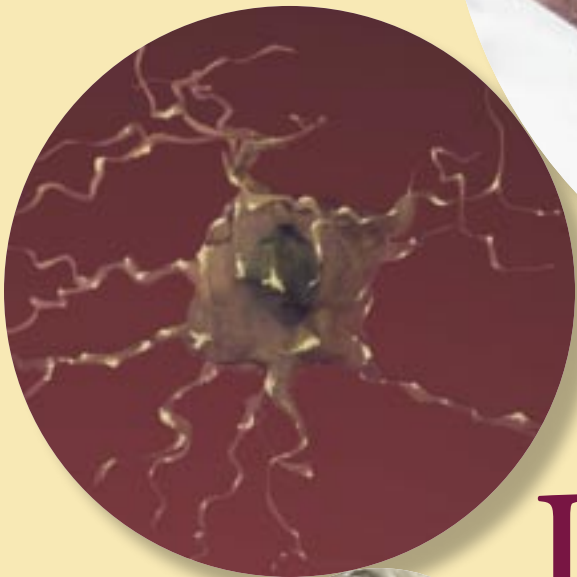




**PROGRESS REPORT ON
ALZHEIMER'S DISEASE
2004 - 2005**



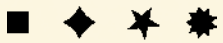
New
Discoveries,
New
Insights



U.S. Department of
Health and Human Services



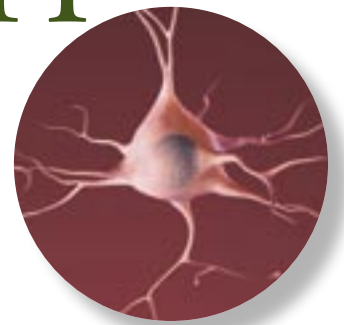
PROGRESS REPORT ON ALZHEIMER'S



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

DISEASE 2004-2005

Research Advances at NIH





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 *2004-2005 Progress Report on*

Alzheimer's Disease summarizes recent AD research conducted or supported by NIA and other components of NIH, including:

- National Cancer Institute (pages 43, 62)
- National Center for Complementary and Alternative Medicine (page 62)
- National Center for Research Resources (pages 14, 16)
- National Heart, Lung, and Blood Institute (page 50)
- National Institute of Biomedical Imaging and Bioengineering (page 26)
- National Institute of Child Health and Human Development (pages 18, 31, 44)
- National Institute of Diabetes and Digestive and Kidney Diseases (pages 25, 52)
- National Institute of Environmental Health Sciences (page 24)
- National Institute of Mental Health (pages 16, 25, 39, 41, 47, 58, 62, 63, 67, 71)
- National Institute of Neurological Disorders and Stroke (pages 23, 24, 30, 31, 38, 67, 71)
- National Institute of Nursing Research (pages 62, 63, 64, 65, 67)

AD research efforts also are supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute on Alcohol Abuse and Alcoholism, National Institute of Dental and Craniofacial Research, National Institute of Deafness and Other Communication Disorders, National Human Genome Research Institute, National Center on Minority Health and Health Disparities, John E. Fogarty International Center, the NIH Office of the Director, and the NIH Roadmap Initiative.

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Alzheimer's disease is an age-related and irreversible brain disorder that develops over a period of years. Initially, people experience memory loss and confusion. These symptoms gradually lead to behavior and personality changes, a decline in other cognitive abilities (such as thinking, decision-making, and language skills), 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, termed 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.

The Impact of AD

AD is the most common cause of dementia among people age 65 and older. It presents a major health problem for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. Scientists estimate that 4.5 million people currently have the disease, and the prevalence (the number of people with the disease at any one time) doubles for every 5-year age group beyond age 65.

