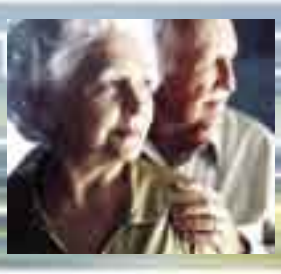
2005–2006 PROGRESS REPORT ON **ALZHEIMER'S DISEASE**

Journey to DISCOVERY

U.S. Department of
Health and Human Services



2005–2006

PROGRESS REPORT ON ALZHEIMER'S DISEASE

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), has primary responsibility for basic 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 *2005-2006 Progress Report on Alzheimer's Disease* summarizes recent AD research conducted or supported by NIA and other components of NIH, including:

- National Center for Complementary and Alternative Medicine (pages 29, 44)
- National Center for Research Resources (page 25)
- National Heart, Lung, and Blood Institute (pages 22, 23, 31, 33, 34, 44)
- National Institute of Biomedical Imaging and Bioengineering (pages 15, 36, 57)
- National Institute of Child Health and Human Development (page 29)
- National Institute of Mental Health (pages 30, 43, 50, 51, 52, 57)
- National Institute of Neurological Disorders and Stroke (pages 28, 51, 57)
- National Institute of Nursing Research (pages 52, 53, 57)

Additional AD research efforts also are supported by the National Cancer Institute, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute on Alcohol Abuse and Alcoholism, National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Environmental Health Sciences, National Center on Minority Health and Health Disparities, and the John E. Fogarty International Center.

In Remembrance

This *Progress Report on Alzheimer's Disease* is dedicated to Leon Thal, M.D. (1944–2007), a leading AD researcher, exceptional scientist, consensus builder, caring and talented clinician, and wonderful human being of extraordinary wisdom and energy. Many, many people will deeply miss him.

CONTENTS

Introduction

PART 1

Alzheimer's disease is an age-related, irreversible brain disorder that develops over a period of years. Initially, people experience memory loss and confusion, which can be mistaken for age-related memory change. These symptoms gradually lead to behavior and personality changes, a decline in cognitive abilities (such as decision-making and language skills), an inability to recognize family and friends, and ultimately to a severe loss of mental function. These losses are related to the breakdown of the connections between certain nerve cells in the brain and the eventual death of many of these cells. AD is one of a group of disorders, called dementias, that are characterized by cognitive and behavioral problems.

The course of this disease varies from person to person, as does the rate of decline. In most people with AD, symptoms first appear after age 65. Although the risk of developing AD increases with age, AD and dementia symptoms are not part of normal aging. AD and other dementing disorders are caused by diseases that affect the brain, although age-related brain and body changes can affect the development of dementia.

Alzheimer's Disease: A Looming National Crisis

For many older adults and their families, AD stands in the way of the "Golden Years." And the impact of the disease doesn't stop there, for it presents a major problem for our health care system and society as a whole as well:

- AD is the most common cause of dementia among people age 65 and older. Scientists estimate that 4.5 million people in the U.S. currently have the disease, and 13.2 million Americans will have AD by 2050 if current population trends continue and prevention is still not possible (Hebert et al., 2003).
- A 2005 Census Bureau report on aging in the U.S. notes that the population age 65 and older is expected to double in size to about 72 million within the next 25 years (He et al., 2005). Moreover, the 85 and older age group is now the fastest growing segment of the population. This is important for AD because the prevalence of AD (the number of people with the disease at any one time) doubles for every 5-year age interval beyond age 65. One study shows that nearly half of all people age 85 and older have AD (Evans et al., 1989).
- The number of AD caregivers—and their needs—can be expected to escalate rapidly as the population ages and as the number of people with AD grows. During their years of AD caregiving, spouses, relatives, and friends experience great emotional, physical, and financial stress. As the disease runs its course and the abilities of people with AD steadily decline, family members face difficult decisions about the long-term care of their loved ones. Frequently, they turn to assisted living facilities, then nursing homes, for care and support.
- The growing number of people with AD and the costs associated with the disease put a heavy economic burden on society. The national direct and indirect costs of caring for AD patients are estimated to be as much as $100

billion a year (Ernst and Hay, 1994; Ernst et al., 1997; Huang et al., 1988). A study commissioned by the Alzheimer's Association and conducted by the Lewin Group provides a sobering picture of the impact of AD by projecting the future costs to Federal health programs of AD if current trends continue (Lewin Group, 2004). The study estimates that total Medicare spending on treating beneficiaries with AD will increase from $62 billion in 2000 to $189 billion in 2015. By 2050, Medicare will be spending more than $1 trillion on AD-related costs, or 4 out of every 10 dollars spent by the program. State and Federal Medicaid spending also will show large increases. The study estimates that this spending will increase from $19 billion in 2000 to $118 billion in 2050.

AD Research: A National Priority

Given our aging population, AD is a steadily increasing national health problem. This makes the disease an urgent research priority. Interventions that could delay or prevent the onset of AD would have an enormous positive public health impact because they would greatly reduce the number of people with the disease. This, in turn, would reduce the personal and financial costs of caring for people with AD.

Our knowledge about the origins and development of AD and about potential preventive and treatment strategies has progressed rapidly in recent years. The ultimate goal of reducing the individual and societal burden of this devastating disease is within our reach if we can:

- Improve diagnostic tools, such as neuropsychological tests, imaging tests, and biological markers, so that AD can be diagnosed accurately and early, and treatments can be monitored more effectively;
- Develop better medicines and behavioral techniques to treat AD;
- Create improved strategies for caregiving and better coping mechanisms for caregivers; and
- Devise approaches that could delay the onset of AD or even prevent the disease.

Educating and Informing: Another Vital Mission

Efforts to educate and inform people with AD, their families, the public, providers, and others interested in the disease are an important complement to NIA's research initiatives in AD.

The NIA Alzheimer's Disease Education and Referral (ADEAR) Center (www.nia.nih.gov/alzheimers) provides a variety of materials on AD, including information about caregiving, diagnosis and treatment, and results of research findings. For example, the online publication *Alzheimer's Disease: Unraveling the Mystery*, uses illustrations and text to explain AD, highlight ongoing research, and describe efforts to support caregivers of people with AD. *Genes, Lifestyles, and Crossword Puzzles: Can Alzheimer's Disease be Prevented?* summarizes the latest research findings on AD risk factors and potential prevention strategies. These booklets for the general public are available free of charge from the ADEAR Center.

ADEAR also maintains a database of AD clinical trials, develops recommended reading lists, and provides referrals to AD resources. In addition, all of the NIA-supported Alzheimer's Disease Centers (ADCs) have education and information programs that work locally to disseminate information about AD (see p. 47 for more about the ADCs).

The 2005-2006 AD Progress Report: A Journey's Tale

Sometimes journeys are straightforward. Point B lies in a direct line some distance ahead of Point A. Other journeys are more circuitous—travelers must take many winding and intersecting paths, and even go around a few traffic circles to get from Point A to Point B. Scientific research in complex diseases like AD certainly falls into this latter category. Progress depends on the accumulation of results from many studies. Findings from one study add to or support findings from other studies. Unexpected findings can mean that investigators must head in a new direction. A promising track may suddenly become a scientific dead end, requiring researchers to rethink their original hypotheses. A possible intervention may have serious negative side effects in animals or humans, necessitating an alternative approach. Investigators may travel from laboratory "bench" to clinical "bedside" and back again before an intervention is thoroughly tested and refined.

By following many pathways over the past 30 years, scientists have built a solid body of evidence about AD. Initially, research defined the major characteristics of AD, the course of the disease, and some aspects of its etiology (causal factors). As this knowledge base developed, scientists were able to design increasingly sophisticated studies to understand more about the early changes in the brain of a person with AD, and the many factors that contribute to the development of these pathologies, or damage caused by the disease. They also were able to expand into other areas of research. These research paths necessarily intersect and depend on each other:

- Test tube and animal studies are revealing fundamental information about why, how, and when biological events occur in AD. They provide a major foundation for translational research (research that facilitates the two-way transfer of knowledge between basic scientific observations and clinical care and clinical trials; see p. 38 for more information). These studies also have increased our appreciation of the differences between species and the fact that findings in animals do not necessarily translate to humans.

- Epidemiologic studies in humans can show associations between basic characteristics and factors that are hypothesized to cause a disease. Epidemiologic studies are valuable because they pave the way for additional testing in clinical trials.

- Clinical trials test possible interventions suggested by test tube, animal, and epidemiologic studies. These trials can control variables known to be important, thereby lending greater certainty to conclusions about cause and effect (see p. 44 for more information).

- Findings from clinical trials feed back to suggest new pathways to explore in test tube, animal, and epidemiologic studies.

Part 2 of the *2005-2006 Alzheimer's Disease Progress Report* describes recent milestones in this ongoing journey down the many paths of AD research.

In addition to a map, journeys also require a means of transport. **Part 3** describes NIH programs and initiatives that have nurtured the essential research infrastructure, allowing scientists to push forward the basic science, conduct essential observational and clinical studies, and begin to develop new drugs and other treatment approaches.

Finally, travelers must plan ahead for future challenges as the journey unfolds. The final section of this report, **Part 4**, provides such an outlook for the future in AD research.

A Brief Primer on AD

The healthy human brain is made up of billions of different kinds of nerve cells (neurons) that are connected through a diverse array of 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.

The nucleus 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 down to the end of the axon. Here, it triggers the release of special chemicals, called neurotransmitters, that move across a gap, called a 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 other dendrites, 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 nerve cells stop functioning, lose connections with other nerve cells, and die because communication, metabolism, and repair are disrupted.

At first, AD destroys neurons in parts of the brain that control memory, including the entorhinal cortex, the hippocampus, and related structures. AD later attacks the 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 caused by the disease are:

- **Amyloid plaques.** Plaques are found in the spaces between neurons. They consist of largely insoluble deposits of a protein fragment called beta-amyloid peptide, together with 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 (see p. 12 for more details on the plaque formation process).
- **Neurofibrillary tangles (NFTs).** NFTs, which are found inside neurons, are abnormal collections 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 and back. *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 NFTs. When this happens, the microtubules disintegrate and the neuron's transport system collapses.
- **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 they die. As neuronal death spreads through the brain, affected regions begin to shrink in a process called brain atrophy. By the final stage of AD, damage is widespread and brain tissue has shrunk significantly.

What Causes AD?

In a very few families, people develop AD in their 30s, 40s, and 50s. These people have a mutation in one of three genes that they have inherited from a parent. We know that mutations in these genes cause AD in these "early-onset" cases.

More than 90 percent of AD develops in people older than 65. This form of AD is called "late-onset" AD, and its development and pathology are very similar to that 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 the elderly. 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 in AD.

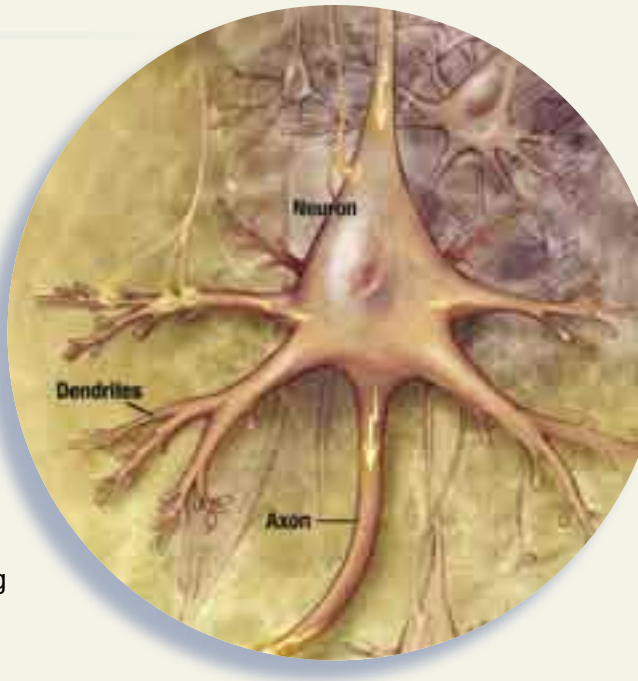
How is AD Diagnosed?

Clinicians today use a range of tools to diagnose "possible AD" (dementia could also 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 usually, brain scans. Knowledge about the clinical and behavioral characteristics of the disease also helps in diagnosing AD. In specialized research facilities, clinicians can now diagnose AD with up to 90 percent accuracy. At this time, however, AD can be diagnosed conclusively only by an autopsy of the brain of a person with dementia.

Early, accurate diagnosis is crucial because it tells people not only whether they **do** or **do not** have AD but also whether they have something else instead, such as a stroke, tumor, Parkinson's disease, or side effects of medications. It 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 even before symptoms emerge.

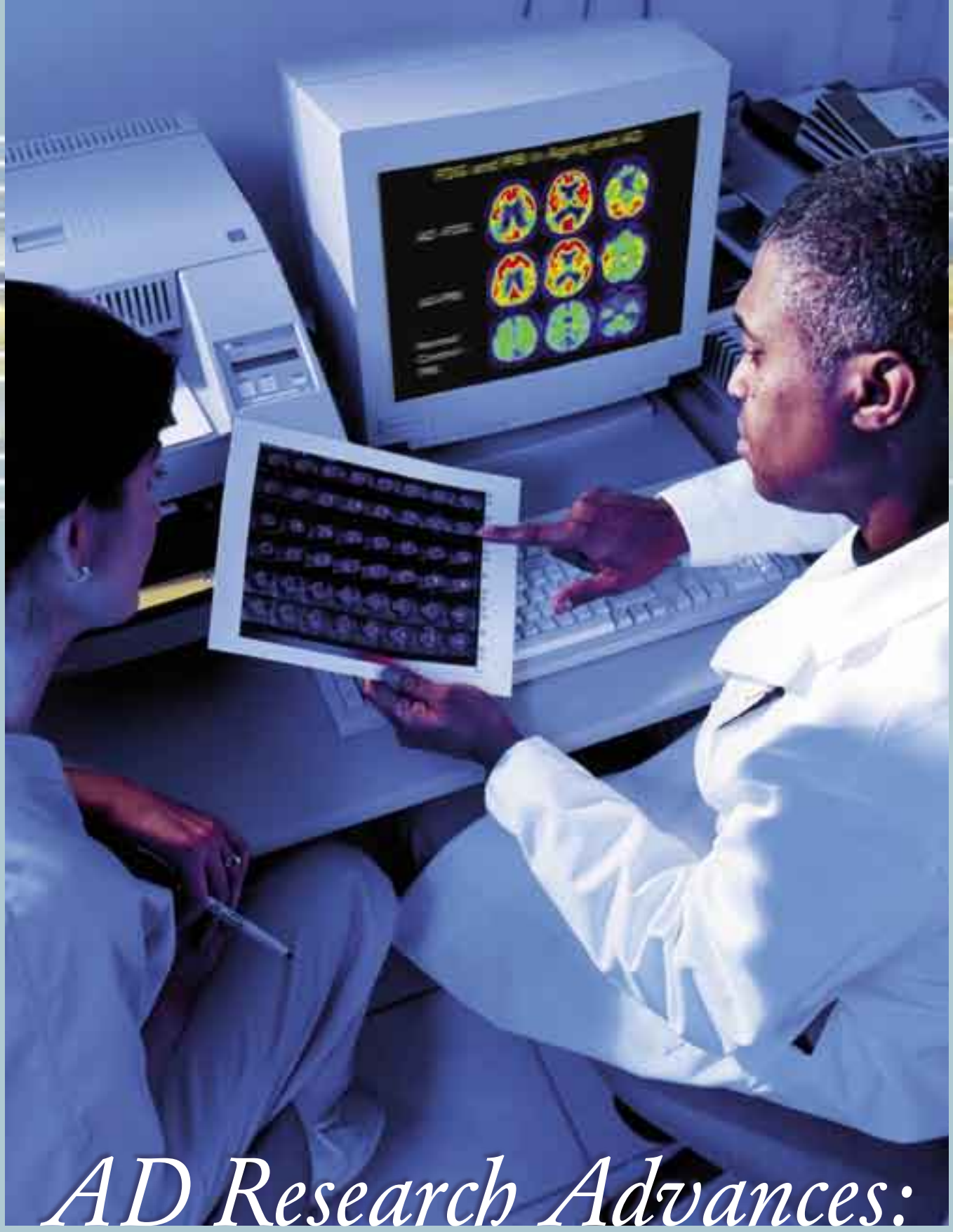
How is AD Treated?

AD treatments are needed to control cognitive loss as well as behavioral and psychiatric problems that occur as AD progresses. Four FDA-approved medications are used to treat AD symptoms. Donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl) are prescribed to treat mild to moderate AD symptoms. Donepezil was recently approved to treat severe AD as well. 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; may maintain some thinking, memory, or speaking skills; and can help with certain behavioral symptoms. However, they will not stop or reverse AD and appear to help patients only for months to a few years.



The newest AD medication is memantine (Namenda), which 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 will not stop or reverse AD.

In addition to these medications, physicians use drug and non-drug approaches to treat behavioral and psychiatric problems. These problems include agitation, verbal and physical aggression, wandering, depression, sleep disturbances, and delusions.



AD Research Advances: Many Paths To The Goal

PART 2

This section of the *Progress Report* describes some of the many paths that investigators are taking to the ultimate goal of discovering a cure for AD. These descriptions are organized around several major research questions:

- How does AD begin, and what causes it to progress?
- Can lifestyle interventions slow the disease process?
- How do we translate scientific discoveries into effective treatments?

How Does AD Begin, and What Causes it to Progress?

AD research has expanded greatly since the early days, when investigators focused on understanding the manifestations and natural progression of the disease. Findings from these studies, combined with advances in many scientific areas—imaging, genetic analysis, molecular and cellular biology, and development of highly sophisticated animal models, to name a few—have led to an explosion of knowledge about AD.

We still have a lot to learn about the fundamental questions of AD pathology and etiology, however, and this continues to be a critical portion of the overall AD research portfolio. Learning more about the basic science is essential to understanding normal age-related change as well as how and why AD begins and how it progresses over time. For example, we know that as AD develops, neurons go through a process from a healthy state to some loss of molecular efficiency, to a loss of synaptic function, to loss of synapses, and, ultimately, to cell death. We also know that the damage begins in the areas deep within the brain that control memory, including the entorhinal cortex, the hippocampus, and related structures. The damage then spreads to the cerebral cortex (the outer layer of neurons in the brain), and eventually to many other brain regions. But we don't fully know how long this process takes or how much may be reversible. What event (or series of events) causes normal age-related change to become a disease? What normal pathways of molecular communication are disrupted during the early development of AD? How will understanding these pathways lead to the development of drugs to block them? At what points could other types of interventions, such as diet, exercise, social and intellectual stimulation, or other lifestyle factors, slow down the disease process? Answers to questions like these are essential not only because

Healthy neuron

Dying neuron

they improve our overall knowledge about AD and other neurodegenerative diseases, but because they point to a range of strategies to treat or prevent AD. Some of these strategies are already being tested in animal studies and clinical trials. Recently, investigators made important headway in four main areas of basic AD research: beta-amyloid and synapses, *tau*, the cell cycle, and vascular dysfunction.

