD are still minimal.

Making the Most of Translational Research and Clinical Trials

Translational initiatives and federally supported clinical trials should provide important new approaches for AD prevention and treatment because they will ensure that researchers with promising therapies have opportunities to develop them. Many compounds that test well in animal models and that have a sound theoretical basis fail in clinical trials because of safety or efficacy problems. It is important to understand why this happens. Many different therapeutic targets must be pursued besides the obvious ones of beta-amyloid and *tau*.

By funding clinical trials, NIA also hopes to provide the necessary foundation for private industry or NIH to support "follow-up" clinical studies of the most promising leads.

Cultivating Research Infrastructure and Resources

NIH will continue to provide the framework through which investigators can conduct interdisciplinary and collaborative AD research. For example, in 1999, NIA established the National Alzheimer's Coordinating Center (NACC) (*www.alz.washington.edu*) so that data on healthy people and patients from the Alzheimer's Disease Centers could be pooled and shared. By 2005, information on more than 75,000 Alzheimer's Disease Center study participants and neuropathologic data on more than 9,000 brains from autopsied participants had been collected. Much of this material is

available for research by qualified scientists.

In 2006, NACC launched the Alzheimer's Disease Center Uniform Data Set (UDS), a system that improved upon a previous data collection system by standardizing data collection across research sites. Initially developed to gather information on healthy participants and those with aMCI and early AD, the UDS has since expanded to collect data on participants with frontotemporal dementia, Lewy body dementia, and vascular dementia. More than 15,000 individuals are now being evaluated using the UDS. Data are available to qualified researchers through NACC.

Workshops and meetings, such as the AD Planning Meeting held in October 2006 and the Cognitive Aging Summit held in October 2007, provide an opportunity for experts to gather and assess basic, translational, and clinical research efforts and to assess future strategies for maximizing public investment.

NIA and other NIH Institutes and Centers that conduct research on AD collaborate with many others to push the boundaries of our knowledge about this disease. For example, the Institutes work with the Foundation for the National Institutes of Health to identify appropriate funding opportunities with private industry. NIA collaborates with private foundations, such as the Alzheimer's Association and the Alzheimer's Drug Discovery Foundation, on specific initiatives. NIA has worked with both organizations on the Alzheimer's Disease Neuroimaging Initiative through the Foundation for the National Institutes of Health and with the AD Discovery Foundation on translational research projects. NIH scientists also work with colleagues at the Centers for Disease Control and Prevention, the FDA, and other Federal agencies to ensure expeditious efforts to find the best combinations of behavioral and drug interventions for AD and age-related cognitive decline.

Conclusion

The theme of the *2007 Alzheimer's Disease Progress Report* is "Discovery and Hope." It's a fitting description for, during 2007, AD researchers continued to push the boundaries of knowledge through discoveries on a number of fronts—basic and genetics research on the fundamental nature of the disease and its relationship to normal aging; epidemiologic studies on associations between AD risk, lifestyle factors, and chronic disease; studies on early physiologic changes that signal AD development; translational research studies; clinical trials; and studies to help caregivers.

These discoveries are fostering hope that our richer understanding of the disease (and our growing appreciation of its complexities) are leading to the development of improved techniques for diagnosing AD early and accurately and to the identification of a range of potential therapeutic targets. There is also new hope for the development of effective strategies for helping caregivers cope and even for the identification of possible factors that may reduce AD risk.

At the same time, we cannot forget that AD remains an urgent health problem for our Nation and that we still have much to learn about the disease. Our task is to build on these recent discoveries through continued support for multidisciplinary, collaborative AD research so that its potential will become a reality for millions of older adults.

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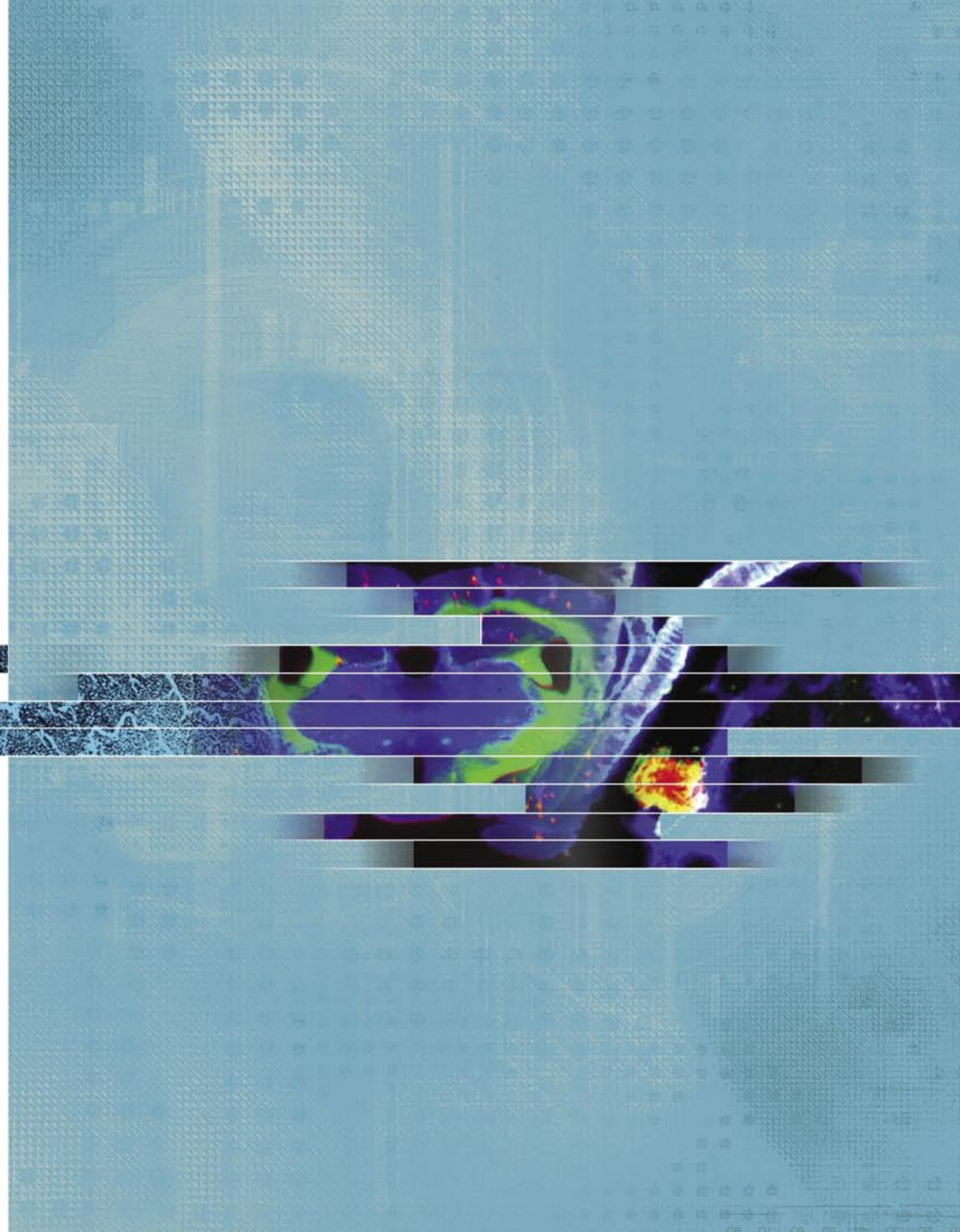

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