These numbers are significant now and will become even more so in the future because of dramatic increases in life expectancy since the turn of the century. Researchers estimate that by 2050, 13.2 million Americans will have AD if current population trends continue and no preventive treatments become available (Hebert et al., 2003). Approximately 4 million Americans are age 85 years or older, and this age group is one of the fastest growing segments of the population. It is also the group with the highest risk of AD. The U.S. Census Bureau estimates that nearly 19 million Americans will be age 85 and older by the year 2050. Some experts who study population trends suggest that the number could be even greater. This trend is not only apparent in the U.S. but also worldwide. As more and more people live longer, the number of people affected by diseases of aging, including AD, will continue to grow. For example, one study showed that nearly half of all people age 85 and older have some form of dementia (Evans et al., 1989).

These prevalence trends translate into a huge impact on people with the disease, their families and friends, and caregivers. Slightly more than half of AD patients receive care at home, while the remainder are cared for in a variety of health care institutions. During their years of AD caregiving, spouses, relatives, and friends experience emotional, physical, and financial stress.

They watch their loved ones become more and more forgetful, frustrated, and confused. Eventually, the person with AD does not even recognize his or her nearest and dearest relatives and friends.



Caregivers—most of whom are women—must juggle child care, jobs, and other responsibilities along with caring for relatives with AD who cannot function on their own. 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 number of caregivers—and their needs—can be expected to escalate rapidly as the population ages and as the number of people with AD grows.

The increasing number of people with AD and the costs associated with the disease mean that AD puts a heavy economic burden on society. The annual national direct and indirect costs of caring for AD patients have been estimated to be as much as \$100 billion (Ernst and Hay, 1994; Ernst et al., 1997; Huang et al., 1988).

AD: An Urgent National Research Priority

Given our aging population, the magnitude of AD as a national health problem is steadily increasing. This makes the disease an urgent research priority.

Interventions that could delay 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 associated with caring for them.

AD research supported by the Federal Government is divided into three broad, overlapping areas: causes/risk factors, diagnosis, and treatment/caregiving. Research into the basic biology of the aging nervous system is critical to understanding what goes wrong in the brain of a person with AD. Understanding how nerve cells lose their ability to function and communicate with each other and the reasons why some nerve cells die and others do not is a central part of scientific efforts to discover what causes AD. Assessing factors that may increase or decrease risk of developing AD is a growing component of this research effort.

Many researchers are also looking for better ways to diagnose AD in the early stages and to identify the earliest brain changes that could indicate that the AD process has begun. Investigators are striving to identify markers of early dementia, improve ways to test patient function, improve neuroimaging technologies, and enhance case-finding and sampling methods for population studies.

Other researchers are working to discover and develop interventions that may help treat symptoms, slow the progress of AD, delay its onset, or even prevent the disease. Many of these interventions are now being tested in clinical trials. Finally, scientists and many health care professionals are seeking better ways to help people with AD and their caregivers cope with the

decline in mental and physical abilities and the problem behaviors that accompany the disease.

An important complement to the National Institutes of Health's (NIH) research initiatives in AD are its efforts to educate and inform people with AD, their families, the public, providers, and others interested in the disease. The National Institute on Aging (NIA) Alzheimer's Disease Education and Referral (ADEAR) Center (www.alzheimers.org) provides a variety of materials on AD, including information about caregiving, diagnosis and treatment, and results of research findings. For example, NIA's booklet for the general public, *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. Another booklet for lay audiences, *Genes, Lifestyles, and Crossword Puzzles: Can Alzheimer's Disease be Prevented?*, summarizes the latest research findings on AD risk factors and potential prevention strategies. The ADEAR Center also maintains a database of AD clinical trials, develops recommended reading lists, and provides referrals to local 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.

We now know a lot about AD—what it is, who can get it, how it develops, and what course it follows. We also have made

significant progress in the critical area of early diagnosis and have some promising leads on possible treatments. All of the research has deepened our understanding of this devastating disease. It also has expanded our knowledge about other late-life neurodegenerative diseases, brain function in healthy older people, and ways in which to minimize normal age-related cognitive decline.