Beta-amyloid and Its Damaging Effects on Neurons

Beta-amyloid has fascinated scientists for years. Long considered a key player in

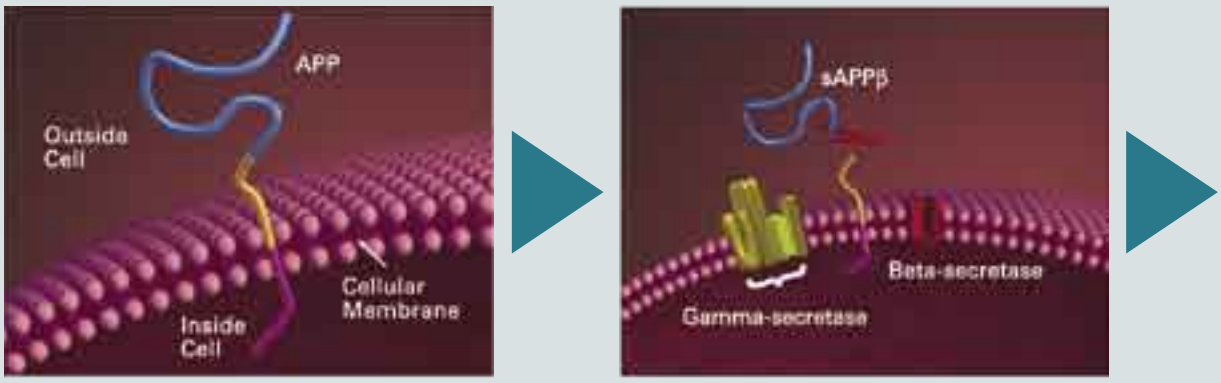
Beta-amyloid: From APP to Plaques (But Not Always)

It's a tale with terrific characters: elusive enzymes, a principal player protein whose ultimate character (hero or villain) depends on the location of a cut, and plaques that maybe aren't the evildoers everyone thought they were. After painstaking research, many scientists in laboratories across the country have teased apart the biological clues provided by these characters. The result? A storyline that continues to evolve, some radically new thinking about beta-amyloid and plaques, and several potentially promising new treatment approaches.

The story starts with amyloid precursor protein (APP), a large protein that is thought to be important to the health of neurons. APP is embedded in the neuronal membrane, residing partly inside and outside the cell. At some point, APP is cut, or cleaved, into several fragments. For a long time, scientists were pretty certain that one or more enzymes (proteins that cause or speed up a chemical reaction) were responsible for this cleaving, but they weren't able to identify them. Eventually, investigators identified the three cleaving enzymes, which they named alpha-secretase, beta-secretase, and gamma-secretase. In a major breakthrough, scientists discovered that, depending on which enzyme does the cleaving and where the cleaving happens, APP processing can follow one of two pathways that have very different consequences.

In one, considered the usual pathway, alpha-secretase cleaves the APP molecule **within** the portion that has the potential to become beta-amyloid. Cleaving at this site results in the release into the space outside the neuron of a fragment called sAPPα. This fragment may have beneficial properties, such as promoting neuronal growth and survival. The remaining APP fragment, still tethered in the neuron's membrane, is then cleaved by gamma-secretase at the end of the beta-amyloid sequence. The smaller of the resulting fragments also is released, while the larger fragment remains within the

Pathway to Harm



APP sticks through the neuron's membrane.

Beta-secretase cleaves APP at one end of the beta-amyloid peptide.

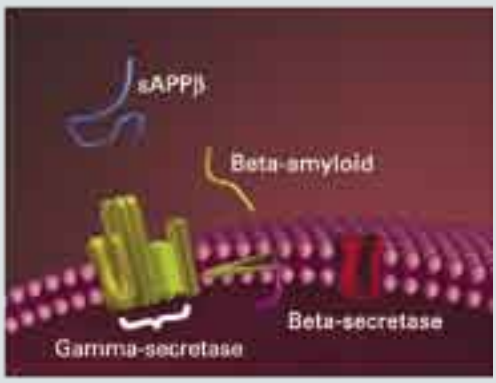
the development and progression of AD, it held its secrets closely. In the past several years, however, it has gradually begun to give up many of these secrets. Scientists have learned an enormous amount about how beta-amyloid plaques are formed and the toxic effects that these structures as well as the earlier forms of beta-amyloid have on neurons and synapses. These findings have opened up new avenues of investigation and new possibilities for therapeutic targets. Here are a few highlights from recent beta-amyloid work.

neuron and is believed to enter the nucleus. No beta-amyloid is produced in this pathway.

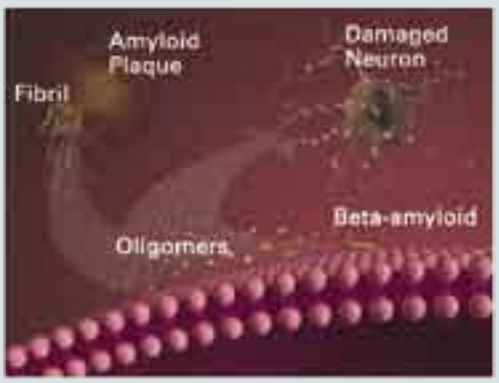
In the second pathway, beta-secretase cleaves the APP molecule at **one end** of the portion that has the potential to become beta-amyloid, releasing a fragment called sAPPβ. Then, gamma-secretase cleaves the remaining fragment at the other end of the beta-amyloid sequence. Following its cleavage at both ends, a beta-amyloid peptide is released into the space outside the neuron. This pathway spells trouble for neurons because the beta-amyloid peptide begins to stick together with other similarly cleaved beta-amyloid peptides.

These small, soluble beta-amyloid clumps are called Aß-derived diffusible ligands, or ADDLs. The number of individual beta-amyloid peptides within ADDLs varies, but collectively, they are called "oligomers." It is likely that some oligomers are cleared from the brain. If they cannot be cleared from the brain, they clump together with more beta-amyloid peptides and other proteins and cellular material. As the process continues, these clumps grow larger, becoming increasingly insoluble entities called protofibrils and fibrils. Eventually they coalesce into the well-known plaques that are characteristic of AD. The rate at which beta-amyloid aggregates to form plaques is likely to be slowed by lowering the rate at which it is made or by increasing the rate at which it is degraded or physically removed from the brain.

Being able to spell out with greater clarity the sequence of steps from APP to beta-amyloid peptides to plaques has allowed scientists to think in new ways about these AD players. Many scientists now think that oligomers may be the most toxic culprit, not plaques. This thinking also has allowed investigators to pursue avenues of related research that may ultimately lead to new AD treatments.



Gamma-secretase cleaves APP at the other end.



Single beta-amyloid peptides clump into soluble oligomers. Eventually this clumping leads to plaques.

Change in Amount Affects Neuronal Function

Based on recent evidence, some scientists think that oligomers harm neurons by attaching themselves to a receptor site on dendrites where messages are received (this site is called the post-synaptic membrane). When this happens, the synapses can't function properly and can't receive messages from other neurons. Unable to communicate, the neurons lose function and eventually die. In test tube studies and in animal studies with AD transgenic mice (mice that are genetically programmed to develop features of AD, such as amyloid plaques and memory problems), scientists at Rockefeller University explored how this disruptive process may occur (Snyder et al., 2005). First, the researchers found that applying beta-amyloid to neuronal cells in culture promoted the movement of NMDA receptors away from the cell surface and into the cell. Cell surface receptors are binding sites for neurotransmitters (see p. 8 for more on these chemical messengers) and are essential in cell-to-cell communication and function. NMDA receptors are necessary for signal transmission across synapses in response to the neurotransmitter glutamate. Thus, beta-amyloid reduces signal transmission across these synapses, which reduces synaptic plasticity. Synaptic plasticity, the term neuroscientists use to describe the inherent capacity of the synapse to alter its behavior in response to neural activity, is the basis for learning and memory.

Next, the researchers examined the neurons of transgenic mice in tissue culture and found that they had reduced amounts of NMDA receptors on the surface of their neurons. When they reduced the production of beta-amyloid in these cultures, they found that NMDA receptor expression on the surface of neurons was restored. These findings are important because they show that the amount of beta-amyloid present affects the level of a key receptor, and that, in turn, interferes with the cell's ability to function. These results suggest another way that beta-amyloid disrupts synaptic function and contributes to AD damage.

A Second Pathway Also Reduces Synaptic Plasticity

Another group of researchers, working at New York University School of Medicine, also focused on pathways involved in synaptic plasticity. These researchers hoped to discover a second pathway by which amyloid exerts its effects (Puzzo et al., 2005). In studies with transgenic mice, these investigators found that beta-amyloid also interferes with a particular molecular pathway, called the nitric oxide/cGMP/cAMP-responsive element-binding protein, or CREB, cascade. Beta-amyloid's interference with this pathway suppressed synaptic plasticity in the hippocampus. The results from both of these synaptic plasticity studies suggest an approach to treating AD by blocking beta-amyloid's effects on these particular molecules and cellular pathways.

Function (or Dysfunction) Follows Form

Though many investigators these days are focusing on the early, oligomer, stage of beta-amyloid activity, other investigators remain interested in exploring the end product: beta-amyloid plaques. Some scientists now think that plaque formation actually may be a protective action by the brain to sequester beta-amyloid so that it

Sophisticated New Imaging Technology Helps Scientists See Inside Living Cells

In recent years, scientists have learned a lot about gamma-secretase, one of the enzymes that cleave APP into fragments. They now know that it is composed of four proteins: presenilin, nicastrin, Aph-1, and Pen-2. Gamma-secretase cannot be active unless all four of these proteins are present.

One of the gamma-secretase components—presenilin—has intrigued scientists for a long time, for another reason. To date, only four of the approximately 30,000 genes in the human genetic map (the "genome") have been conclusively shown to affect AD development. Mutations in three genes—the APP gene found on chromosome 21, the PS1 gene on chromosome 14, and the PS2 gene on chromosome 1—are linked to the rare, early-onset form of AD. The APP gene is responsible for making APP, the precursor to beta-amyloid. PS1 and PS2 are responsible for making the presenilin protein. The fourth gene, APOE, affects the course of late-onset AD, depending on which allele, or variation, of the gene is inherited. (APOE-ε2 may provide some protection against AD, APOE-ε3 may play a neutral role in AD, and APOE-ε4 increases the risk of developing AD.)

A Massachusetts General Hospital team of researchers supported by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) used a technique called fluorescence lifetime imaging microscopy to determine what effect mutations in the PS1 gene might have on the activity of the presenilin protein and, by extension, on the progress of early-onset familial AD (Berezovska et al., 2005). This highly sophisticated imaging technique allows scientists to follow biochemical reactions in fluorescently-labeled molecules, thus imaging biochemical activity in specific cellular compartments of living cells.

The researchers found that the mutation changed the spatial relationship of certain key molecules in the presenilin protein and also was associated with a consistent change in the configuration of the PS1-APP complex. They suggest that these changes may provide a molecular mechanism that underlies the pathology of early-onset AD across a wide range of PS1 mutations.

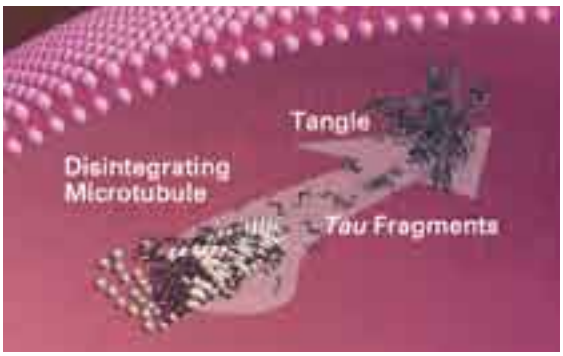
Identifying exactly how PS1 mutations cause early-onset AD may ultimately help investigators devise therapies to reduce the mutated gene's effect on brain cells.

cannot harm neurons, but a research team at Massachusetts General Hospital and Harvard Medical School has found that plaques may still have a damaging effect on synapses (Spires et al., 2005). In studies with AD transgenic mice, they discovered that plaques cause a change to the trajectory of dendrites. Plaques get in the way of a dendrite's normal path and cause the dendrite to curve around the plaque. They also reduce the number of spines, or doorknob-shaped structures, that extend out from the dendrites and that are essential to signal transmission between neurons. These physical changes have damaging physiological effects because they disrupt synapse networks, which weakens neurons' ability to communicate with each other.

New Developments in *Tau* Research

As mentioned earlier, one of the hallmarks of AD is the formation of NFTs, which consist largely of an abnormal form of *tau*. Long considered by many investigators to have a secondary role in AD, *tau* has, in recent years, come into its own as a leading player in AD research. Findings from the past several years clearly show why *tau* is generating new excitement.

NFTs are found in a variety of human diseases other than AD, including corticobasal degeneration, progressive supranuclear palsy, and frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17). These diseases are called "*tau*opathies." Even though no mutations have been found in the *tau* gene in AD, inherited mutations do occur in other *tau*opathies that can change the structure of the protein from normal to abnormal. Previously, only transgenic mice that had been bred to have mutated *tau* demonstrated NFTs. Now, a research group at the Albert Einstein College of Medicine in New York, has developed a new mouse model of human AD (Andorfer et al., 2005). These "h*Tau*" mice have non-mutant human *tau* protein and accumulate an excessive amount of an abnormal form of *tau*. They also form clumps of *tau* filaments in a region-specific fashion that is similar to AD. This new mouse model will allow researchers to investigate the relationship between cell death, accumulation of altered *tau*, and the development of NFTs. This study also provides compelling evidence that neuronal death in AD may not result directly or primarily from NFT formation, but rather from disrupted axon transport (in other words, a loss of normal *tau* function). The scientists found that the presence of *tau* filaments did not directly correlate with death within individual cells. Instead, they found that it was associated with the appearance of cell-cycle molecules and the initiation of DNA synthesis, which suggests that cell death can occur independently of NFT formation. Possibly, the neurodegeneration occurring in the h*Tau* mice may be at least partially due to abnormal, incomplete initiation of the cell-cycle process (see the following section for more on the cell-cycle process).



In a second *tau* advance, scientists at the University of Minnesota Medical School were able to partially rescue memory function in a transgenic mouse model that had a form of a mutant *tau* gene whose synthesis could be suppressed by a drug (SantaCruz et al., 2005). This meant that production of the mutant *tau* could be precisely regulated. As the mice aged, they produced more mutant *tau* and began to accumulate NFTs. Their neurons began to die, brain tissue shrank, and memory was lost. The researchers were able to stop the production of the mutant *tau* by giving the mice the drug that turned off the gene. Once the mutant gene was suppressed, the scientists found, much to their surprise, that not only did

New Evidence Links Beta-Amyloid and *Tau*

Immunizing against the beta-amyloid peptide is a promising therapeutic approach (see p. 40 for a description of current research in this area). Several studies have demonstrated in mouse models of AD that this approach, called "beta-amyloid immunotherapy," leads to a dramatic reduction in beta-amyloid deposition in the brain. The availability of new brain imaging techniques and mouse models that have both beta-amyloid and *tau* pathology has made it possible to tackle some key questions about the pathologic processes that may be alleviated by beta-amyloid immunotherapy and about how damage from beta-amyloid and *tau* relate to one another.

Scientists from the University of California at Irvine injected anti-beta-amyloid antibodies in the brains of transgenic mice that develop both beta-amyloid deposits and NFTs. This treatment led to a rapid reduction of beta-amyloid deposits outside as well as inside neurons and reversed the early signs of *tau* pathology, namely accumulation of abnormal *tau* within neuronal bodies and dendrites (Oddo et al., 2004). When the anti-beta-amyloid antibodies were removed, the beta-amyloid pathology re-emerged. This was followed by the reappearance of *tau* pathology. In a follow-up study, these investigators used anti-beta-amyloid antibodies to determine which aspect of beta-amyloid pathology coincides with early cognitive impairments in the same animal model. They found that clearance of beta-amyloid accumulations within the neurons was correlated with reverses in the early signs of cognitive dysfunction (Billings et al. 2005).

These findings from animal models provide proof that beta-amyloid and *tau* pathology are linked in that levels of beta-amyloid deposits influence levels of NFTs. These findings also show that the accumulation of beta-amyloid within the neuron occurs before any apparent beta-amyloid deposits and coincides with early signs of cognitive impairment.

the memory loss stop, it actually was partially reversed. Even more striking, memory function improved even though NFTs formed from *tau* that had already been made continued to accumulate in the brains of the mice. The fact that memory function improved in mice carrying the mutant *tau* gene when the gene was turned off, despite continued NFT accumulation, implies that the processes that lead to memory loss and those that cause NFTs are separate. Perhaps NFTs do not invariably cause neuronal death, but an earlier, toxic form of abnormal *tau* does. Some investigators are suggesting that NFTs, like beta-amyloid plaques, may even be a protective response by the brain that is aimed at preventing abnormal *tau* from damaging the neuron (Tanzi, 2005).

Tau studies are one of the most active areas of AD research, and, as with other areas of AD research, new findings are emerging all the time. Current and future studies in animal models are examining whether it might, in fact, be possible to "turn on and off" the synthesis of abnormal, damaging *tau* and beta-amyloid and exploring whether the brain could even regain some cognitive function once the disease process has begun.

Cell Cycle: Bringing Life or Death?

Most cells in the body undergo a constant process of formation, maturation, and division—this is called the cell cycle and it's an essential part of normal life and growth. Neurons are different, however. Once formed, they generally do not divide. Forcing a mature neuron to reenter the cell cycle and undergo cell division will cause it to die (Herrup et al., 2004).

Based on findings from recent studies showing that the vulnerable neurons in AD brains contain proteins related to entry into the cell cycle, some researchers now hypothesize that the death of neurons in AD may be related to abnormal initiation of the cell cycle in these cells. Researchers at Case Western Reserve University, in Cleveland, Ohio, found that the cell-cycle process was initiated in three different transgenic mouse models of AD in a pattern similar to that seen in human AD (Yang et al., 2006). Unlike human AD, though, the mouse neurons did not die. These results suggested to the research team that although cell-cycle events may be necessary to cause the death of neurons, they are not sufficient, and that a second, triggering, event may be needed to cause cell death. Another key finding of the study was that the cell-cycle process in these mice began before beta-amyloid plaques or NFTs began to accumulate, once more suggesting that earlier forms of beta-amyloid may be the molecular trigger. Significantly, this cell-cycle process in these mouse models closely mimics that in humans with AD, thereby supporting the utility of these models in AD research, even in the absence of cell death or formation of NFTs.

Scientists at the Brigham and Women's Hospital and Harvard Medical School have been pursuing a similar line of investigation by using *Drosophila* flies to study the impact of activating the cell-cycle process in neurodegenerative diseases, like AD, that feature abnormal deposits of *tau* protein (Khurana et al., 2006). These researchers found that activating the cell-cycle process caused *tau*-induced neurodegeneration, and interfering with the process substantially reduced neurodegeneration.

Vascular Dysfunction May be a Key Element in AD

Even though the brain makes up only 2 percent of the body's mass, it receives 20 percent of the body's blood flow. The blood delivers oxygen and glucose to neurons. Maintaining a constant and adequate blood flow in the brain is essential for neuronal survival and brain function, and decreased blood flow in parts of the brain affected by AD is an early feature of the disease.