Interventions that could delay the onset of AD would have an enormous positive public health impact.

The *2004-2005 Progress Report on Alzheimer's Disease* describes this important research effort. It begins with a description of our current knowledge about AD. This provides the foundation for the next section, which highlights recent studies supported by NIA and other NIH Institutes. The report closes with a section called "Outlook for the Future," which takes a look at some exciting AD research initiatives. These initiatives are designed to accelerate laboratory and clinical research and collaboration across the Federal Government and in association with the private sector so that research findings can be translated expeditiously into real advances for patients, families, and caregivers.



Part 2

KNOWLEDGE AND UNDERSTANDING CONTINUE TO GROW

In healthy aging, nerve cells (neurons) in the brain are not lost in large numbers. In AD, however, many nerve cells stop functioning, lose connections with other nerve cells, and die. At first, AD destroys neurons in parts of the brain that control memory, including the entorhinal cortex and the hippocampus (structures in the brain that help form and store short-term memories) and related structures. As nerve cells in these structures stop working properly, short-term memory fails, and a person's ability to do easy and familiar tasks can begin to decline. AD later attacks the cerebral cortex (the outer layer of neurons in

the brain), particularly the areas responsible for language and reasoning. At this point, AD begins to take away language skills and changes a person's ability to make judgments. Personality changes also may occur. Emotional outbursts and disturbing behaviors, such as wandering, begin to happen and can become more frequent as the disease progresses. Eventually, many other areas of the brain are damaged and the person with AD becomes bedridden, helpless, and unresponsive to the outside world.

Structure and Function of the Brain

The brain is essential to our survival. With the help of motor and sensory nerves throughout the body, it integrates, regulates, initiates, and helps control the body's functions. The brain governs thinking, personality, moods, the senses, and physical action. We can speak, move, remember, and feel emotions and physical sensations because of the complex interplay of chemical and electrical processes that takes place in our brains. The brain and the rest of the nervous system also regulate body functions that happen automatically, such as breathing and digesting food.

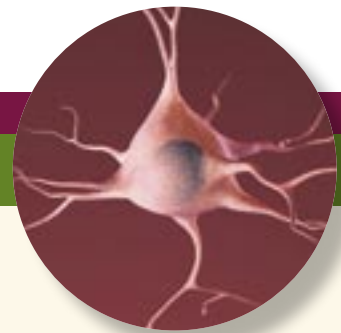
The healthy human brain is made up of billions of neurons that share information with one another through

a diverse array of biological and chemical signals. A typical neuron has a cell body, an axon, and many dendrites, all surrounded by a cell membrane. The nucleus, which is found inside the cell body and contains genes composed of deoxyribonucleic acid (DNA), helps to regulate the cell's activities in response to signals from outside and inside the cell. The axon, which extends from the cell body, transmits messages to other neurons, sometimes over very long distances. Dendrites, which also branch out from the cell body, receive messages from axons of other nerve cells or from specialized sense organs. Axons and dendrites collectively are called neurites. Neurons are surrounded by glial

cells, which support and nourish them.

Neurons generally communicate with each other and with sense organs by producing and releasing special chemicals called neurotransmitters. As a neuron receives messages from the dendrites of surrounding cells, an electrical charge (nerve impulse) builds up within the cell. This charge travels down the axon until it reaches the end. Here, it triggers the release of the neurotransmitters that move from the axon across a gap, called a synapse, between it and the dendrites or cell bodies of other neurons. Scientists estimate that

(continued on page 6)



What are the Main Characteristics of the Brain in AD?

The brain in AD has three major characteristics that contribute to the pathology, or damage, of the disease. Though scientists have known about these characteristics for many years, recent research has revealed much about their nature and their possible roles in the development of AD.