Recent research has focused on the many micro blood vessels that constitute a critical part of the brain's blood supply. Two aspects of these capillaries are important in AD:

- The brain's ability to grow new micro vessels is diminished in AD.
- The brain uses the micro vessels to get rid of toxic beta-amyloid peptides. It appears that clearance of beta-amyloid across the blood-brain barrier (BBB) into the circulation is impaired in AD. The BBB is a protective barrier formed by the blood vessels of the brain to prevent large molecules from entering the brain.

For some time now, the study of the brain's blood vessel system (vasculature) in the context of AD has been a productive line of inquiry. A scientific team at the

University of Rochester Medical Center has proposed a "neurovascular hypothesis of AD," which pulls together a decade's worth of disparate research on the brain and its blood vessels (Zlokovic, 2005). This hypothesis states that faulty clearance of beta-amyloid peptides across the BBB, abnormal development of new micro vessels, and accelerated or abnormal aging of the brain's blood vessel system could start a process that leads to BBB compromise, chemical imbalances in the neuronal environment, and synaptic and neuronal dysfunction.

If it is true that diminished or abnormal functioning of the neurovascular system contributes substantially to AD, then a recent study by the University of Rochester team may go some of the way toward explaining the role of vasculature cells in the damage done by AD (Wu et al., 2005). This study focused on lipoprotein receptor-related protein 1 (LRP), a protein located in the endothelial cells that line the inside of brain micro vessels. LRP is responsible for transporting beta-amyloid peptides out of the brain across the BBB into the body's circulation. The endothelial cells in the brains of people with AD produce less LRP compared to healthy older people. As a result, clearance of beta-amyloid is impaired and the toxic peptide accumulates in the brain. Until now, scientists have not been able to understand why LRP production falls.

The researchers approached this important question by comparing the pattern of expression of genes in endothelial cells isolated from brain tissue of people who had died of AD to the genetic expression pattern of endothelial cells isolated from brain tissue of cognitively healthy old and young people who had died of other causes. They found that the expression of a gene called MEOX2, which is known to be involved in the growth and development of brain micro vessels, was specifically reduced in AD. They also discovered that when the expression of this gene was stopped, a protein involved in endothelial cell death began to be produced. Using transgenic mice that express half the normal amount of MEOX2, the investigators discovered that when production of MEOX2 was reduced, the brain also was less able to grow new micro vessels in response to injury. When MEOX2 expression was reduced, the amount of LRP also was reduced, and the brain was not able to remove beta-amyloid efficiently across the BBB.

For some time now, the study of the brain's blood vessel system in the context of AD has been a productive line of inquiry.

Clearly, much more work needs to be done to answer remaining questions about beta-amyloid, the cell-cycle process, *tau*, vascular dysfunction, and other factors that may promote or retard the AD process. However, these and other basic research studies are making an invaluable contribution to our understanding of AD, and they are opening promising new avenues in the search for AD therapeutic strategies.

Learning More About Mild Cognitive Impairment

The best-known consequence of AD is memory loss, but this is not the only feature. A person with AD has other problems as well, including difficulties in processing and organizing information; problems with judgments and making decisions; personality changes; hallucinations, delusions, and other psychiatric problems; depression; loss of impulse control; perceptual-motor problems (for example, having trouble getting out of a chair); and physical problems that become pronounced as the disease nears its end.

As some people grow older, they develop memory problems greater than those expected for their age. But they do not experience the personality changes or have the cognitive or other problems that are characteristic of AD. Their condition, then, may not meet all the medically-defined criteria for AD. These people have a condition called mild cognitive impairment (MCI).

People with MCI are a critically important group for research into the causes of AD because a higher percentage of them go on to develop AD compared to older people without these memory problems. It is not known whether all people with MCI will advance to AD. This puzzle has raised a number of questions for scientists. Is MCI an early stage of AD, or are they entirely separate conditions? Why and when does MCI sometimes, but not always, develop into AD? Do people with MCI who don't go on to develop AD have some special protective characteristics? Can MCI be prevented or its progress delayed or interrupted?

These questions have created some obvious research objectives:

- Define MCI and the relationship between MCI and AD
- Learn about the underlying causes and courses of MCI
- Understand the pathology of MCI
- Explore strategies that could prevent or delay MCI and AD

In recent years, investigators have made major progress in achieving these objectives. For example, scientists have developed a framework for understanding the causes and courses of MCI by defining subtypes of the condition based on cause (for example, degenerative, vascular, psychiatric, and medical), and on which aspects of cognition are predominantly affected. The subtype that features memory impairment most prominently is called MCI with memory loss, or "amnestic MCI." This definition of MCI already has been widely used by research teams working on AD treatment strategies in clinical trials. Scientists working in ADCs have reported that about eight in 10 people who meet criteria for amnestic MCI progress to AD within 6 years of diagnosis. The chart on the next page illustrates current thinking about the transition from healthy cognitive aging to amnestic MCI to AD.

Individuals with other MCI subtypes may have prominent deficits in other cognitive functions, such as language skills or visuospatial ability (the ability to recognize objects and determine where they are in relation to each other, and to mentally rearrange them). Other degenerative diseases, such as frontotemporal dementia, dementia with Lewy bodies, and vascular dementia also can cause these symptoms (Petersen, 2005). The development of a clear description of these conditions and the elements and extent of cognitive function affected by amnestic MCI has been a major contribution to AD research, particularly to the conduct of clinical trials.

Investigators pursuing many avenues of research have provided valuable additions to our storehouse of knowledge. Here are a few things we've recently learned about MCI:

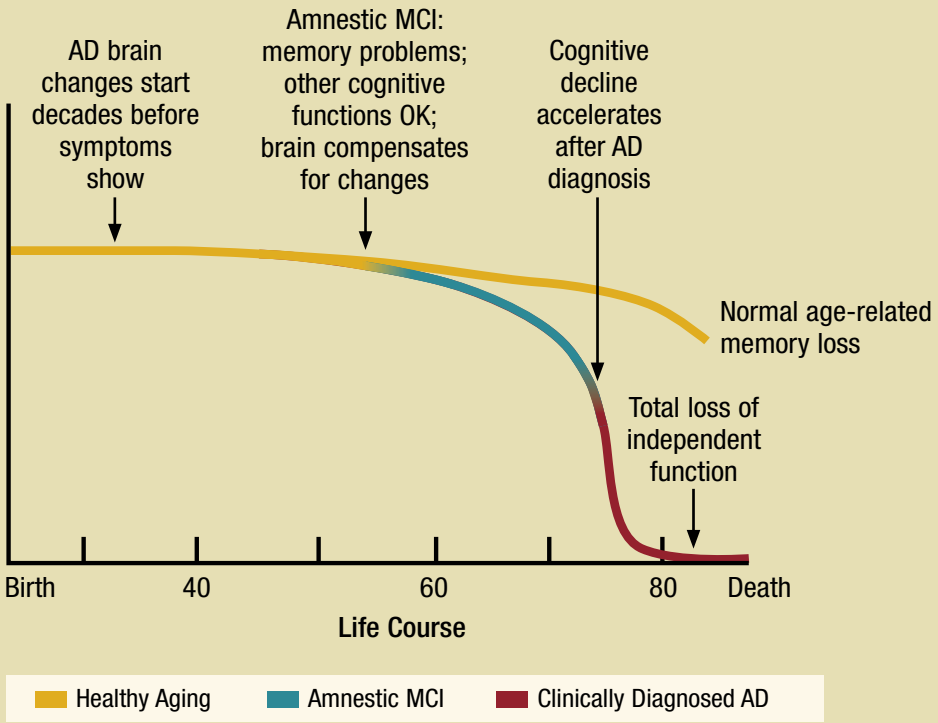
- Genetic risk factors appear to play a role in MCI as they do in AD:
  - Investigators at a number of research laboratories have found that people with MCI who also have the APOE- 4 allele progress to AD more rapidly than those without APOE- 4 (Fleisher et al., 2005; Petersen et al., 1995; Tschanz et al., 2006).
  - In the recently completed 3-year Memory Impairment Study, one of NIA's Alzheimer's Disease Cooperative Study (ADCS) clinical trials (see p. 44 for more on the ADCS), investigators compared the effectiveness of vitamin E, donepezil, and a placebo in delaying the onset of a diagnosis of AD in 769 people with amnestic MCI (Petersen et al., 2005). In the subset of study participants who

carried the APOE-ε4 allele, donepezil appeared to decrease the risk of progression to a diagnosis of AD for the full 36 months of the study. For other participants, donepezil reduced risk of progressing to AD during the first 12 months of the study, but this benefit disappeared by 18 months. Vitamin E did not appear to slow the progression to AD.

- Different brain regions appear to be activated in cognitively healthy people and those with MCI during certain types of cognitive activities. Using brain imaging techniques, University of Pittsburgh investigators participating in the Ginkgo Evaluation of Memory (GEM) trial were able to detect differences in an aspect of cognitive function called attentional control (Rosano et al., 2005). These changes are likely to be related to early cognitive impairment. (see p. 44 for more about the GEM trial).
- The rate of brain atrophy can predict cognitive impairment and dementia. Investigators compared magnetic resonance imaging (MRI) scans over time in the same individuals with either normal cognition or MCI (Jack et al., 2005). They found that higher brain atrophy rates predicted increased impairment and dementia.
- Treatment with raloxifene (Evista), a selective estrogen receptor modulator used to treat osteoporosis, may reduce the risk of developing cognitive impairment and AD. The Multiple Outcomes of Raloxifene Evaluation (MORE) study was a prevention clinical trial conducted with nearly 5,400 postmenopausal women with osteoporosis (Yaffe et al., 2005). The women were divided into three groups: one group received a placebo, one group received 60 mg/day of the drug, and the third group received 120 mg/day. After 3 years of treatment, there was no difference between the 60 mg/day group and the placebo group. However, women who took 120 mg/day had a statistically significantly lower risk of developing amnestic MCI and a somewhat lower risk of developing AD and any cognitive impairment than did the women who took the placebo. (See p. 42 for a description of a treatment clinical trial in which investigators are examining raloxifene's effect in women who already have AD.)

In addition to conducting studies like these, investigators are using a variety of sophisticated tools to push the boundaries of knowledge about the very early stages of the AD process. Several of these tools are described in greater detail on p. 36.

Charting the Course of Healthy Aging, MCI, and AD



Can Lifestyle Interventions Slow the Disease Process?

We now know that exercise, a healthy diet, and not smoking can help people stay healthy as they grow older. Research has shown that several chronic diseases and conditions that commonly affect people as they age—including diabetes, heart disease, stroke, and high blood pressure—are heavily influenced by lifestyle factors. Investigators are realizing that AD also may share some of these risk factors and have even begun to examine how lifestyle might contribute to the overall emotional health and cognitive abilities of older adults. A number of studies have shed light on this important topic.

Lessons Learned from Couch Mice, Marathon Mice, and Men and Women Who Like to Walk

These days, exercise and physical activity are big buzz words. People are physically active—or know they should be—because they've heard the message: Exercise is good for everyone, whether we are young children or older adults. Exercise builds muscles, improves heart and lung function, helps prevent osteoporosis, and improves mood and overall well-being. Exercise is good for those who are already healthy, and it can improve the health of people with chronic conditions, including hypertension, diabetes, arthritis, obesity, and cardiovascular disease (Daniels, 2006; Klieman et al., 2006; McDermott and Mernitz, 2006; Michael and Shaughnessy, 2006).

So, it is not surprising that scientists began to think that if exercise benefited all parts of the body from the neck down, it surely must benefit the brain as well. They have conducted a number of epidemiologic studies to examine the associations between exercise, cognitive function, and risk of AD (Abbott et al., 2004; Larson et al., 2006), as well as a number of small clinical trials to assess the impact of exercise on cognitive function (Colcombe and Kramer, 2003). Findings have been intriguing.

Epidemiologic studies have examined whether exercise and physical activity are associated with beneficial effects on cognitive performance. For example, in an NIA-funded study, researchers at the Harvard School of Public Health analyzed data from almost 19,000 women aged 70-81 who participated in the Nurses' Health Study, a large study funded by the National Heart, Lung, and Blood Institute (NHLBI) in which nearly 122,000 nurses are asked questions every 2 years about their health, illnesses, diet, and lifestyles (Weuve et al., 2004). Comparing women at various levels of long-term (over several years) physical activity, they found that women at higher activity levels had better cognitive performance and reduced cognitive decline than women at lower activity levels. The cognitive benefit was similar to being about 3 years younger in age. And the association wasn't confined only to the vigorous exercisers. Walking the equivalent of at least 1½ hours per week at a 21-30 minute-per-mile pace also was associated with better cognitive performance. Researchers at the University of Pittsburgh found similar results when they studied exercise patterns and cognitive function

among rural residents in a relatively low socioeconomic area (Lytle et al., 2004).

Other investigators have gone further and looked at the possible association of physical activity and risk of developing dementia among older adults (Abbott et al., 2004). Researchers at the Kuakini Medical Center in Hawaii examined data from the men in the Honolulu-Asia Aging Study (HAAS), a long-term epidemiologic study of stroke, neurodegenerative diseases, and aging in older Japanese-American men (see p. 32 for other studies using HAAS data). The investigators found that walking less than a quarter of a mile every day was associated with almost twice the risk of developing dementia compared to walking more than two miles a day. A group of researchers from the Johns Hopkins University and the University of Pittsburgh examined this issue using data from older participants in the Cardiovascular Health Cognition Study (CHCS). The NIA-funded CHCS is an add-on study to NHLBI's Cardiovascular Health Study (CHS). Since 1988, the CHS has examined risk factors for the development of heart disease and stroke in elderly adults. The Johns Hopkins and University of Pittsburgh investigators found that the highest energy expenditure and the greatest number of physical activities pursued were associated with a reduced risk of dementia, AD, and vascular dementia (Podewils et al., 2005). This association was stronger in people who did not have the APOE-ε4 allele than in people who did have it. These researchers speculate that the number of physical activities may be as important, or even more important, to risk of dementia than the frequency, duration, or intensity of the activities. A third group of researchers at the Group Health Cooperative in Seattle, Washington, followed older adults for 6 years and found that regular exercise (defined in this study as 3 or more times a week) was associated with about one-third the risk of developing dementia as less frequent exercise (Larson et al., 2006). Interestingly, they found that the greatest risk reduction occurred in those who were least physically fit at the beginning of the study.

These observational studies suggest that physical activity and exercise may protect the health of the brain in some way, especially as physical activity and exercise were associated with cognitive health in each of the studies. However, other kinds of studies are needed to firm up these associations and clarify why exercise might reduce the risk of cognitive decline and dementia.

Scientists have looked to studies with experimental animals for some of the answers. To date, several studies have shown positive effects of aerobic exercise on the structure and function of the brain in older animals. For example, in research with rats and mice, investigators have found that exercise increases the number of capillaries that supply blood to the brain and the number of connections between neuronal synapses. It also increases levels of brain-derived neurotrophic factor (BDNF) in the hippocampus, the brain region most affected by AD. BDNF is a protein that

What's the Difference Between an Association and Cause and Effect?

You may have noticed in this section that we've always been careful to say that one thing is **associated with** another thing, rather than to use other words that might suggest a more definitive **cause-and-effect** relationship. Why do the words matter? It's because of the type of research we're describing.

In this section and in several others, we highlight findings from epidemiologic studies. This type of research compares the lifestyles, behaviors, and characteristics of groups of people. Scientists have used these studies to identify risk and protective factors for many types of diseases. For example, in the early days of heart disease research, epidemiologic studies were crucial to naming high-fat diets and smoking as major risk factors.

However, epidemiologic studies are observational, gathering information about people who are going about their daily lives. Study participants follow many behaviors and practices. It's difficult, therefore, to tease out the exact benefits or risks of one particular behavior from all the healthy or harmful behaviors followed by the participants. That's why, in epidemiologic studies of AD, scientists restrict themselves to saying that a behavior is associated with AD, or not. The epidemiologic evidence linking a behavior and AD is, at best, suggestive, but we don't know whether the behavior actually helps to cause or prevent AD.

Other types of research—test tube studies, studies in animals, and clinical trials—add to the findings from epidemiologic studies. Scientists use these to examine the same issue but in circumstances in which the various factors that might influence a result are controlled to a greater degree. This element of control allows them to be more certain about why they get the results they do. It also allows them to use more definitive words to describe their results. (To see what we mean, take a look at the animal studies described on these two pages and at *Full-scale AD Treatment Clinical Trials* on p. 42-43.) Of course, showing a cause-and-effect relationship in tissue culture or even in animal studies still does not mean that this result will be the same in humans. Clinical trials in humans are the gold standard for deciding whether a specific treatment actually prevents or delays AD.

supports the survival of existing neurons and encourages the development of new neurons. In a recent study with rats, researchers at the University of California at Irvine found that both daily exercise on a running wheel and exercise on alternate days increased BDNF levels and that BDNF levels remained elevated even after several days of rest (Berchtold et al., 2005). Moreover, animals that had exercised enough to raise BDNF levels and then had rested for a number of days needed only a brief return to exercise to increase BDNF to levels that would take a "couch potato" rat several weeks to reach.

Using these clues, investigators have used animal studies to probe even more deeply into the relationships between physiological changes in the brain and effects on cognitive performance and progression of AD pathology. A group of researchers at the Salk Institute for Biological Studies in La Jolla, California, for example, wanted to see whether the age of the animal and the age at which

they began to exercise made a difference (van Praag et al., 2005). They found a beneficial effect even in mice that became active later in life—these mice learned and remembered a maze better than did old mice that weren't exercisers. They also found that the older running mice also were able to form healthy new neurons at a similar rate to those of younger mice, suggesting that voluntary exercise can restore learning and neuronal formation in aged mice.

Two other research groups set out to test the effects of exercise and an enriched environment on the progression of AD pathology itself. One group, from the University of California at Irvine, divided transgenic AD mice into two groups—one had access to an exercise wheel and the other did not (Adlard et al., 2005). The scientists found that the exercising mice were better able to learn than the non-exercisers. Five months after the experiment began, the scientists examined the brains of the mice and found that the exercising mice also had significantly fewer beta-amyloid deposits in the hippocampus and cortex than did the non-exercisers. Using a different transgenic AD mouse model, researchers funded by NIA and the National Center for Research Resources found that mice living in an "enriched" environment that challenged them mentally as well as physically had significantly less beta-amyloid in the cortex and hippocampus compared to those housed in standard conditions (Lazarov et al., 2005). Upon further analysis, the University of Chicago investigators determined that long-term exposure to the enriched environment led to an increase in the brain's capacity to degrade beta-amyloid and stimulated the expression of genes associated with learning and memory, cell survival, and generation of new neurons.

All of these epidemiologic and animal studies have suggested that regular exercise may, indeed, have benefits from the neck up as well as the neck down. Further, they point to some possible reasons why these benefits exist. However, some major questions remain. For example, does a person have to be fit throughout life, or can physical activity late in life still help? How much does a person have to exercise to reap the benefits? How do the benefits change with a person's level of fitness? How long do the positive effects last? Does exercise interact in some way with cognitively stimulating activities (such as doing games and puzzles or participating in social networks) to benefit the brain, and if so, how do those interactions work? Are sedentary people who later develop dementia and AD less active because they are already in the early stages of the disease, or is it the reverse—the dementia is partially due to a history of physical inactivity? Another avenue of research—clinical trials—is well suited to examine some of these questions and provide some concrete answers.