Amyloid Plaques

Plaques are found in the spaces between the brain's nerve cells. They were first discovered by Alois Alzheimer nearly 100 years ago, in 1906. They consist of largely insoluble (cannot be dissolved) deposits of a protein peptide, or fragment, called beta-amyloid, together with other proteins, remnants of neurons, non-nerve cells such as microglia (cells that surround and digest damaged cells or foreign substances), and other glial cells, such as astrocytes (see p. 36 for more on these cells).

Beta-amyloid is snipped, or cleaved, from a larger protein called amyloid precursor protein (APP). APP is associated with the cell membrane, but its normal function in the cell is not yet fully known. In AD, plaques develop first in areas of the brain used for memory and other cognitive functions.

Most people develop some plaques in their brain tissue as they age. However, the AD brain has many more plaques in certain brain regions. For many years, scientists thought that these structures might cause all the damage to neurons that is seen in AD. However, that concept has evolved considerably in the past few years. Many scientists now think that beta-amyloid clusters at an earlier stage in the plaque development process—called A β -derived diffusible ligands, or ADDLs (also known as soluble oligomers)—may be a major culprit. Many also think that plaques are a late-stage attempt by the brain to get harmful beta-amyloid away from neurons (see p. 20 for more on this rapidly developing area of research).

Structure and Function *continued*

a typical neuron has up to 15,000 synapses. Neurotransmitters bind to specific receptor sites on cell bodies and the receiving end of dendrites of adjacent nerve cells. In this way, signals travel between neurons in a fraction of a second. Millions of signals continuously flash through the brain.

Groups of neurons in the brain have specific jobs. For example, some neurons are involved in thinking, learning, remembering, and planning. Others are responsible for vision or hearing, regulating the body's biological clock, or managing the many other tasks that keep the human body functioning.

The survival of neurons in the brain depends on the healthy

functioning of several processes all working in harmony. These processes are communication, metabolism, and repair. The first process, communication between neurons, depends on the integrity of the neuron and its synapses, as well as the production of neurotransmitters.

The second process is metabolism, or all the chemical reactions that take place in the cell. Some of these reactions break down substances, which releases energy. Other reactions involve building complex substances that the cell needs to function out of simple "building block" molecules. Efficient metabolism requires adequate blood circulation to supply the cells with

oxygen and glucose (a sugar), the brain's major fuel.

The third process is repair. Unlike most other body cells, most neurons are already formed at birth. Neurons are programmed to live a long time—even more than 100 years. In an adult, when neurons die because of disease or injury, they are usually not replaced, although we now know that new neurons can be generated in several areas of the brain. To prevent their own death, living neurons must constantly maintain, repair, and remodel themselves.

Research shows that the damage seen in AD involves changes in all three of these neuronal processes: communication, metabolism, and repair.

Neurofibrillary Tangles

The second hallmark of AD pathology, also found by Alois Alzheimer, consists of abnormal collections of twisted protein threads found inside nerve cells. The chief component of these structures, called neurofibrillary tangles, is a protein called *tau*. Healthy neurons are internally supported in part by structures called microtubules, which help transport nutrients and other cellular components from the body of the cell down 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 *tau*. As a result of this “phosphorylation” process, *tau* disengages from the microtubules and begins to aggregate with other threads of *tau*. Ultimately, these *tau* threads become enmeshed with one another, forming tangles. When this happens, the microtubules disintegrate and the neuron’s transport system collapses (see p. 29 for more on this active area of research). This may result first in malfunctions in communication between neurons and later in the death of the cells.

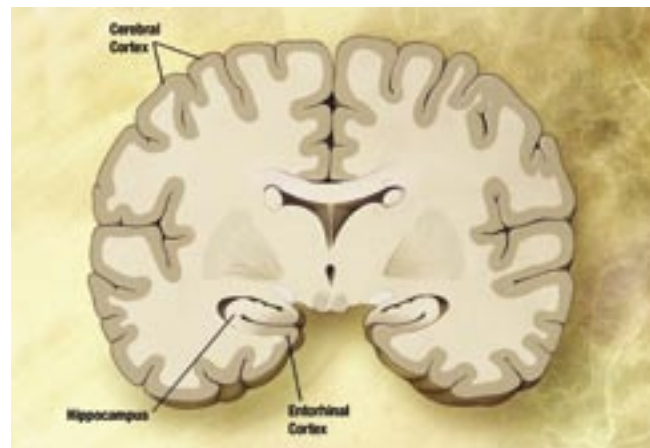
Loss of Connections Between Cells and Cell Death

The third major pathological feature of AD, only described in the past 30 years, is the gradual loss of connections between neurons. This process damages neurons to the point that they cannot function properly. Eventually, they die. As the death of neurons 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.

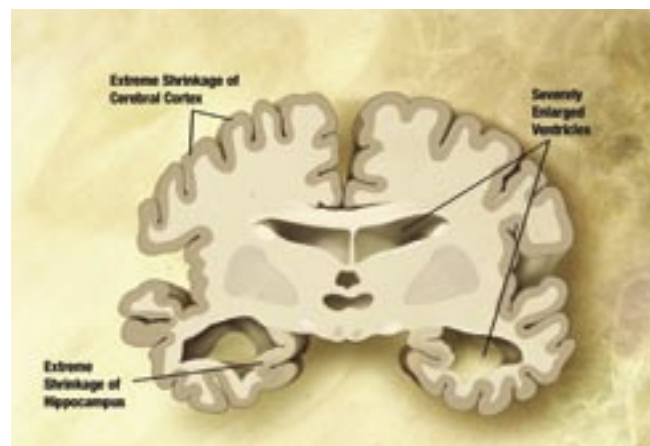
What Causes AD?

In a very few families, about half of the children of a parent with AD develop the disease in their 30s, 40s, and 50s. These people have inherited mutations in one of three genes. (See p. 41 for more about the genetic aspects of AD.) So, in these “early-onset” cases, we know exactly what causes AD.

However, the vast majority of AD cases—more than 90 percent—develop in people older than 65. This form of AD is called “late-onset” AD. We don’t yet completely understand the causes of late-onset AD, but they probably include a mix of genetic, environmental, and lifestyle factors. The importance of these factors in increasing or decreasing the risk of developing the disease may differ from person to person.