NIA supports several clinical trials to explore issues related to exercise, cognitive function, and dementia risk:

- **Aerobic exercise to improve executive function in sedentary older adults.** This trial is examining the impact of a 6-month cardiovascular training program (walking briskly on a treadmill) on the ability of 80 older adults to carry out selected types of executive function tasks (for example, ability to block out irrelevant information and ability to switch easily from task to task) and on brain electrical activity.

- **Aerobic exercise to improve cognitive and brain function in sedentary older adults.** This clinical trial is exploring the hypothesis that improvements in aerobic fitness in older adults will benefit cognitive function and brain structure and activity. One hundred and forty sedentary older adults will be enrolled in a 1-year aerobic fitness intervention (walking briskly on a treadmill) and assessed for changes in brain and cognitive function.

- **Aerobic fitness to maintain or improve cognitive function in people with amnestic MCI.** A small-scale 12-week trial is examining the effect of an aerobic fitness program on cognitive function in 102 sedentary older adults with MCI. The investigators are studying the impact of exercise in delaying, arresting, or reversing the progression of age-related cognitive decline.

For more information about ongoing clinical trials described in the Progress Report, *visit NIA's ADEAR Center website.*

- **Combination of group exercise and health education to improve cognitive function in people with amnestic MCI.** This trial of 170 sedentary older adults with MCI is testing a combined intervention of group exercise and a health promotion program over 36 months. Individuals will be evaluated for the effectiveness of this intervention on cognitive, emotional, and physical function, as well as quality of life and rate of conversion from MCI to dementia.

Because the research area of physical activity and cognitive function is so important, NIA also is considering adding a cognitive component to future exercise trials that ask questions about exercise effects on other body systems. Scientists hope that the results of these lines of research not only will answer questions about the cause and development of MCI and AD, but also will provide motivation for individuals to become and stay physically active to promote and preserve the health of their brains as well as their bodies.

A Healthy Diet May Be Important to Brain Health as Well as Body Health

A nutritious diet rich in fruits, vegetables, and whole grains and that is low in fat and added sugar can reduce the risks of many chronic conditions, including heart disease, diabetes, obesity, and some forms of cancer. In recent years, investigators have used epidemiologic, animal, and test tube studies and clinical trials to explore whether diet can play a role in preserving cognitive function or even reducing risk of AD.

A long-held theory about aging suggests that, over time, damage from free radicals (molecules that chemically react easily with other molecules) can build up in neurons, causing loss of function. This damage is called oxidative damage. The brain's unique characteristics, including its high rate of metabolism and its long-lived neurons, may make it particularly vulnerable to oxidative damage. Previous epidemiologic and laboratory studies have suggested that fruits and vegetables that are high in antioxidants might protect

the brain against this kind of damage. A group of Harvard Medical School researchers explored this possibility by examining data from more than 13,000 Nurses' Health Study participants aged 70 and older (Kang et al., 2005). They found that the women who ate the most vegetables—especially green leafy vegetables (like spinach and romaine lettuce) and cruciferous vegetables (like broccoli and cauliflower)—experienced a slower rate of cognitive decline than did women who ate the least vegetables. The scientists were careful to account for other factors that might influence the results, such as use of vitamin supplements, physical activity, smoking and alcohol use, and educational attainment. Interestingly, fruit consumption did not appear to be associated with any change in cognitive ability. The scientists speculate that the abundant antioxidant and folate (a nutrient that appears to be important for proper neural activity and cognitive function) content of the green leafy and cruciferous vegetables was responsible for these results.

As with physical activity studies, these epidemiologic studies can only suggest associations between diet and cognitive performance. That's why researchers have turned to animal studies to explore in greater detail possible diet and AD relationships. Dogs are a good model for this type of AD research because they can perform sophisticated and complex cognitive tests, their brains accumulate beta-amyloid plaques with age, and the degree of beta-amyloid deposition is related to the severity of cognitive decline. Investigators at the University of Toronto and the University of California at Irvine completed a 2-year study that assessed whether long-term treatment with a combination of "behavioral enrichment" (extra attention and lots of training and stimulation) and a diet rich in antioxidants and mitochondrial cofactors from vitamins E and C and fruit and vegetable extracts could reduce age-related cognitive decline (Milgram et al., 2004; Milgram et al., 2005). This study included both old and young dogs. Some received both the fortified food and enriched environment, some received one or the other enrichment, and some received neither. At the end of the first year, the researchers tested the dogs on two learning tasks. They found that antioxidant supplementation was effective only when it was combined with behavioral enrichment. The 2-year results, however, showed that the supplemented food by itself had a beneficial effect on the older dogs' ability to perform the learning tasks, suggesting that the effects of the antioxidant supplementation became stronger over time. In both studies, the effects of the treatments were most evident in the dogs who received the dietary as well as the behavioral enrichment. In another similar study with dogs, these same researchers found that an antioxidant-enriched diet improved the performance of older dogs when they performed learning tests for the first time, but not on repeat tests, suggesting

that the enriched diet was particularly helpful when the dogs had to process new information (Siwak et al., 2005).

Curcumin is the main ingredient of turmeric, a bright yellow spice used in curry. Scientists are extremely interested in this compound because it has powerful anti-inflammatory and antioxidant properties and can suppress the accumulation of beta-amyloid in brain tissue. In test tube and transgenic mice studies, a research group supported by NIA and the National Institute of Neurological Disorders and Stroke (NINDS) found that curcumin was able to cross the blood-brain barrier and bind directly to beta-amyloid peptides (Yang et al., 2005). These investigators, from the Greater Los Angeles Veterans Affairs Healthcare System, found that the curcumin actually had several different anti-amyloid properties. By binding to the beta-amyloid peptide, curcumin prevented the aggregation of the peptides into oligomers and inhibited the toxic effect of the oligomers (see p. 12 for more on the process by which beta-amyloid aggregates into oligomers and ultimately plaques). When fed to aged mice that had significant plaque accumulation, the curcumin was able to reduce amyloid levels and the overall amount of plaque.

This research team also examined the effects of another dietary component—the omega-3 fatty acid called docosahexaenoic acid (DHA), which is found in abundance in some kinds of fish. DHA is a primary component of the membranes of nerve cells in the brain and is involved in multiple brain functions, including nerve cell communication. DHA is reduced in the brains of people with AD, and some evidence suggests that higher levels of DHA in the blood may be protective for dementia and AD (Schaefer et al., 2006). In studies with transgenic mice, the researchers found that deficits in DHA can damage brain biochemistry, structure, and cognitive abilities (Calon et al., 2004). In contrast, a diet high in DHA reduced beta-amyloid and reduced the overall amount of plaque in the brain, especially in the hippocampus and parietal cortex, and reduced the amount of APP, the beta-amyloid precursor protein (Lim et al., 2005; Cole et al., 2005).

Research teams at the University of Southern California, in Los Angeles, and the Mt. Sinai School of Medicine, in New York, also have used transgenic mice to investigate another possible link between diet and cognitive decline and AD. It is known that a calorie-restricted diet slows various aging processes in laboratory animals, so these investigators examined what effect calorie restriction might have on the AD process in transgenic mice. In one study, calorie restriction substantially decreased the accumulation and size of beta-amyloid plaques (Patel et al., 2005).

It also reduced the activation of certain glial cells called astrocytes near beta-amyloid plaques. Beta-amyloid plaques in the AD brain are usually surrounded by numerous activated astrocytes. The Mt. Sinai team found that a calorie-restricted diet also promoted the activity of alpha-secretase, the enzyme involved in cleaving APP in a beneficial way. This prevented new beta-amyloid peptides from being formed and plaques from being deposited in brain tissue (Wang et al., 2005).

These studies have provided intriguing hints about possible associations between various dietary elements, oxidative damage and inflammation in brain tissues, and AD pathology. To confirm these results, scientists have turned to clinical trials:

- **Fish oil, alpha-lipoic acid, and AD.** In test tube studies, fish oil and alpha-lipoic acid, a mitochondrial antioxidant, have been shown to decrease oxidative stress, inflammation, and lipid levels, making them candidates for therapies designed to slow the progression of AD. In this pilot clinical trial, investigators are assessing the effect of the fish oil and alpha-lipoic acid supplements on oxidative stress and cognition associated with disease progression. The research team also is closely monitoring the safety of the treatment. Enrollment of the 39 participants in this trial is complete, and data collection and analysis are ongoing. Pilot studies like this are used to collect initial data on the safety, effectiveness, and best dosage of a potential treatment. Results are used to design a full-scale clinical trial to assess the effects and potential benefits of the compound under investigation.

- **Vitamin E, Down syndrome, and AD.** People with Down syndrome are vulnerable to a form of AD that is indistinguishable from late-onset AD. This multi-center trial will evaluate whether high-dose vitamin E, a cellular antioxidant, will slow the rate of cognitive and functional decline in 350 older people with Down syndrome, who are at very high risk of developing AD. Recruitment is ongoing. This trial is jointly sponsored by NIA, the National Institute of Child Health and Human Development, and the National Center for Complementary and Alternative Medicine (NCCAM).

Studies have provided intriguing hints about possible associations between various dietary elements, oxidative damage and inflammation in brain tissues, and AD pathology.

- **Combination vitamin supplement in the treatment of AD in Down syndrome.** In this 24-month trial, a high-potency supplement consisting of two cellular antioxidants (vitamins E and C) and a mitochondrial antioxidant (alpha-lipoic acid) has been tested in 60 people with Down syndrome and AD to assess safety and tolerability and to determine whether cognitive function improved with antioxidant supplementation. Enrollment for this trial is complete, and data collection and analysis are ongoing.

Emerging Evidence about Moderate Alcohol Consumption and Cognitive Function

Many news reports lately have touted the possible beneficial effects of moderate alcohol consumption, especially to prevent heart disease. These helpful qualities are due to the fact that alcohol reduces inflammatory proteins in the blood and increases levels of HDL (the "good" cholesterol).

A growing body of evidence is now suggesting that factors that play an important role in heart disease and stroke also may be important in AD. Could a glass of wine or beer help prevent AD, then?

Several epidemiologic studies have examined this question. They have found that moderate alcohol consumption was not associated with impaired cognitive function and actually is correlated with reduced risk of cognitive decline and AD (Bond et al., 2004; Evans and Bienias, 2005; Ganguli et al., 2005; Luchsinger et al., 2004; Stampfer et al., 2005). As with heart disease, the beneficial effect of alcohol on cognitive abilities may occur because alcohol can reduce inflammatory proteins and increase HDL.

Animal research also has linked certain compounds with beneficial effects on the brain. For example, a team of researchers at the North Shore-Long Island Jewish Institute for Medical Research supported by the National Institute of Mental Health (NIMH), found in test-tube studies that resveratrol, a naturally occurring compound mainly found in grapes and red wine, markedly lowered the level of beta-amyloid in cells (Marambaud et al., 2005). Resveratrol did not inhibit the production of beta-amyloid, but rather promoted its degradation within the cell.

However, these findings come with lots of caveats. For one thing, we don't know enough about alcohol's effects on AD pathology to recommend it directly as a way to reduce cognitive decline or AD risk. For another, observational and epidemiologic research can reveal associations, but do not establish cause and effect. These limitations make it hard to say that the alcohol itself is responsible for reducing risk of cognitive decline. Many other factors about participants' lifestyles and health also may play a role. Another complication is that the studies define "moderate" consumption differently, making it difficult to come to a definite conclusion about whether and how much alcohol may be beneficial.

Finally, it's important to remember that heavy alcohol consumption has well-established harmful effects, and older people can be more affected by alcohol than younger people.

- **Isoflavones and AD.** This 6-month trial is examining the effects on cognitive functioning of soy isoflavones (a class of chemicals found in plants that act like estrogen in the body) in older adults with AD. The recent findings about increased health risks, including cognitive decline, associated with hormone replacement therapy has increased interest in the potential of soy isoflavones as an alternative therapy. Preliminary findings suggest that these compounds may have cognitive benefits, but no data exist about AD-associated cognitive decline. Investigators plan to enroll 60 participants, and nearly half that number have already joined the trial.

As with other areas of research into lifestyle factors and AD, we have tantalizing hints about particular dietary components but few firm conclusions about diet as a whole and its relationship to cognitive decline and AD. One reason for this is the complexity of the diet. Because a person's diet has numerous components and varies from day to day, researchers often must rely on supplements to isolate particular factors. Nutrient supplements on their own are not the same as nutrients within the context of whole foods, however, so caution is in order when applying these results to actual dietary patterns. Despite these limitations, findings to date about diet, cognitive decline, and AD are consistent with, and provide additional support for, current recommendations about the components of a nutritious and health-promoting diet.

Managing Chronic Illness: A Possible Preventive Strategy for AD?

As we've seen with exercise and diet, evidence suggests that what may be good for the heart may be good for the brain. Moreover, metabolic changes that occur in a variety of chronic diseases of aging, such as heart disease, stroke, high blood pressure, and diabetes, may contribute to the development of AD, affect the severity of AD, or cause vascular dementia (Luchsinger et al., 2005; Curb, 2005).

However, it has been difficult to untangle the association between AD and these chronic diseases. Scientists have offered several possible explanations. For example, many believe that atherosclerosis, which may or may not be clinically apparent as heart disease or stroke, may add to or accelerate cognitive decline in people who already have AD. Or, it is possible that metabolic changes related to chronic disease, such as elevated insulin levels in diabetes, may actually increase the amount of AD pathology that accumulates in brain tissue and directly contribute to the development of AD. Other possibilities or a combination of factors also may explain the associations. As we develop new strategies to treat AD, it will be important to know whether the metabolic changes related to chronic vascular disease actually increase the amount of AD pathology or whether they independently cause dementia.

These relationships need to be sorted out because heart disease and stroke are major causes of illness and death. Diabetes, high blood pressure, and other risk factors for these chronic diseases can, to a large extent, be modified by diet, exercise, and other lifestyle changes, so it is important to know whether reducing risks of or controlling diabetes and high blood pressure also may reduce AD risk.

Heart Disease and Stroke

Currently, much of our knowledge about the associations between heart disease, stroke, cognitive decline, and dementia comes from epidemiologic studies. For example, the NHLBI's Cardiovascular Health Study and NIA's Cardiovascular Health Cognition Study have provided valuable data about the relationships between cardiovascular risk factors and AD because they include cognitive decline and dementia related to vascular disease as a key element of their

design. In two recent analyses of CHS data, University of Pittsburgh investigators explored the relationships between cardiovascular disease and dementia. In the first study, the investigators showed that the risk of AD was 30 percent higher in people who had a history of cardiovascular disease other than stroke, compared with those without such a history (Newman et al., 2005). In the second study, investigators showed that vascular dementia and mixed dementia (vascular dementia and AD occurring simultaneously) account for a large proportion of new dementia cases (Kuller et al., 2005). An important result of the study was that it demonstrated the value of MRI as a diagnostic tool (see p. 50 for more on NIA's Neuroimaging Initiative).

Investigators working with HAAS data explored whether men with beta-amyloid plaques and NFTs had an increased chance of crossing the threshold to clinical dementia if they also had cerebrovascular damage (Petrovitch et al., 2005). These Pacific Health Research Institute investigators found that, indeed, in men who had NFTs, dementia increased with increasing plaque density, particularly in the presence of cerebrovascular damage. This association was strongest in men who had the fewest plaques, suggesting that preventing cerebrovascular damage may be critically important in preserving cognitive abilities in older people.

As this area of research has blossomed, investigators have conducted studies of additional groups to explore associations between vascular disease and AD. For example, researchers from the Rush University Alzheimer's Disease Center have included cerebrovascular disease measures when examining brain tissue samples from deceased participants of the Religious Orders Study, a long-term study of aging among members of 40 religious communities (Bennett et al., 2005). Consistent with other studies, participants who had amnestic MCI had evidence of intermediate levels of both AD and stroke damage in their brain tissue. They also had clinical symptoms that were in between those of people without cognitive impairment and those of people with dementia.

Findings from these and other studies have provided sufficient evidence for NIA to support several clinical trials to investigate the association between heart disease risk and AD:

- **Simvastatin and AD progression.** This 18-month Alzheimer's Disease Cooperative Study trial, which began in 2003, is testing whether simvastatin (Zocor), a commonly prescribed cholesterol-lowering drug, can safely and effectively slow the rate of cognitive decline in people with mild to moderate AD. Data from some, but not all, epidemiologic studies suggest that high blood

cholesterol levels are a risk for late-life cognitive decline and AD. In animal studies, high cholesterol levels increase AD plaques and affect cognition, and these effects are reversed by statin treatment. Nevertheless, few positive data about cognition have emerged to date from statin longitudinal studies or drug trials. The ADCS trial will be a rigorous test of the statin hypothesis in people who already have AD. The trial is being conducted in dozens of sites around the country, and the enrollment of 406 participants is complete. Data are now being collected and analyzed. Some participants receive 20 mg of simvastatin for 6 weeks and then 40 mg of the statin for the rest of the study period. Others receive a placebo during the entire study. Clinical trial staff are tracking changes in participants' cognitive functioning by measuring a number of indicators, including mental status, functional ability, behavioral disturbances, and quality of life.

- **Supplements to reduce homocysteine and slow the rate of cognitive decline.** Previous studies have shown that elevated levels of the amino acid homocysteine are associated with both heart disease and AD and that high homocysteine levels make some neurons vulnerable to dysfunction and death. Homocysteine levels can be reduced by high-dose supplements of folate and vitamins B6 and B12. NIA is currently supporting an ADCS clinical trial to determine whether reduction of homocysteine levels with high-dose supplements of folate, vitamin B6, and vitamin B12 will slow the rate of cognitive decline in older adults with AD. Participants in this clinical trial, which began in 2003, are divided into two groups: 60 percent of participants receive daily high-dose supplements (5 mg of folate, 25 mg of vitamin B6, and 1 mg of vitamin B12) and 40 percent receive a placebo. The research team has completed the enrollment of 400 participants, and data collection and analysis are ongoing.

- **Preventing cognitive decline in women.** This trial is an add-on to two ongoing NHLBI clinical trials of chronic disease prevention in women—the Women's Health Study (WHS) and the Women's Antioxidant Cardiovascular Study (WACS). WHS tested low-dose aspirin and antioxidant supplementation in healthy women, and WACS tested antioxidant and folate supplements in women who already had heart disease. Scientists hypothesize that these agents also may prevent AD. The add-on trial is examining whether these treatments provided any protection against cognitive decline. Both WHS and WACS have been completed, and study investigators are analyzing study results.