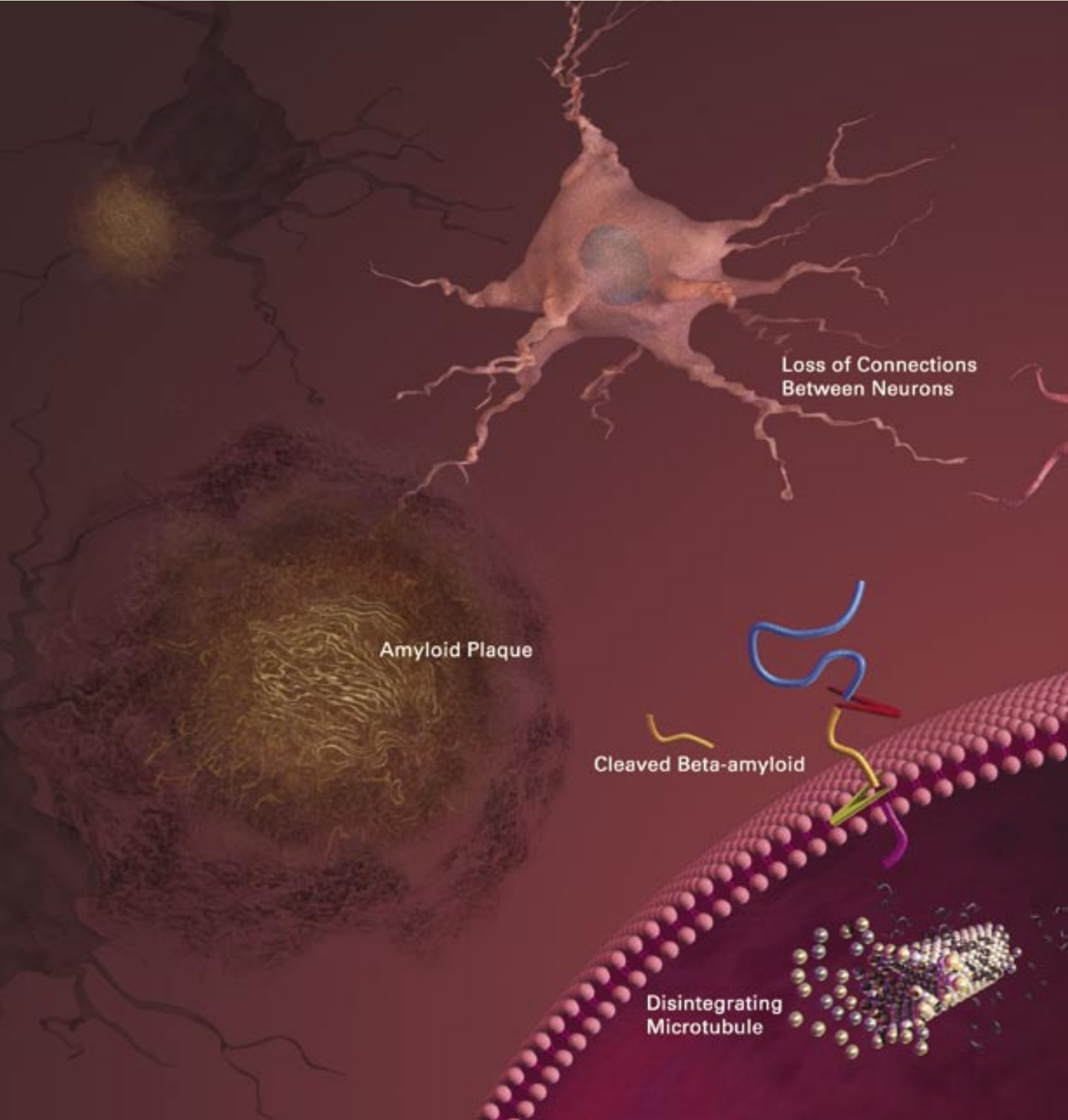


Healthy brain



AD brain

The Main Characteristics of AD





Although many questions about the players and steps involved in the causes and development of AD have been answered, our knowledge still has some surprising gaps. For example, we don't yet fully understand the normal function of several key players, such as APP. Certainly a better knowledge of normal function would give us clues about the causes of AD.

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, even those individuals who are born with disease-causing mutations? One possibility is that the environment of the aging brain is subtly different from that of the young brain. We may need to understand more about how the brain changes normally as we age before we can fully understand AD.

Scientists supported by the NIH are working in laboratories and research institutions all across the U.S. and in other countries to assemble the many bits of new knowledge that, combined with our existing understanding, will some day explain this complex biological puzzle.

What Do We Know About Diagnosing AD?

AD can be diagnosed conclusively only by examining in an autopsy the brain of a person with dementia to determine whether the plaques and tangles in certain brain regions are characteristic of AD. However, clinicians use a range of tools to diagnose "possible AD" (dementia can also be due to another condition) or "probable AD" (no other cause of dementia can be found) in a living person who is having difficulties with memory or other mental functions. These tools include a medical history; physical exam; tests that measure memory, language skills, and other abilities related to changes in brain function; and sometimes, brain scans.

Much is known about the clinical and behavioral characteristics of the disease, and this also helps in diagnosing AD. The diagnostic process is crucial in identifying AD accurately as well as in ruling out other conditions that might be causing cognitive problems or dementia, such as stroke, tumors, Parkinson's disease (PD), or side effects of medications. In many older people, AD co-exists with other conditions, such as cerebrovascular disease, that may also cause dementia.