Diabetes and AD

The possible association of diabetes, insulin processing, and AD also is generating much interest among AD investigators. Type II diabetes mellitus is a major public health problem in the U.S. because it affects about one in five Americans older than 65 and has many serious

health complications. A number of epidemiologic studies have suggested that people with diabetes have an increased risk of late-life cognitive problems, including MCI and AD, either as a direct result of high levels of blood sugar (hyperglycemia) or because of the conditions that are often associated with diabetes, namely high blood pressure, abnormal blood cholesterol levels, or too much insulin in the blood (Launer, 2005). Laboratory studies also have identified several pathways through which hyperglycemia can reduce neuronal viability (Launer, 2005). These include increases in oxidative stress, damage to endothelial and vascular function, and changes in gene transcription and expression in neurons.

NIA is currently funding several diabetes clinical trials to see whether treating diabetes will affect cognitive health and AD progression.

This evidence has spurred research on a variety of fronts, from epidemiologic studies, to test tube and animal studies, to clinical trials. The objective of these studies is to determine whether diabetes is a risk factor for cognitive decline, and if so, whether treatment for diabetes may help lower risk of cognitive decline or AD. NIA is currently funding several diabetes clinical trials to see whether treating one or other aspect of diabetes will affect cognitive health and AD progression:

- **ACCORD-MIND.** This trial is an NIA-funded sub-study nested within NHLBI's Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. ACCORD is aimed at evaluating whether intensive glucose, blood pressure, and lipid management can reduce cardiovascular disease in people with diabetes. ACCORD-MIND (ACCORD-Memory in Diabetes) will test whether these intensive 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. ACCORD-MIND participants will undergo periodic cognitive testing and MRI scans to assess change over time.

- **Glucose regulation and memory in AD.** There is growing evidence suggesting that insulin's role in the brain's energy metabolism is not properly regulated in AD. Individuals with AD are at increased risk of insulin resistance (a condition in which muscle, fat, and liver cells are not able to use insulin properly; people who are insulin resistant are at high risk of developing diabetes). A key hypothesis that has emerged from work on diabetes and AD is that insulin resistance induces inflammation and elevations in free fatty acid levels, which interact with insulin-associated increases in damaging beta-amyloid. In this short-term trial, researchers from the University

of Washington will test this hypothesis by examining the effects of induced and improved insulin resistance on cognition, beta-amyloid levels, and inflammation. They predict that inducing insulin resistance will increase beta-amyloid levels and inflammatory markers and will impair cognition, and that these effects will be greater for participants with AD and those who are overweight. The trial also will determine whether improved cognition after treatment with rosiglitazone (Avandia), a drug that has anti-inflammatory properties and that improves the body's ability to use insulin, will be associated with reduced levels of insulin, free fatty acids, and inflammation. The researchers hope that this study will provide valuable information about the mechanisms through which insulin resistance increases the risk of AD and about possible treatment approaches for reducing this risk.

- **Rosiglitazone and amnestic MCI.** In this 18-month multi-center trial, researchers from the University of Washington also will test the effects of rosiglitazone on attention and memory skills in older adults with amnestic MCI. This trial will examine the effects of this medication on brain structures that support memory and other cognitive abilities, as well as on biological markers associated with inflammation, insulin resistance, and cardiovascular disease. Study participants will be divided into two groups—one group will receive rosiglitazone, the other a placebo. 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. This 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 amnestic MCI.

- **Innovative insulin administration and cognitive function.** A 4-month clinical trial is being conducted to examine the effects of administering 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 AD. AD is associated with reduced levels of insulin in cerebrospinal fluid, and treatment with insulin has been shown to improve memory performance. However, insulin injections (a common way to administer insulin) can be problematic because they can sometimes result in hypoglycemia (low blood sugar). A nasal spray delivers insulin directly to the brain. Preliminary data on this alternative 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.

Sophisticated Tools Help Investigators Learn More About

As people get older, changes occur in all parts of the body, including the brain. In the brain:

- Synapses become less efficient or are lost.
- Some neurons shrink, especially large ones in areas important to learning, memory, planning, and other complex mental activities. This translates into some shrinkage of brain volume over the course of years, even in healthy older people.
- Tangles develop inside certain neurons in particular brain regions and amyloid plaques develop in the spaces between some neurons.
- Damage by free radicals increases.

The impact of these changes differs among people as they age. Healthy older people may notice only a modest reduction in their ability to learn new things, retrieve information from memory, and plan and make decisions. Other people, however, experience much greater declines in their memory and cognitive abilities as they grow older because they are developing a neurodegenerative disease and these changes are occurring to a much greater extent. Understanding the difference between changes that occur with healthy aging and a neurodegenerative process is an important key to unlocking the secrets of AD.

It is now clear that by the time the symptoms of amnestic MCI or AD become evident, the disease process is well underway—neurons have died, plaques and tangles have become abundant in different brain regions, and damage from inflammation and free radicals has greatly increased. Decades earlier, biological processes may have begun that predisposed the individual to develop AD or another neurodegenerative disease. As the previous sections of this report show, it is also increasingly clear that these biological processes are directed by a complex interaction of many factors, including genetic, lifestyle, and environmental influences.

If the disease process actually starts many years before it becomes evident, while a person still appears to be healthy, then it is imperative for researchers to learn as much as possible about its early stages so that they can identify those who may be at high risk and develop interventions to disrupt or prevent the disease. Advances in several key tools are helping scientists understand these early changes in the brain:

- **Neuroimaging.** Increasingly sophisticated brain imaging techniques, especially MRI and positron emission tomography (PET) allow investigators not only to measure brain structure, volume, and activity but also to correlate changes in these measures with cognitive performance. These findings provide valuable insights into what happens in the brain as the disease progresses. For example, Massachusetts General Hospital researchers recently showed that people with MCI may compensate for the damage already done by the condition by activating a larger portion of particular brain regions when they are asked to do a cognitive task than do less impaired people (Dickerson et al., 2005). This increased activation may serve as a marker for impending clinical decline.

The NIBIB supports a broad portfolio of neuroimaging research, some of which is particularly relevant to AD. For example, cerebral amyloid angiopathy (CAA), the deposition of beta-amyloid in blood vessels in the brain, has been implicated as a common cause of hemorrhagic stroke and other forms of vascular disease. CAA also is frequently seen in AD. NIBIB-supported researchers at Massachusetts General Hospital are using low magnification imaging of brains from an AD mouse model to define the characteristics of CAA during disease progression and to develop a classification system correlating the severity of CAA deposition with the advancement of disease. This approach may enable clinicians to monitor the response to treatment more accurately (Domnitz et al., 2005).

- **Neuropsychological testing.** These tests, which measure delayed recall, verbal fluency, reasoning and decision-making abilities, and many other aspects of memory and cognition, are highly accurate in distinguishing between cognitively healthy people and those with mild AD, so long as differences caused by education, life experience, and age are adequately accounted for. They also are able to track changes in memory and cognitive function over time. These changes are the best way to differentiate between slow age-related changes and more rapid declines that are characteristic of amnestic MCI or AD. These

capabilities make neuropsychological testing an essential tool for various purposes, including ensuring accurate diagnosis, measuring disease progression, and measuring response to treatments. Tests that may be practical for use in a doctor's office, such as the AD-8, a brief 8-item questionnaire for caregivers, are being developed to differentiate those with very early clinical symptoms of dementia from adults with healthy cognition (Galvin et al., 2005).

- **Biomarkers.** Techniques to measure specific components of blood, urine, and cerebrospinal fluid (CSF) are increasingly being tested in the laboratory. Understanding these biological markers—how they function and how, when, and why their levels change—will help investigators answer questions about the causes and early development of AD. They also will help scientists track changes in the brain and cognitive function over time and monitor response to treatments.
- **Sensory studies** also are adding to our knowledge of ways in which the body signals that a disease process may be unfolding. For example, problems with identifying smells occur early in the course of AD. Researchers at the New York State Psychiatric Institute and Columbia University have demonstrated that a short smell identification test was able to differentiate people with MCI and AD from those who were cognitively healthy (Tabert et al., 2005). Results also strongly predicted whether people with MCI would go on to develop AD. More recently, a research team at the University of Chicago has found that both visual and hearing impairment were associated with an increased risk of cognitive and functional decline over time in older women (Lin et al., 2004).

Putting the Tools Together

A New York University School of Medicine group recently conducted a longitudinal study of cognitively healthy people and those with MCI. This study, the first to combine data from memory testing, MRI scans, and CSF biomarkers, found that combining these different types of measures consistently improved diagnostic accuracy (de Léon et al., 2006). Compared to cognitively healthy people, those with MCI showed decreased memory performance, decreased hippocampal size, and increased CSF levels of *tau* and isoprostane, two substances known to be often abnormal in AD. Moreover, levels of isoprostane increased significantly over a 2-year time period. This elevation was associated with decreases in CSF beta-amyloid levels and decreased hippocampal volume, suggesting a progression of degeneration consistent with AD.

Looking Toward the Future

For the moment, these technologies are used primarily in experimental contexts but, some day, they could be used more widely in clinical settings as a diagnostic tool. The findings from the New York University School of Medicine study, for example, support the idea that an accurate, reliable, and possibly specific clinical diagnosis of AD in the MCI stage is a reasonable expectation. As these tools improve and become more widely available, they also could be used to predict and follow the course of AD and other neurodegenerative diseases as well as to explain similarities and differences among them. Another important application of these advances is in measuring response to treatments, which would be invaluable in clinical trials of new drugs. Some day, as the influence of diet, exercise, intellectual stimulation, and other lifestyle factors on AD risk is clarified, these tools may even be useful in tracking changes in risk that result from behavioral and lifestyle changes. (For more on how this might be done, see the Alzheimer's Disease Neuroimaging Initiative described on p. 50.)

How Do We Translate Scientific Discoveries Into Effective Treatments?

Previous sections of this report have focused on the basic science research portfolio and on research into the lifestyle factors that increasingly appear to be related to the development, and possibly prevention, of AD. Findings from this growing body of knowledge have suggested a number of potential therapeutic targets, allowing investigators to intensify their hunt for AD treatments. Given the complex and long-term nature of the disease, it is unlikely that a "silver bullet" treatment will ever be possible. Rather, researchers hope to discover a range of drug and non-drug approaches that could be productively applied to delay the onset or slow the progress of AD or that could effectively treat AD symptoms. One focus of this area of research is the relatively new field of translational research. This work underpins the continuing emphasis on traditional treatment clinical trials.

The Emerging Field of AD Translational Research

Translational research is a multidisciplinary effort that creates a two-way bridge between basic science laboratory studies and clinical research. In essence, translational research provides a vital link between "bench" and "bedside," allowing valuable knowledge from the laboratory to be quickly applied to potential new tests or interventions in the clinical setting. Translational research also serves as a crucial venue for collaboration between scientists who focus on understanding the cellular, molecular, and pathologic dimensions of disease and those who focus on treating people. These collaborations are essential to developing safe and effective treatments. Collaborative and training opportunities in translational research encourage scientists to identify and conduct research on neurobiological questions of clinical relevance, learn how to move knowledge gained from basic research into clinical studies, and appreciate how findings in clinical research inform and refine basic research.

NIA's Translational Initiative

NIA supports the flow of potentially useful therapeutic compounds from the test tube to treatment of people through the NIH Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STRR) grant programs. These grants enable small businesses to explore the potential of compounds and other AD treatments. They also serve as a valuable link between laboratory work, clinical trials, and commercial development.

However, these programs alone are not sufficient to tap into and leverage the enormous potential of basic research in academic institutions that could possibly be "translated" into new therapies. As a result, in 2004, NIA launched a multi-component translational initiative to facilitate early drug discovery and drug development research by academic scientists and small biotechnology companies for treating and preventing AD, MCI, and age-related cognitive decline. This initiative provides small grants for early, exploratory drug discovery efforts and larger cooperative grants for various stages of preclinical drug development, in which new compounds are tested for

safety and efficacy in test tube and animal studies before being tested in humans. The grants are awarded to investigators who have identified new compounds that need to be refined and characterized in relevant animal models in order to receive FDA's Investigational New Drug (IND) approval. With these programs, NIA is broadening the range of potential treatments and expanding the number of therapeutic targets by investing relatively small amounts of money at critical steps of translational research that are traditionally not supported by the pharmaceutical industry. Undoubtedly, these are high-risk projects, but the compounds that successfully move through the translational process have high potential promise for patients.

To facilitate this process further, NIA offers funding through its longstanding investigational new drug toxicology program for academic and small business investigators who have promising compounds to treat and/or prevent AD, MCI, or age-related cognitive decline, but lack the resources to perform the required safety studies in multiple animal species, which are necessary to obtain IND status.

Finally, the translational initiative is complemented by a grant program that aims to support pilot clinical trials of promising compounds and non-pharmacologic interventions. This mechanism adds to NIA's existing ADCS and clinical trials program.

Basic Research Continues to Inform Translational Efforts

Basic research can make significant contributions to the pursuit of effective and safe therapies. Here are two examples that illustrate this contribution.

More Support for Beta-Secretase as a Therapeutic Target

As we described earlier, beta-amyloid is produced as a result of the activity of two APP-cleaving enzymes: beta-secretase and gamma-secretase. Scientists have devoted considerable effort to devising strategies to inhibit the activities or suppress the production of these enzymes in hopes that this could reduce beta-amyloid production and, consequently, slow the progression of AD.

Recent discoveries have provided support for the validity of beta-secretase (also known as BACE1) as a therapeutic target. For example, scientists from the Salk Institute for Biological Studies in La Jolla, California, developed specially engineered RNA molecules known as "small interfering RNAs" (siRNAs), which were attached to a gene delivery system to silence the production of BACE1 in the brains of AD transgenic mice (Singer et al., 2005). Reducing BACE1 levels slowed the production of beta-amyloid peptides and amyloid plaques, and diminished the damage to neurons and synapses in the brains of these mice. Most importantly, the transgenic mice that received this gene therapy treatment had less difficulty in learning a task compared to their littermates that did not receive the treatment.

The Search for Safer AD Immunotherapy

Immunizing people against disease has been a cornerstone of medical practice for decades. With this in mind, investigators wondered whether it might be possible to immunize people against AD by injecting them with beta-amyloid, which would cause their immune systems to make antibodies that lower the levels of brain amyloid (a technique called active immunization). Early animal studies, in which AD transgenic mice were actively immunized with a beta-amyloid peptide, were successful at decreasing the number of plaques and improving performance on memory tests. This led to a clinical trial in humans to test the safety and effectiveness of active immunization with the beta-amyloid immunogen (a substance designed to elicit an immune response). However, because about 6 percent of participants in the trial developed brain inflammation in response to the treatment, the trial was stopped. The adverse reaction was likely due to a T-cell reaction (part of the body's immune response) against the beta-amyloid immunogen. Despite this setback, the interest in developing an AD vaccine remains high.

The key issue in ongoing immunotherapy work is how to develop a vaccine that protects the brain against beta-amyloid toxicity without promoting or worsening brain inflammation. To this end, researchers at Harvard Medical School tested alternative immunogens that contained only the first 15 amino acids of the beta-amyloid peptide but not the T-cell reactive sites of the full-length peptide (Maier et al., 2006). In trying this approach, the researchers hoped to avoid stimulating the harmful T-cell response. Immunizing non-transgenic mice with this short beta-amyloid peptide resulted in a high, non-inflammatory, anti-beta-amyloid antibody response. When AD transgenic mice were immunized with the same short peptide, they also produced significant numbers of non-inflammatory anti-beta-amyloid antibodies. This was accompanied with a greatly reduced amyloid plaque load and improved learning compared to the control mice. These results are encouraging because they show that this novel immunogen approach may have promise for future AD vaccines.

Another approach that is garnering scientific interest is passive immunization. In this approach, instead of administering beta-amyloid directly, which then leads to antibody production, researchers administer anti-beta-amyloid antibodies. Several studies over the past few years have indicated that passively administered anti-beta-amyloid antibodies can effectively remove beta-amyloid peptides from the brain. Scientists at the University of South Florida carried out a passive immunotherapy trial in aged transgenic AD mice (Wilcock et al., 2004). Over 5 months, the mice were given weekly injections of anti-beta-amyloid antibodies. This regimen resulted in complete reversal of learning and memory deficits in these mice 3 months after the beginning of treatment. At the end of the 5-month treatment, beta-amyloid deposits in the animals' brains were dramatically reduced, indicating that even well-established amyloid deposits are susceptible to immunotherapy in these mice. However, the amount of beta-amyloid in the micro vessels of the treated mice was elevated and these vascular beta-amyloid deposits were sometimes associated with leakage of the micro vessels (microhemorrhages),

presumably as a result of the beta-amyloid being removed into the bloodstream. Because the cognitive benefits of the passive immunotherapy persisted in spite of the presence of vascular beta-amyloid and microhemorrhages, these data suggest that this promising approach needs to be further explored and modified to prevent the potential adverse events associated with microhemorrhages.

Putting Treatment Hypotheses to the Test in Clinical Trials

Previous sections of this report have described some of NIH's ongoing pilot and full-scale AD clinical trials that are testing exercise, diet, and chronic disease intervention strategies (see pp. 25, 29, and 32). This section describes other treat-ment clinical trials, most of which are testing drugs for their effects on AD progression or on behavioral symptoms.

The Long and Winding Road to AD Treatment Medications

In the mid-1970s, scientists discovered that levels of the neurotransmitter acetylcholine fell sharply in the brains of people with AD. This was a crucial discovery, for it was one of the first pieces of evidence that definitively linked AD with biochemical changes in the brain. Investigators studied acetylcholine intensively and found that neurons in the hippocampus and cerebral cortex, areas heavily damaged in AD, depend on this neurotransmitter in the memory formation process. All but one of the currently approved medications used to treat AD are cholinesterase inhibitors. That is, they stop or slow the action of acetylcholinesterase, an enzyme that breaks down acetylcholine.

Because these medications don't stop or reverse the disease process and appear to help patients for only a relatively short time, many scientists are working to develop alternative AD medications. For example, researchers at NIA's Intramural Research Program have designed and synthesized a number of novel compounds that have proved useful in defining the role of an enzyme called butyrylcholinesterase (BChE), which is found in the brain (Greig et al., 2005). Like acetylcholinesterase, BChE inactivates the neurotransmitter acetylcholine, so the NIA investigators began to look for ways to disrupt the action of BChE.

The investigators were able to develop potent, reversible, and brain-targeted BChE inhibitors. In rats, these compounds caused long-term inhibition of brain BChE and elevated extracellular acetylcholine levels, without inhibiting acetylcholinesterase. The scientists found that the rats showed improved performance on a maze test, which indicated improved cognitive performance. When the scientists examined brain tissue from the rats, they found that BChE inhibition augmented communication across synapses. In cultured human cells, inhibition of BChE led to reduced levels of APP and beta-amyloid peptide without affecting cell survival. Transgenic mice that overexpressed human mutant APP also were treated with the BChE inhibitors and they, too, showed lower beta-amyloid peptide brain levels compared to untreated mice.

Though these results appear promising, much additional work needs to be done before the BChE inhibitors can be tested in people. As a first step in that process, the NIA investigators are conducting additional studies to define optimal concentrations of the BChE compounds for further preclinical characterization.