An early, accurate diagnosis of AD is especially important to people with AD and their families because it helps them plan for the future and pursue care options while the person with AD can still take part in making decisions. Researchers are making progress in developing accurate diagnostic tests and techniques. In specialized research facilities, clinicians can now diagnose AD with up to 90 percent accuracy. Scientists are working on methods to improve the ability of clinicians to make accurate diagnoses of AD even earlier in the disease process. These advances are providing important insights into the initial changes that occur in the brain of a person with AD even before a clinical diagnosis is made. For example, the newest neuropsychological diagnostic tests for AD, which measure delayed recall, verbal fluency, and overall cognitive status, are highly accurate in distinguishing between cognitively healthy individuals and people with mild AD. Various neuroimaging techniques, such as positron emission tomography (PET) scanning and magnetic resonance imaging (MRI) also are being used in the laboratory to track early changes that may indicate AD (see p. 16 for more on neuroimaging).

Insights from ongoing studies will help scientists understand the natural history of AD and the ways in which changes in

A Recent Study Sheds Light on Length of Survival After a Diagnosis of AD

After a diagnosis of AD, one of the first things that the patient and family want to know is how long the person may be expected to live with the disease. However, until a recent study conducted by scientists at the University of Washington and the Group Health Cooperative (GHC) in Seattle, little information was available on this vitally important question (Larson et al., 2004).

During the study period—1987 to 1996—the GHC, a health maintenance organization, had about 23,000 members age 60 and older. At the start of the study, 521 members of this group were newly diagnosed with AD. Not surprisingly, the scientists found that people with AD had a significantly decreased survival compared with the average life expectancy of the U.S. population. For example, men had a median survival of 4.2 years from their initial diagnosis, and women had a median survival of 5.7 years.

Men had poorer survival across all age groups compared to women. The life expectancy of 70-year-old men with AD was 4.4 years compared to 9.3 years for the U.S. population. Survival for 70-year-old women with AD was shortened to 8.0 years compared to 15.7 years for the U.S. population. For men age 85, survival was 3.3 years compared to 4.7 years for the U.S. population. Survival for women at age 85 was 3.9 years compared to 5.9 years for the U.S. population.

Other factors, including severity of cognitive impairment, decreased ability to carry out daily activities, history of falls, and chronic illnesses such as diabetes and heart disease, further shortened the lifespans of people with AD.

memory and other cognitive functions differ in normal aging, AD, and other dementias. This knowledge will help clinicians diagnose AD earlier and more accurately and also will help researchers pinpoint changes that could be targets for drug therapy.

How Is AD Treated Today?

For those who already suffer from the effects of AD, the most immediate need is for treatments to control cognitive loss as well as problem behaviors, such as verbal and physical aggression, agitation, wandering, depression, sleep disturbances, and delusions. Treatments are needed that work on many people with AD, remain effective for a long time, ease a broad range of symptoms, improve a person's cognitive function and ability to carry out activities of daily living, and have no serious side effects. Eventually, scientists hope to develop treatments that attack earlier AD processes, preventing the disease from progressing and damaging cognitive function and quality of life.

The U.S. Food and Drug Administration (FDA) has approved five medications to treat AD symptoms, though only four are used today. The first drug to be approved, tacrine (Cognex), has been replaced by three other drugs—donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne, previously known as Reminyl). These three drugs, which are prescribed to treat mild to moderate AD symptoms, act by stopping or slowing the action of acetylcholinesterase, an enzyme that breaks down acetylcholine. Acetylcholine, a neurotransmitter that is critically important in the process of forming memories, is used by many neurons in the hippocampus and cerebral cortex—regions devastated by AD. These drugs improve some patients' abilities to carry out activities of daily living; may improve certain thinking, memory,

or speaking skills; and can help with certain behavioral symptoms. However, these medications 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 (Reisberg et al., 2003; Tariot et al., 2004). This drug appears to work by lowering glutamate levels in the brain. Glutamate is another neurotransmitter involved in memory function, but high levels may damage neurons. Like the cholinesterase inhibitors, memantine will not stop or reverse AD. In addition to these medications, physicians use a number of drug and non-drug approaches to treat the behavioral and psychiatric problems that occur frequently as AD progresses.