Pilot MCI and AD Treatment Trials

Before beginning a full-scale clinical trial, investigators often conduct pilot clinical trials. The data gathered in these trials help scientists determine which interventions should go on to the next step. Here are a few of the current pilot clinical trials in MCI and AD:

- **Nicotine skin patch and amnestic MCI.** Some of the 60 non-smoking participants in this study are being given a nicotine patch and others a placebo patch. Nicotine imitates many of the actions of acetylcholine. Preliminary studies have suggested that short-term administration of nicotine appears to improve memory in patients with mild memory loss and early AD. Furthermore, nicotine administration appears to have significant neuroprotective effects, and it may have positive influences on APP processing. The primary goal of this pilot trial is to demonstrate whether the nicotine patch is safe to administer over a 1-year period to the participants with amnestic MCI. Study investigators also hope to determine whether nicotine can reduce memory loss and improve other cognitive symptoms over the longer term and whether it can help delay the progression of cognitive impairment and development of AD.

- **Raloxifene and women with AD.** This 12-month pilot trial will examine the effects of the osteoporosis drug, raloxifene, on cognitive function, ability to carry out daily activities, and biomarkers in older women with AD. In animal studies, raloxifene affects neuronal activity in ways that might be expected to improve cognitive function, and recent clinical data support the idea that this drug could lessen dementia symptoms in women with AD.

Full-scale AD Treatment Clinical Trials

At the time of this report, the NIH is supporting more than 30 clinical trials of treatments for people with AD. Many of these are part of the Alzheimer's Disease Cooperative Study. Here are highlights of a few of these trials.

- **Divalproex sodium and agitation.** A previous ADCS clinical trial of divalproex sodium (Valproate), conducted in 150 nursing home residents, was designed to see whether the medication could ease agitation in people with severe AD. In contrast to other trials, results from this multi-center trial did not show that divalproex sodium was helpful for people with severe AD. A trial currently underway is examining whether valproate therapy can delay or prevent agitation and psychosis in people with mild to moderate AD. Enrollment is nearly complete, with close to 300 people already participating. Researchers also are interested in seeing whether its possible neuroprotective properties have any effect on slowing the rate of cognitive decline.

- **Huperzine A and cognitive function.** This ADCS trial is evaluating whether huperzine A, a natural cholinesterase inhibitor derived from the Chinese herb *Huperzia serrata*, can slow the progression of cognitive decline in people with mild to moderate AD. A number of small, randomized controlled trials in China have indicated that people with AD who were treated with huperzine A performed better on memory tests than those on placebo. Investigators also are interested in huperzine A because it has

antioxidant and neuroprotective properties that suggest it may be useful in treating AD. The study, which has enrolled 140 of the 150 participants, is taking place in about 28 sites nationwide, and recruitment is ongoing. Participants are being randomly assigned to three equal groups—two groups will receive varying amounts of huperzine A every day and the third group will receive a placebo.

- **Growth hormones and MCI.** Some data suggest that a particular set of growth hormones that work together has a significant beneficial effect on memory and reasoning ability. This hormonal group—growth hormone releasing hormone/growth hormone/insulin-like growth factor 1 (GHRH)—is also called the somatotrophic hormonal axis. This clinical trial is determining whether GHRH is beneficial for individuals with amnestic MCI. Investigators will examine the effects of GHRH on the cognitive function of 80 healthy older adults and 80 older adults with amnestic MCI.

- **Depression in AD.** Major depression affects approximately 25 percent of people who have AD, so finding effective ways to treat this condition is an important priority for AD research. In fact, depression in AD is increasingly recognized as a condition separate from major depression. NIMH-funded researchers at Johns Hopkins University have developed and published criteria for health care providers to use in diagnosing depression of Alzheimer's disease (dAD) (Rosenberg et al., 2005). These criteria are broader than those used to diagnose major depression, and importantly, were developed with the help of AD caregivers. The researchers are conducting a clinical trial of dAD treatment and will validate the new diagnostic criteria as part of the trial. They have completed one clinical trial of the antidepressant medication sertraline (Zoloft) to examine the effects of antidepressant treatment on cognition and daily functioning, as well as on caregiver burden (Munro et al., 2004). Overall, results from the cognitive measures for the trial's 44 participants indicate that neither improved mood nor use of sertraline was associated with cognitive changes over time in the participants. Further exploration of the data suggested that the cognitive abilities of women treated with sertraline improved, compared to women who did not receive treatment. In contrast, the cognitive abilities of men taking sertraline worsened compared to those not treated.

- **Atypical antipsychotics to treat psychosis in AD.** NIMH-funded investigators at the University of Southern California Keck School of Medicine recently published results from a clinical trial called the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Schneider et al., 2006). This trial was designed to assess the effectiveness of atypical antipsychotic drugs for use in people with AD who experience hallucinations, delusions, agitation, or aggression. These symptoms are common in people with AD, and they can be very distressing to caregivers. The results from the trial showed no significant differences between the antipsychotic medications or placebo. Thus, the findings suggest a lack of significant clinical benefit of treatment with atypical antipsychotic medications in AD.

A Closer Look at Two Aspects of AD Clinical Trials

As the *Progress Report* has shown, clinical trials are essential to continued progress in AD research. Clinical trials, which compare a potential new treatment with a standard treatment or with a placebo, are the primary way that researchers find out whether a promising treatment is safe and effective. Clinical trials also tell researchers which treatments are more effective than others. Some clinical trials focus on treatment strategies—helping people with AD preserve cognitive function for as long as possible, for example, or helping people with behavioral or psychiatric problems associated with AD. Other clinical trials focus on prevention strategies—using specific interventions or drugs to help people reduce the risk of developing AD in the future. Here's a look at two critical aspects of clinical trials research.

Establishing the Infrastructure to Conduct Clinical Trials

In 1991, NIA launched the Alzheimer's Disease Cooperative Study (ADCS; http://adcs.ucsd.edu), a consortium of research sites around the country. The ADCS conducts clinical trials on compounds that are not generally of interest to large pharmaceutical companies. These include drugs that are off patent, drugs that are patented and marketed for another use but may be useful in treating cognitive and behavioral symptoms of AD, and novel compounds from individual investigators or small companies without adequate resources for clinical trials. Currently, the ADCS is supporting five clinical trials.

The latest renewal of the ADCS in 2006 will support new clinical trials to test drugs for their effectiveness in slowing the progression or treating the symptoms of AD, as well as to investigate new methods for conducting dementia research. Most of the new trials will focus on possible therapies aimed at affecting beta-amyloid and *tau*:

- **Docosahexaenoic Acid (DHA).** This trial will examine whether treatment with DHA will slow 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 brain levels of beta-amyloid, oxidative damage associated with beta-amyloid, and neurotoxicity (see p. 29 for more on this research).
- **Intravenous Immunoglobulin (IVIg).** Interest in passive immunization strategies against AD is growing (see p. 40 for more on these strategies). IVIg contains naturally-occurring antibodies against beta-amyloid, and preliminary studies have shown that IVIg may improve cognition. In addition, research has demonstrated that IVIg increased levels of anti-beta-amyloid antibodies in plasma and promoted clearance of beta-amyloid from cerebrospinal fluid. The new ADCS trial will demonstrate whether IVIg is useful clinically for treating AD.
- **Lithium.** The biological activity of lithium, which has been shown in animal studies to block abnormal changes in *tau*, is of interest to ADCS investigators. They will undertake a pilot biomarker study to see whether the drug can lower *tau* and beta-amyloid levels in cerebrospinal fluid and be safely tolerated in older AD patients.

Innovative Ways to Recruit and Retain Participants

One of the major limitations in conducting trials in older adults is recruiting and retaining individuals who can effectively participate in lengthy evaluations in a specialized clinic setting. Many older people, particularly the very elderly, have physical, social, and health limitations that make it difficult for them to take part in research. Thus, NIA AD investigators are examining ways to make it easier for volunteers to participate in clinical research, and they are developing novel procedures and measures that can be administered at home or in other community settings:

- **The GEM trial.** Extracts of leaves from the Ginkgo biloba tree are thought to have beneficial effects on brain function, especially those related to dementia and AD. This 10-year clinical trial, which began in 2000 and is co-funded by NCCAM, NHLBI, and NIA, is comparing ginkgo to placebo in people older than 75 who were cognitively healthy or who had MCI at the beginning of the trial (DeKosky et al., 2006). The study's main goal is to determine whether ginkgo is helpful in preventing or delaying the onset of dementia, though researchers also are interested in assessing participants' rate of cognitive and functional decline, the incidence of cardiovascular and cerebrovascular events, and causes of death. All participants have extensive neuropsychological evaluations at the beginning of the study. Each also has someone who has agreed to provide an independent assessment of the functional and cognitive abilities of the participant. Assessments are repeated

ADCS Study Sites in 2006

every 6 months. Significant cognitive decline at any visit leads to a repeat detailed neuropsychological assessment and a neurological and medical evaluation. Side effects and adverse events also are closely monitored.

As with all clinical trials, recruitment was an important challenge. The researchers' goal was to enroll about 3,000 people age 75 and older at four sites in the U.S. (Fitzpatrick et al., 2006). The investigators understood early on that recruiting participants in this age range would be difficult, and they carefully planned a systematic approach that included ways to collect data on the recruitment process. From the beginning, they tracked eligibility and refusal rates, which allowed for adjustments as needed. Study staff began their enrollment efforts by mailing 243,400 brochures about the study to potential participants. Follow-up phone calls to 14,603 households yielded 12,186 successful contacts. Out of these 12,186 people, 2,149 people were ineligible to participate because of cognitive, medical, or other reasons. Of the remaining people, 6,944 decided not to join. The end result was that 3,072 people enrolled in the study, a recruitment rate of about 25 percent based on telephone contacts made, or about 1 percent based on the initial mailing.

- **ADCS Prevention Instrument Project.** Investigators are designing and developing new questionnaires and other instruments that can be used to evaluate individuals' overall cognitive functioning, memory, ability to carry out activities of daily life, and quality of life. These instruments, which are mostly self-administered, can be completed in a less time-consuming and more cost-efficient manner than was possible with previous instruments. The aim of this project is to evaluate the effectiveness of these new tests in identifying change over time and conversion to MCI or AD in cognitively healthy elderly and to compare assessments completed in the clinic (the traditional in-person method) with those completed at home. The 4-year study simulates a primary prevention trial, a type of trial that aims to prevent the development of a disease. This study has enrolled 644 healthy adults 75 years of age and older. Participants have been randomized to one of two groups, where baseline and follow-up assessments are completed at home or in the clinic. Results obtained from both venues are being analyzed to determine whether the home evaluations are equivalent to those done in the clinic. Data collection and analysis are continuing.
- **Home-Based Assessment.** This new ADCS study, conducted in people aged 75 and older, will further examine the development and use of home-based assessments. Three types of in-home assessment and data collection procedures are being examined: a) low-technology telephone assessment; b) a high-technology automated telephone assessment; and c) a high-technology computer assessment. Cognition, daily functioning, mood, and other factors will be evaluated in each of the methods. These innovative assessment and data collection methods will again be compared against traditional in-person methods. The findings from this study will provide information on how home-based assessments might be used in prevention trials. Such methods could significantly reduce the cost and increase the feasibility of participation in these long-term clinical trials.

How We're Getting To The Goal

PART 3

As we noted at the beginning of this book, journeys require a means of transport. In this case, AD researchers need financial, technical, and scientific support to pursue their work. NIH has created and nurtured the essential research infrastructure that allows scientists to push the basic science forward, conduct epidemiologic and other clinical studies, and develop new drugs and therapeutic approaches. The advances and new knowledge that result are bringing us ever closer to a full understanding of the causes of this devastating disease and to effective prevention and treatment strategies.

NIA Initiatives for AD Research

Several NIA initiatives provide critical venues through which investigators can conduct interdisciplinary and collaborative AD research.

Alzheimer's Disease Centers

The NIA-funded Alzheimer's Disease Centers (ADCs) promote basic research, training and education, and technology transfer (www.nia.nih.gov/Alzheimers/). They also conduct multi-center and collaborative studies of diagnosis and treatment in AD, age-related neurodegenerative diseases, and normal aging.

Many milestones in AD research in the U.S. since 1984 stem from research carried out at the ADCs. For example, ADC research has revealed much about the linkage and cloning of genes on chromosomes 1, 14, and 21 in early onset Alzheimer's disease, chromosome 17 in frontotemporal dementia, subsequent studies on processing of proteins coded by these genes, and the identification of the inherited risk factor for late-onset disease, APOE, on chromosome 19. Much of the work related to processing of proteins important for plaque and NFT formation, including the discovery of alpha synuclein in Lewy body dementia, and the recognition of the common properties of amyloids found in various neurodegenerative diseases, has been carried out in the ADCs. Recently, progranulin and the TDP43 protein were both discovered by ADC researchers and have contributed to our understanding of one type of frontotemporal dementia and motor neuron disease. Important studies that correlate pathologic changes in brain structure and function with preclinical and clinical evidence of disease are being conducted with people enrolled in ADC clinical studies. Complementary studies, such as imaging studies and autopsy evaluations, also are conducted at ADCs. In recent

years, the centers have placed increasing emphasis on evaluating cognitive function in healthy aging and the transition to amnestic MCI and early dementia, as well as mixed dementias and overlapping dementia syndromes. Another growing focus for the ADCs is collaborative trans-center projects and collaborations with investigators outside the centers' network.

In addition to performing cutting edge research, the ADCs provide essential resources from which other research projects like the ADCS, the AD Genetics Initiative, and the AD Neuroimaging Initiative can draw (see the following sections for more on these initiatives). These resources include a cadre of researchers well versed in all aspects of AD, access to patient and family data, brain and other tissue samples, and molecular probes, as well as outreach programs that work with diverse groups, including minority and rural populations.

National Alzheimer's Coordinating Center

In 1999, NIA established the National Alzheimer's Coordinating Center (NACC) so that data on patients from the ADCs could be pooled and shared (www.alz.washington.edu). At the beginning, it was only possible to collect a minimum data set (MDS) with a limited number of variables. Eleven collaborative multi-center studies were funded by NACC and an additional seven collaborative investigator-initiated grants funded by NIA were linked to NACC and used data from the MDS. Between 1984 and 2005, information on more than 75,000 ADC study participants and neuropathological data on more than 9,000 brains from autopsied participants were collected in the MDS. Much of this material is available for research by qualified scientists.

Although the MDS collected the same data from all study participants, the centers did not collect the data in a standardized way, and the number of data points was limited. This prevented investigators from comparing data from one center to another. Standardized data collection allows data from multiple centers to be pooled, creating larger samples and the potential for more sophisticated and informative analyses than would be possible with data from only one center. The Uniform Data Set (UDS), which replaced the MDS in 2005, contains many more data elements and will be much more useful for research. The clinical task force designed the UDS initially for healthy participants and those with amnestic MCI and early AD, and is now developing new modules to collect data on participants with frontotemporal dementia, Lewy body dementia, and vascular dementia. More than 7,000 individuals are now being evaluated using the UDS, and the data are available to qualified researchers through NACC.

Major AD Research Initiatives

The NIA continues to support several major initiatives in which the clinical, genetic, imaging, and biological data and samples that are collected are being made widely available to qualified investigators through secure web-based systems. As a result, these initiatives have become a critical national and international resource for scientists who are interested in AD, other neurodegenerative diseases, healthy aging, and related topics.

NIA initiatives have become a critical national and international resource for scientists who are interested in AD.

Alzheimer's Disease Genetics Initiative

Genetic studies of complex neurodegenerative diseases such as AD have focused on two key issues—whether a gene might influence a person's overall risk of developing a disease and whether a gene might influence some particular aspect of a person's risk, such as the age at which the disease begins. So far, scientists have discovered three mutations that cause the rare early-onset form of familial AD and one mutation that affects the risk of developing late-onset AD (see p. 15 for more on these genes). Scientists estimate that an additional four to seven risk factor genes exist for late-onset AD. Evidence uncovered by NIA investigators also suggests that variability in the genes that cause early-onset AD may increase the risk of developing late-onset AD (Myers et al., 2005; Singleton et al., 2004).

As AD genetics research has intensified, it has become increasingly clear that scientists need many samples of genetic material if they are to continue making progress in identifying new risk factor genes, as well as identifying associated environmental factors and understanding the interactions of genes and the environment. These advances will ultimately allow investigators to identify people at high risk of developing AD and help them focus on new pathways that may be amenable to prevention or treatment.

The goal of the NIA Genetics Initiative is to identify at least 1,000 families with members who have late-onset AD as well as unaffected family members, and encourage these individuals to provide blood samples and other clinical data for the initiative. More than 900 families already have been recruited but more are needed, so NIA is providing funding to the ADCs to help recruit the remaining participants. The NIA ADEAR Center is collaborating with the Alzheimer's Association to develop media and community outreach programs to foster participation in the initiative among families who have two or more living members with late-onset AD.

The Genetics Initiative collects blood samples and other clinical data from people with AD and their unaffected familiy members. This allows investigators to create and maintain "immortalized" cell lines—cells that are continuously regenerated in the laboratory. These cell lines are crucial for the exhaustive DNA analysis studies needed to identify risk factor genes, each of which may have relatively small effects on AD development. The National Cell Repository for AD (NCRAD), located at Indiana University, serves as the centralized repository for the initiative (http://ncrad.iu.edu), providing DNA and cell lines to qualified investigators for genetics studies. In 2006, NIA opened the Genetics of Alzheimer's Disease Data Storage Site at Washington University. Scientists who use NCRAD samples and data and AD geneticists funded by NIA are asked to submit published genetics data to the Storage Site for additional analysis by qualified investigators. An initial subset of cases has recently undergone a whole genome scan, and results are now available on the website. Many AD researchers also are taking advantage of a large sample repository and genetics database already developed by NIMH. Beginning in 2006, data from combined NIMH and NIA sample sets will be available through a unique data repository shared by the two Institutes.

Alzheimer's Disease Neuroimaging Initiative

NIA has launched the multi-year AD Neuroimaging Initiative, which will use serial MRI and PET scans to examine how brains change as MCI and AD progress. The project will follow approximately 200 cognitively healthy individuals for 3 years, 400 people with MCI for 3 years, and 200 people with early AD for 2 years. Funding for the initiative began in 2004 and enrollment of participants is nearly complete. By using MRI and PET scans at regularly scheduled intervals, investigators hope to learn when and where in the brain degeneration occurs as memory problems develop.

Scientists will correlate this imaging information with clinical, neuropsychological, and biological markers from blood, cerebrospinal fluid, and urine samples collected at intervals from individuals in the study. Potential markers include levels of beta-amyloid and *tau*, indicators of inflammation, and measures of oxidative stress. Rigorous imaging and biomarker standards developed as a result of this initiative will help in early diagnosis and provide measures for the success of potential treatments. This would substantially increase the pace and decrease the cost of developing new treatments.

This initiative is a partnership among the NIA, university investigators, the pharmaceutical and imaging equipment industries, the FDA, and the NIH Foundation, with participation from the Alzheimer's Association and the Institute for the Study of Aging. An important aspect of this initiative is that the clinical, imaging, and biological data collected will be shared and made available to all qualified scientific investigators for further analyses. For more information about the Neuroimaging Initiative, visit www.nia.nih.gov/Alzheimers.

The Cognitive and Emotional Health Project

A large number of people are at substantial risk for cognitive impairment from many causes as they age. The same is true for emotional disorders. Although research into biological mechanisms and environmental and social effects is yielding promising results in both animal and human studies, much remains to be discovered. These gaps in current knowledge spurred NIA, NINDS, and NIMH to jointly create the trans-NIH Cognitive and Emotional Health Project: The Healthy Brain. This initiative will spur advances in understanding changes in cognition and emotion in adulthood and what can be done to preserve and enhance positive outcomes—advances that are central to the missions of the participating Institutes. The overall goal of the Cognitive and Emotional Health Project is to assess the state of longitudinal and epidemiologic research on demographic, social, and biologic determinants of cognitive and emotional health in aging adults, and to accelerate identification of ways to maintain cognitive and emotional health. The Project also is examining the pathways by which cognitive and emotional health may influence each other. Project staff have completed a detailed evaluation of the scientific literature on factors involved in maintaining cognitive and emotional health in adults (Hendrie et al., 2006). The NIH Blueprint for Neuroscience Research has funded a 5-year effort to create the NIH Toolbox for Assessment of Neurological and Behavioral Function (www.neuroscienceblueprint.nih.gov). This effort will use state-of-the-art research and novel testing methods to develop an integrated set of measures of cognitive, emotional, and sensory health. These measures will be appropriate for use in large-scale studies and clinical trials. For more information on project activities currently underway to accomplish these goals, visit http://trans.nih.gov/CEHP.

Helping People with AD and their Caregivers Cope

Perhaps one of the greatest costs of AD is the toll on families, caregivers, and friends. Investigators supported by NIA, NIMH, and the National Institute of Nursing Research (NINR) are exploring the emotional, psychological, and physical costs of caregiving and are investigating ways to ease the burden. Here are a few highlights of recent research.

Improving the Chances of Success in Assisted Living

Assisted living is a popular option for older adults, yet little is known about the impact of cognitive abilities, moods, and overall health on how well people in these facilities function. NIMH is supporting the Maryland Assisted Living Study to improve researchers' knowledge about this important issue. A study team from the Johns Hopkins University School of Medicine has looked at 22 facilities to determine the prevalence, recognition, and treatment of dementia and other psychiatric disorders (Rosenblatt et al., 2004), and to examine factors that impair people's ability to function well (Burdick et al., 2005).

In the first study, the Johns Hopkins team found that dementia and psychiatric disorders were common—nearly 68 percent of the 198 participants had dementia and 26 percent had a psychiatric disorder—and that recognition and treatment were not as good as they could be. In the second study, the researchers found, not surprisingly, that cognitive difficulties, memory problems, depression, and poor overall health had a significantly negative impact on the residents' ability to carry out their daily activities. Results from both of these studies may help assisted living facilities develop models of care that improve recognition of dementia and psychiatric disorders, incorporate key predictors of functional impairment, and improve resident care.

Helping People Express Care Preferences

All caregivers want to provide care that reflects the lifelong values and preferences of the person with AD. As the disease progresses and the person's ability to form ideas and express thoughts diminishes, it becomes increasingly difficult to gauge these preferences. It is all the more important, therefore, to help people with AD and their families articulate these preferences early, when it is possible to discuss them and plan for the future.

NIMH-supported scientists at the Margaret Blenkner Research Institute, in Cleveland, Ohio, have developed and validated just such an approach (Whitlatch et al., 2005). The Values and Preferences Scale, a 24-item questionnaire that can be used in research or practice settings, was developed with the help and advice of practitioners, researchers, family caregivers, and people with cognitive impairment.

Finding Low-tech Solutions for Behavioral Symptoms

Bathing can be one of the hardest aspects of AD caregiving because it often triggers agitation and aggression in the person with AD. A research group at the University of North Carolina developed and tested two methods of bathing—person-centered showering and a new type of in-bed bath with no-rinse soap called a towel-bath (Sloane et al., 2004). Agitation and aggression declined significantly with the new methods. Both methods also

improved skin condition and neither increased potentially harmful skin bacteria. Simple interventions like these can easily be learned and applied to improve the quality of life of the person with AD and ease the burden on family caregivers.

Researchers at Pennsylvania State University explored a different kind of solution. They tested different types of recreational activities to see which might be best at lessening agitation and passivity, two common problems among nursing home residents (Kolanowski et al., 2005). They compared activities that only matched residents' interests, activities that only matched their skills, and activities that reflected both. Though all three types of activities lessened agitation and negativity, the interest-only and combined activities had the greatest positive effect. The authors suggest that these findings can help explain factors that produce behavioral symptoms and can help care facilities successfully tailor activities for residents with dementia.

Improving Support for Caregivers

Recent studies have contributed to a growing understanding not only of the burdens of caregiving, but of the wide range of physical and psychological reactions that caregivers have and to their diverse needs for support at various stages of caregiving. Resources for Enhancing Alzheimer's Caregiver Health (REACH) is a long-term caregiver clinical trial supported jointly by NIA and NINR. Findings from Phase I of the project have clearly shown that social service and medical contacts and support interventions must be culturally appropriate and sensitive to the factors that influence (both positively and negatively) caregivers' attitudes to their caregiving responsibilities.

These findings have been applied to the second phase of the clinical trial, REACH II, and results have just been published (Belle et al., 2006). The REACH II study included more than 600 Hispanic, white, and African-American dementia caregivers in five locations around the country. Caregivers within each ethnic/racial group were randomly assigned either to an intervention or a control group. Caregivers in the intervention group received intensive help with caregiving strategies through information sharing, instruction, role playing, problem solving, skills training, stress-management techniques and telephone support groups. Those in the control group received a packet of dementia education materials and two brief "check-in" telephone calls.

After 6 months, improvements in overall quality of life were significant among the caregivers who took part in the intervention. Clinical depression also was significantly lower.

Caregivers in the intervention group reported that taking part in the program helped them feel more confident in working with their loved one, made life easier for them, improved their caregiving ability, improved the care

recipient's life, and helped them keep their loved one at home. Many members of the control group said they also benefited from participating in the study, suggesting that even minimal support and attention can help caregivers.

Based on these results, investigators hope that the REACH approach can be used widely in the community, especially if the outcomes are replicated by others and the program is found to be cost-effective.

Outlook for the Future

PART 4

Dementia is not new. Ancient Greeks and Romans wrote about it, and it even makes an appearance in Shakespeare. But it wasn't until 1906 that Alois Alzheimer, a German scientist who pioneered investigations into various psychiatric disorders and brain diseases, first presented a case study of a 51-year old German woman, Auguste D., who had been admitted to the hospital in 1903 with symptoms that included reduced comprehension and memory, an inability to speak or understand speech, disorientation, unpredictable behavior, and other behavioral and psychiatric problems. When Dr. Alzheimer conducted an autopsy of his patient, he had the benefit of the latest scientific technology—new techniques for staining brain tissues and greatly improved microscopes. These innovations allowed him to identify many globs of sticky proteins between neurons and tangled bundles of fibrils within cells throughout the cortex, or outer layer of neurons in her brain. Of course, these plaques and tangles are two characteristic features of the disease that now bears his name.

We've come quite a long way since then. But, as this report shows, some things remain the same. Scientists are still pushing the bounds of technology to develop new methods and tools that can enhance their ability to learn about AD and other neurodegenerative diseases. Investigators are still combining dogged persistence with imagination and insight to improve their understanding of AD.

With that increased knowledge, however, comes heightened sense of urgency. As our population ages and the number of people age 65 and older steadily climbs, the prevalence of AD and other neurodegenerative diseases, and the costs to families and society, will continue to rise. Our growing appreciation for the decades-long developmental process of the disease and its complex nature means that we must devise multifaceted preventive and treatment strategies that begin early and continue throughout life.

As we said in the Introduction, good travelers plan for how they will meet future challenges as their journey unfolds. NIH has developed a number of resources that will help it meet these challenges in AD. For example, several NIH Roadmap (http://nihroadmap.nih.gov/) initiatives provide innovative infrastructure critical to discovery of the underlying causes and basic biological pathways associated with AD as well as numerous other diseases and conditions:

- The Molecular Libraries and Imaging Initiative offers biomedical researchers access to small molecules that can be used as chemical probes to explore the functions of genes, cells, and biochemical pathways in healthy aging and disease.
- The Building Blocks, Biological Pathways, and Networks Initiative supports exploration of the array of intricate and interconnected

pathways that facilitate communication among genes, molecules, and cells; how these pathways are integrated in humans and other complex organisms; how disturbances in these pathways may lead to disease; and what might be done to restore disturbed pathways to their normal functions.

- The Interdisciplinary Research Initiative is helping to address the complex challenges of AD research by encouraging and facilitating interaction among disciplines that is so critical to the study of a complex disease like AD and the development of research and therapeutic technologies. New reward systems and incentives are being developed to promote the work of multidisciplinary teams that bring together the expertise of neuroscientists, psychologists, social scientists, epidemiologists, geneticists, biologists, imaging specialists, biomedical engineers, and others to build synergy to find solutions for AD.

AD research efforts combine an accelerated search for causes, a vigorous assault on the effects of the disease, and an intensive effort to find ways to interrupt progression or delay onset.

- The Re-Engineering the Clinical Research Enterprise Initiative is supporting work to find the best ways to foster broad community-based participation in clinical studies, including clinical trials. This emphasis is a critical shift for addressing the problems of illnesses like AD, which often require care within the home and in community settings.

NIA also participates in the activities of the multi-Institute NIH Blueprint for Neurosciences Research. This effort provides a framework to enhance and fund cooperative activities and resources among 15 NIH Institutes and Centers to reduce the burden of nervous system disorders, including AD (Baughman RW et al., 2006). These NIH Institutes and Centers are working to make collaboration a day-to-day part of how NIH does neuroscience. By pooling resources and expertise, NIH can take advantage of economies of scale, confront challenges too large for any single Institute, and develop research tools and infrastructure that will serve the entire neuroscience community.

Participants have built on existing programs to develop an inventory of neuroscience tools funded by NIH and other government agencies, enhance training in the neurobiology of disease for basic neuroscientists, and expand ongoing gene expression database efforts. Advances in the neurosciences and the emergence of powerful new technologies

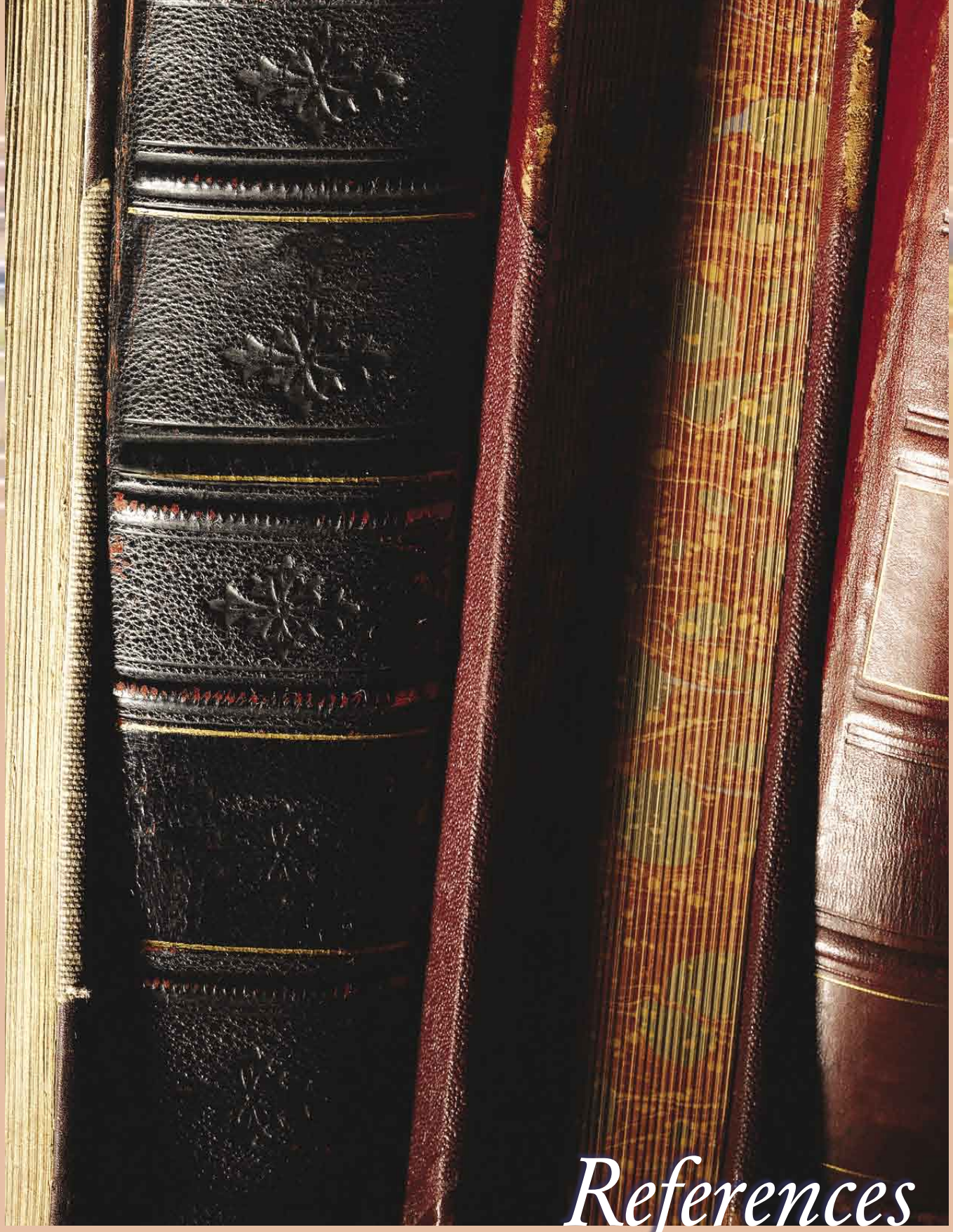
will continue to provide new opportunities for Blueprint activities that will enhance the effectiveness and efficiency of AD and other research across NIH. Systematic development of genetically engineered mouse strains through the Blueprint will be of critical importance to AD research as will training in critical cross cutting areas such as neuroimaging and computational biology.

NIA is also continuing to partner with NIMH, NINDS, and NINR in the AD Prevention Initiative, which is designed to invigorate discovery and testing of new treatments, identify risk and protective factors, enhance early detection methods, and advance basic AD research. This initiative also is aimed at improving patient care strategies and developing approaches to lessen caregiver burdens.

Bringing the best scientific minds together to talk also helps NIA and other NIH Institutes and Centers chart a course for their future efforts in AD research. In October 2006, NIA, NINDS, NIMH, NIBIB, and NINR co-sponsored a conference called "AD: Setting the Research Agenda a Century after Auguste D." Organizers chose this important centennial anniversary of Dr. Alzheimer's first presentation on the disease to ask leading AD scientists to provide an overview of the status of current research from their particular perspective and to articulate the critical questions and issues that need to be addressed for continued progress in AD research. Recommendations from the presentations and the discussion sessions will help guide AD research plans and priorities over the next few years.

Another important way AD research moves forward into the future is through collaboration between investigators from public and private sectors to maximize the quality and impact of research. As **Part 3** of the *Progress Report* showed, there is a growing emphasis on developing standardized data collection systems and sharing data and biological samples with other qualified investigators in a timely fashion. As a result, NIH supports much of the basic research and development that is the foundation for new directions and clinical applications sponsored by the industry.

The multi-faceted, collaborative AD research effort described here combines an accelerated search for causes, a vigorous assault on the effects of the disease, and an intensive effort to find ways to interrupt progression or delay onset. This effort sustains the fight against AD and brings us closer to the day when we will be able to successfully manage or even prevent this terrible disease, which robs our older relatives and friends of their most precious possession—their minds.



References

PART 5

Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. *JAMA* 2004;292(12):1447-1453.

Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *Journal of Neuroscience* 2005;25(17):4217-4221.

Andorfer C, Acker CM, Kress Y, Hof PR, Duff K, Davies P. Cell-cycle reentry and cell death in transgenic mice expressing nonmutant human tau isoforms. *Journal of Neuroscience* 2005;25(22):5446-5454.

Baughman RW, Farkas R, Guzman M, Huerta MF. The National Institutes of Health Blueprint for Neuroscience Research. *Journal of Neuroscience* 2006;26(41):10329-10331.

Belle SH, Burgio L, Burns R, Coon D, Czaja SJ, Gallagher-Thompson D, Gitlin LN, Klinger J, Koepke KM, Lee CC, Martindale-Adams J, Nichols L, Schulz R, Stahl S, Stevens A, Winter L, Zhang S, Resources for Enhancing Alzheimer's Caregiver Health (REACH) II Investigators. Enhancing the quality of life of dementia caregivers from different ethnic or racial groups: a randomized, controlled trial. *Annals of Internal Medicine* 2006;145(10):727-738.

Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology* 2005;64(5):834-841.

Berchtold NC, Chinn G, Chou M, Kesslak JP, Cotman CW. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience* 2005;133(3):853-861.

Berezovska O, Lleo A, Herl LD, Frosch MP, Stern EA, Bacskai BJ, Hyman BT. Familial Alzheimer's disease presenilin 1 mutations cause alterations in the conformation of presenilin and interactions with amyloid precursor protein. *Journal of Neuroscience* 2005;25(11):3009-3017.

Billings LM, Oddo S, Green KN, McGaugh JL, LaFerla FM. Intraneuronal Abeta causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice. *Neuron* 2005;45(5):675-688.

Bond GE, Burr R, McCurry SM, Rice MM, Borenstein AR, Kukull WA, Teri L, Bowen JD, McCormick WC, Larson EB. Alcohol, gender, and cognitive performance: a longitudinal study comparing older Japanese and non-Hispanic white Americans. *Journal of Aging and Health* 2004;16(5):615-640.

Burdick DJ, Rosenblatt A, Samus QM, Steele C, Baker A, Harper M, Mayer L, Brandt J, Rabins P, Lyketsos CG. Predictors of functional impairment in residents of assisted-living facilities: the Maryland Assisted Living study. *Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* 2005;60(2):258-264.

Calon F, Lim GP, Yang F, Morihara T, Teter B, Ubeda O, Rostaing P, Triller A, Salem N Jr., Ashe KH, Frautschy SA, Cole GM. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. *Neuron* 2004;43(5):633-645.

Colcombe S and Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological Science* 2003;14(2): 125-130.

Cole GM, Lim GP, Yang F, Teter B, Begum A, Ma Q, Harris-White ME, Frautschy SA. Prevention of Alzheimer's disease: omega-3 fatty acid and phenolic anti-oxidant interventions. *Neurobiology of Aging* 2005;26S(Suppl 1):133-136.

Curb JD. The tangled story of plaques and arteries. *Journal of the American Geriatrics Society* 2005;53(7):1257-1258.

Daniels J. Obesity: America's epidemic. *American Journal of Nursing* 2006;106(1):40-49.

DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL, Burke G, Fried L, Kuller LH, Robbins J, Tracy R, Woolard N, Dunn L, Kronmal R, Nahin R, Furberg C, GEMS Investigators. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. *Contemporary Clinical Trials* 2006;27(3):238-253.

de Leon MJ, DeSanti S, Zinkowski R, Mehta PD, Pratico D, Segal S, Rusinek H, Li J, Tsui W, Saint Louis LA, Clark CM, Tarshish C, Li Y, Lair L, Javier E, Rich K, Lesbre P, Mosconi L, Reisberg B, Sadowski M, DeBernadis JF, Kerkman DJ, Hampel H, Wahlund LO, Davies P. Longitudinal CSF and MRI biomarkers improved the diagnosis of mild cognitive impairment. *Neurobiology of Aging* 2006;27(3):394-401.

Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, Bertram L, Mullin K, Tanzi RE, Blacker D, Albert MS, Sperling RA. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology* 2005;65(3):404-411.

Domnitz SB, Robbins EM, Hoang AW, Garcia-Alloza M, Hyman BT, Rebeck GW, Greenberg SM, Bacskai BJ, Frosch MP. Progression of cerebral amyloid angiopathy in transgenic mouse models of Alzheimer disease. *Journal of Neuropathology and Experimental Neurology* 2005; 64(7):588-594.

Ernst RL, Hay JW, Fenn C, Tinklenberg J, Yesavage J. Cognitive function and the costs of Alzheimer's disease. An exploratory study. *Archives of Neurology* 1997;54(6):687-693.

Ernst RL and Hay JW. The US economic and social costs of Alzheimer's disease revisited. *American Journal of Public Health* 1994;84(8):1261-1264.

Evans DA and Bienias JL. Alcohol consumption and cognition. *New England Journal of Medicine* 2005;352(3):289-290.

Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, Herbert LE, Hennekens CH, Taylor JO. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. *JAMA* 1989;262(18):2551-2556.

Fitzpatrick AL, Fried LP, Williamson J, Crowley P, Posey D, Kwong L, Bonk J, Moyer R, Chabot J, Kidoguchi L, Furberg CD, DeKosky ST, GEM Study Investigators. Recruitment of the elderly into a pharmacologic prevention trial: the Ginkgo Evaluation of Memory Study experience. *Contemporary Clinical Trials* 2006;27(6):541-553.

Fleisher A, Grundman M, Jack CR Jr, Petersen RC, Taylor C, Kim HT, Schiller DH, Bagwell V, Sencakova D, Weiner MF, DeCarli C, DeKosky ST, van Dyck CH, Thal LJ, Alzheimer's Disease Cooperative Study. Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. *Archives of Neurology* 2005;62(6):953-957.

Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, Miller JP, Storandt M, Morris JC. The AD8: a brief informant interview to detect dementia. *Neurology* 2005;65(4):559-564.

Ganguli M, Vander Bilt J, Saxton JA, Shen C, Dodge HH. Alcohol consumption and cognitive function in late life: a longitudinal community study. *Neurology* 2005;65(8):1210-1217.

Greig NH, Utsuki T, Ingram DK, Wang Y, Pepeu G, Scali C, Yu QS, Mamczarz J, Holloway HW, Giordano T, Chen D, Furukawa K, Sambamurti K, Brossi A, Lahiri DK. Selective butyrylcholinesterase inhibition elevates brain acetylcholine, augments learning and lowers Alzheimer beta-amyloid peptide in rodent. *Proceedings of the National Academy of Sciences, USA* 2005;102(47):17213-17218.

He W, Sengupta M, Welkoff VA, DeBarros KA, U.S. Census Bureau. *65+ in the United States: 2005.* Current Population Reports, P23-209. Washington (DC): U.S. Government Printing Office, 2005.

Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Archives of Neurology* 2003;60(8):1119-1122.

Hendrie HC, Albert MS, Butters MA, Gao S, Knopman DS, Launer LJ, Yaffe K, Cuthbert BN, Edwards E, Wagster MV. The NIH Cognitive and Emotional Health Project: report of the Critical Evaluation Study Committee. *Alzheimer's & Dementia* 2006;2(2):12-32.

Herrup K, Neve R, Ackerman SL, Copani A. Divide and die: cell cycle events as triggers of nerve cell death. *Journal of Neuroscience* 2004;24(42):9232-9239.

Huang LF, Cartwright WS, Hu TW. The economic cost of senile dementia in the United States, 1985. *Public Health Reports* 1988;103(1):3-7.

Jack CR Jr, Shiung MM, Weigand SD, O'Brien PC, Gunter JL, Boeve BF, Knopman DS, Smith GE, Ivnik RJ, Tangalos EG, Petersen RC. Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnestic MCI. *Neurology* 2005;65(8):1227-1231.

Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. *Annals of Neurology* 2005;57(5):713-720.

Khurana V, Lu Y, Steinhilb ML, Oldham S, Shulman JM, Feany MB. TOR-mediated cell-cycle activation causes neurodegeneration in a *Drosophila* tauopathy model. *Current Biology* 2006;16(3):230-241.

Klieman L, Hyde S, Berra K. Cardiovascular disease risk reduction in older adults. *Journal of Cardiovascular Nursing* 2006;21(5Suppl 1):S27-S39.

Kolanowski AM, Litaker M, Buettner L. Efficacy of theory-based activities for behavioral symptoms of dementia. *Nursing Research* 2005;54(4):219-228.

Kuller LH, Lopez OL, Jagust WJ, Becker JT, DeKosky ST, Lyketsos C, Kawas C, Breitner JC, Fitzpatrick A, Dulberg C. Determinants of vascular dementia in the Cardiovascular Health Cognition Study. *Neurology* 2005;64(9):1548-1552.

Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine* 2006;144(2):73-81.

Launer L. Diabetes and brain aging: epidemiologic evidence. *Current Diabetes Reports* 2005;5(1):59-63.

Lazarov O, Robinson J, Tang YP, Hairston IS, Korade-Mirnics Z, Lee VM, Hersh LB, Sapolsky RM, Mirnics K, Sisodia SS. Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell* 2005;120(5):701-713.

Lewin Group. *Saving Lives, Saving Money: Dividends for Americans Investing in Alzheimer Research.* A report commissioned by the Alzheimer's Association. Washington (DC): The Lewin Group, 2004.

Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, Salem Jr. N, Frautschy SA, Cole GM. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. *Journal of Neuroscience* 2005;25(12):3032-3040.

Lin MY, Gutierrez PR, Stone KL, Yaffe K, Ensrud KE, Fink HA, Sarkisian CA, Coleman AL, Mangione CM, Study of Osteoporotic Fractures Research Group. Vision impairment and combined vision and hearing impairment predict cognitive and functional decline in older women. *Journal of the American Geriatrics Society* 2004;52(12):1996-2000.

Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* 2005;65(4):545-551.

Luchsinger JA, Tang MX, Siddiqui M, Shea S, Mayeux R. Alcohol intake and risk of dementia. *Journal of the American Geriatrics Society* 2004;52(4):540-546.

Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M. Exercise level and cognitive decline: the MoVIES project. *Alzheimer Disease and Associated Disorders* 2004;18(2):57-64.

Maier M, Seabrook TJ, Lazo ND, Jiang L, Das P, Janus C, Lemere CA. Short amyloid-beta (Abeta) immunogens reduce cerebral Abeta load and learning deficits in an Alzheimer's disease mouse model in the absence of an Abeta-specific cellular immune response. *Journal of Neuroscience* 2006;26(18):4717-4728.

Marambaud P, Zhao H, Davies P. Resveratrol promotes clearance of Alzheimer's disease amyloid-beta peptides. *Journal of Biological Chemistry* 2005;280(45):37377-37382.

McDermott AY and Mernitz H. Exercise and older patients: prescribing guidelines. *American Family Physician* 2006;74(3):437-444.

Michael KM and Shaughnessy M. Stroke prevention and management in older adults. *Journal of Cardiovascular Nursing* 2006;21(5Suppl 1):S21-S26.

Milgram NW, Head E, Zicker SC, Ikeda-Douglas C, Murphey H, Muggenburg BA, Siwak CT, Tapp PD, Lowry SR, Cotman CW. Long-term treatment with antioxidants and a program of behavioral enrichment reduces age-dependent impairment in discrimination and reversal learning in beagle dogs. *Experimental Gerontology* 2004;39(5):753-765.

Milgram NW, Head E, Zicker SC, Ikeda-Douglas CJ, Murphey H, Muggenburg B, Siwak C, Tapp D, Cotman CW. Learning ability in aged beagle dogs is preserved by behavioral enrichment and dietary fortification: a two-year longitudinal study. *Neurobiology of Aging* 2005;26(1):77-90.

Munro CA, Brandt J, Sheppard JM, Steele CD, Samus OM, Steinberg M, Rabins PV, Lyketsos CG. Cognitive response to a pharmacological treatment for depression in Alzheimer disease: secondary outcomes from the depression in Alzheimer's disease study (DIADS). *American Journal of Geriatric Psychiatry* 2004;12(5):491-498.

Myers AJ, Kaleem M, Marlowe L, Pittman AM, Lees AJ, Fung HC, Duckworth J, Leung D, Gibson A, Morris CM, de Silva R, Hardy J. The H1c Haplotype at the MAPT locus is associated with Alzheimer's disease. *Human Molecular Genetics* 2005;14(16):2399-2404.

Newman AB, Fitzpatrick AL, Lopez O, Jackson S, Lyketsos C, Jagust W, Ives D, DeKosky ST, Kuller LH. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *Journal of the American Geriatrics Society* 2005;53(7):1101-1107.

Oddo S, Billings L, Kesslak JP, Cribbs DH, LaFerla FM. Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. *Neuron* 2004;43(3):321-332.

Patel NV, Gordon MN, Connor KE, Good RA, Engelman RW, Mason J, Morgan DG, Morgan TE, Finch CE. Caloric restriction attenuates Abeta-deposition in Alzheimer transgenic models. *Neurobiology of Aging* 2005;26(7):995-1000.

Petersen RC. Mild cognitive impairment: useful or not? *Alzheimer's & Dementia* 2005;1(1):5-10.

Petersen RC, Smith GE, Ivnik RJ, Tangalos EG, Schaid DJ, Thibodeau SN, Kokmen E, Waring SC, Kurland LT. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *JAMA* 1995;273(16):1274-8. Erratum in: *JAMA* 1995;274(7):538.

Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LJ, Alzheimer's Disease Cooperative Study Group. Vitamin E and donepezil for the treatment of mild cognitive impairment. *New England Journal of Medicine* 2005;352(23):2379-2388.

Petrovitch H, Ross GW, Steinhorn SC, Abbott RD, Markesbery W, Davis D, Nelson J, Hardman J, Masaki K, Vogt MR, Launer L, White LR. AD lesions and infarcts in demented and non-demented Japanese-American men. *Annals of Neurology* 2005;57(1):98-103.

Podewils LJ, Guallar E, Kuller KH, Fried LP, Lopez OL, Carlson M, Lyketsos CG. Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study. *American Journal of Epidemiology* 2005;161(7):639-651.

Puzzo D, Vitolo O, Trinchese F, Jacob JP, Palmeri A, Arancio O. Amyloid-beta peptide inhibits activation of the nitric oxide/cGMP/cAMP-responsive element-binding protein pathway during hippocampal synaptic plasticity. *Journal of Neuroscience* 2005;25(29):6887-6897.

Rosano C, Aizenstein HJ, Cochran JL, Saxton JA, DeKosky ST, Newman AB, Kuller LH, Lopez OL, Carter CS. Event-related functional magnetic resonance imaging investigation of executive control in very old individuals with mild cognitive impairment. *Biological Psychiatry* 2005;57(7):761-767.

Rosenberg PB, Onyike CU, Katz IR, Porsteinsson AP, Mintzer JE, Schneider LS, Rabins PV, Meinert CL, Martin BK, Lyketsos CG, Depression of Alzheimer's Disease Study. Clinical application of operationalized criteria for "Depression of Alzheimer's Disease." *International Journal of Geriatric Psychiatry* 2005;20(2):119-127.

Rosenblatt A, Samus QM, Steele CD, Baker AS, Harper MG, Brandt J, Rabins PV, Lyketsos CG. The Maryland Assisted Living Study: prevalence, recognition, and treatment of dementia and other psychiatric disorders in the assisted living population of central Maryland. *Journal of the American Geriatrics Society* 2004;52(10):1618-1625.

SantaCruz K, Lewis J, Spires T, Paulson J, Kotilinek L, Ingelsson M, Guimaraes A, DeTure M, Ramsden M, McGowan E, Forster C, Yue M, Orne J, Janus C, Mariash A, Kuskowski M, Hyman B, Hutton M, Ashe KH. Tau suppression in a neurodegenerative mouse model improves memory function. *Science* 2005;309(5733):476-481.

Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker LK, Kyle DJ, Wilson PWF, Wolf PA. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. *Archives of Neurology* 2006;63(11):1545-1550.

Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, Weintraub D, Lieberman JA, CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *New England Journal of Medicine* 2006;355(15):1525-1538.

Singer O, Marr RA, Rockenstein E, Crews L, Coufal NG, Gage FH, Verma IM, Masliah E. Targeting BACE1 with siRNAs ameliorates Alzheimer disease neuropathology in a transgenic model. *Nature Neuroscience* 2005;8(10):1343-1349.

Singleton A, Myers A, Hardy J. The law of mass action applied to neurodegenerative disease: a hypothesis concerning the etiology and pathogenesis of complex diseases. *Human Molecular Genetics* 2004;13(Spec No 1):R123-R126.

Siwak C, Tapp PD, Head E, Zicker SC, Murphey HL, Muggenburg BA, Ikeda-Douglas CJ, Cotman CW, Milgram NW. Chronic antioxidant and mitochondrial cofactor administration improves discrimination learning in aged but not young dogs. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2005;29(3):461-469.

Sloane PD, Hoeffer B, Mitchell CM, McKenzie DA, Barrick AL, Rader J, Stewart BJ, Talerico KA, Rasin JH, Zink RC, Koch GG. Effect of person-centered showering and the towel bath on bathing-associated aggression, agitation, and discomfort in nursing home residents with dementia: a randomized, controlled trial. *Journal of the American Geriatrics Society* 2004;52(11):1795-1804.

Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, Greengard P. Regulation of NMDA receptor trafficking by amyloid-beta. *Nature Neuroscience* 2005;8(8):1051-1058.

Spires TL, Meyer-Luehmann M, Stern EA, McLean PJ, Skoch J, Nguyen PT, Bacskai BJ, Hyman BT. Dendritic spine abnormalities in amyloid precursor protein transgenic mice demonstrated by gene transfer and intravital multiphoton microscopy. *Journal of Neuroscience* 2005;25(31):7278-7287.

Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. Effects of moderate alcohol consumption on cognitive function in women. *New England Journal of Medicine* 2005;352(3):245-253.

Tabert MH, Liu X, Doty RL, Serby M, Zamora D, Pelton GH, Marger K, Albers MW, Stern Y, Devanand DP. A 10-item smell identification scale related to risk for Alzheimer's disease. *Annals of Neurology* 2005;58(1):155-160.

Tanzi RE. Tangles and neurodegenerative disease—a surprising twist. *New England Journal of Medicine* 2005;353(17):1853-1855.

Tschanz JT, Welsh-Bohmer KA, Lyketsos CG, Corcoran C, Green RC, Hayden K, Norton MC, Zandi PP, Toone L, West NA, Breitner JC, the Cache County Investigators. Conversion to dementia from mild cognitive disorder: the Cache County Study. *Neurology* 2006;67(2):229-234.

van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. *Journal of Neuroscience* 2005;25(38):8680-8685.

Wang J, Ho L, Qin W, Rocher AB, Seror I, Humala N, Maniar K, Dolios G, Wang R, Hof PR, Pasinetti GM. Caloric restriction attenuates beta-amyloid neuropathology in a mouse model of Alzheimer's disease. *FASEB Journal* 2005;19(6):659-661.

Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. *JAMA* 2004;292(12):1454-1461.

Whitlatch CJ, Feinberg LF, Tucke SS. Measuring the values and preferences for everyday care of persons with cognitive impairment and their family caregivers. *Gerontologist* 2005;45(3):370-380.

Wilcock DM, Rojiani A, Rosenthal A, Subbarao S, Freeman MJ, Gordon MN, Morgan D. Passive immunotherapy against Abeta in aged APP-transgenic mice reverses cognitive deficits and depletes parenchymal amyloid deposits in spite of increased vascular amyloid and microhemorrhage. *Journal of Neuroinflammation* 2004;1(1):24.

Wu Z, Guo H, Chow N, Sallstrom J, Bell RD, Deane R, Brooks AI, Kanagala S, Rubio A, Sagare A, Liu D, Li F, Armstrong D, Gasiewicz T, Zidovetzki R, Song X, Hofman F, Zlokovic BV. Role of the MEOX2 homeobox gene in neurovascular dysfunction in Alzheimer disease. *Nature Medicine* 2005;11(9):959-965.

Yaffe K, Krueger K, Cummings SR, Blackwell T, Henderson VW, Sarkar S, Ensrud K, Grady D. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. *American Journal of Psychiatry* 2005;162(4):683-690.

Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. *Journal of Biological Chemistry* 2005;280(7):5892-5901.

Yang Y, Varvel NH, Lamb BT, Herrup K. Ectopic cell cycle events link human Alzheimer's disease and amyloid precursor protein transgenic mouse models. *Journal of Neuroscience* 2006;26(3):775-784.

Zlokovic BV. Neurovascular mechanisms of Alzheimer's neurodegeneration. *Trends in Neuroscience* 2005;28(4):202-208.

Credits

Writer
Anne Brown Rodgers

Computer Illustrations
Stacy Jannis, Rebekah Fredenburg
Jannis Productions
Cover; pages 1, 11, 12, 13, 16

Medical Illustration
Christy Krames
Page 9

Editors
Patricia D. Lynch and Karen M. Pocinki
NIA Office of Communications and Public Liaison

Design
Kristin Deuel Duffy, Jeffrey Dever
Dever Designs

Project Coordinator
David M. Burton
JBS International, Inc.

Special thanks to:
Marcelle Morrison-Bogorad, Ph.D. and the staff of the NIA Neuroscience and Neuropsychology of Aging Program, and the staff of the NIA Intramural Research Program of the Gerontology Research Center

Photography
Cover, top; page 2, – ThinkStock

Cover, right; inside front cover, left; pages 1, 4, 55 – Stockbyte

Inside front cover, bottom; pages 18, 64 – COMSTOCK

Inside front cover, top; page 10 – Dynamic Graphics

Inside front cover, spread; pages 23, 37, 53, 54, 58 – PhotoDisc

Pages 1, 64 – BlueMoon Stock

Pages 1, 46 – Photos.com

Page 10 – Scans on computer screen courtesy of William Jagust, M.D., University of California, Berkeley

Page 27 – Brand X Pictures

Page 28 – Iconotec

Page 39 – Courtesy of the Alzheimer's Disease Center, University of California, San Diego

Pages 47, 52; back cover – PUNCHSTOCK

Page 50 – Digitalvision

For more information about the National Institute on Aging, please visit www.nia.nih.gov.

For additional copies of this report or further information about Alzheimer's disease, please contact:

Alzheimer's Disease Education and Referral (ADEAR) Center

1-800-438-4380
www.nia.nih.gov/alzheimers

U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Aging
NIH Publication Number: 06-6047
April 2007