Helping people with AD live their daily lives and maintain their cognitive abilities is one of the most important goals of AD treatment research. Many investigators are working to develop new and better treatments to preserve these critical functions for as long as possible. Other investigators are working to improve the quality of life for people with AD and caregivers through research on behavioral management techniques and caregiver skills.

One of the primary characteristics of the NIH AD research effort over the past 25 years has been support for a wide range of studies conducted by a large and multidisciplinary cadre of researchers. All of these studies have contributed to the solid base of knowledge that exists today. The accelerating pace of discovery in AD research continues to expand this base, and it is pointing scientists in new and productive research directions. It is also helping investigators ask better questions about the issues that are still unclear.



Part 3

2004-2005 AD RESEARCH ADVANCES: NEW DISCOVERIES, NEW INSIGHTS

During the past 2 years, scientists supported by NIH have made advances in a number of areas important to AD. This section of the *Progress Report* focuses on recent research that has attempted to answer three key questions:

- What happens in the brain to cause the transformation from healthy aging to AD?
- Can certain factors protect against or increase the risk of AD?
- What can be done to slow the progression of AD or lessen its effects?

These questions are important because they focus on the central issues of AD: What occurs during the very first steps of the disease process, what might we do to prevent AD, and what can be done once the disease process has started? They can be asked only because of the knowledge that has accumulated through past research. Answers to these questions are emerging, and they hold the key to future prevention, treatment, and caregiving strategies.

What Happens in the Brain to Cause the Transformation From Healthy Aging to AD?

As people age, changes occur in all parts of the body, including the brain:

- 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 (Resnick et al., 2003).

- Tangles develop inside neurons and plaques develop in the spaces between neurons.
- Damage by free radicals increases (free radicals, also called reactive oxygen species, are a kind of molecule that reacts easily with other molecules; see p. 32 for more on free radicals).

The impact of these changes differs among people as they age. Some older people may notice only a modest reduction in their ability to learn new things, retrieve information from memory, and plan and make decisions. Their performance on complex tasks of attention, learning, and memory may decline. However, if given enough time, they may ultimately score as well on the task as a younger person. Other people, however, experience much greater declines in these cognitive abilities as they grow older. Understanding the differences between healthy aging and a neurodegenerative process is an important key to unlocking the secrets of AD.

Long ago, before we knew much about AD, many people thought that “senile dementia” was just a part of aging. Now, of course, we know that AD is a distinct disease that affects the brain. Several recent studies and reviews of the scientific literature have provided some evidence that

cognitive decline with age and AD are, in some respects, separate entities that follow different pathways as they evolve. For example, an investigator from Washington University in St. Louis recently published a review of a vast array of data on memory and executive function (the cognitive abilities involved in planning, organizing, and decision-making) in aging and AD (Buckner, 2004). The review suggested that factors that influence executive function more commonly falter with normal aging. In contrast, factors that influence long-term memory function are more impaired in AD. Some of the changes that can take place in normal aging may not necessarily be the cause of AD. In a more direct assessment of this idea, this investigator and colleagues at Washington University used MRI to measure volumes of the hippocampal region and the white matter region between the two

early-stage AD was characterized by significant reductions in hippocampal volume, whereas age alone was associated with only mild reductions in hippocampal volume. These results suggest that AD manifests itself early and significantly in the area of the brain encompassing the hippocampus, whereas normal aging affects the white matter connecting the front regions of the brain. These frontal white matter reductions may underlie the executive function difficulties that are common in normal aging.

Columbia University scientists funded by the National Center for Research Resources (NCRR) and NIA, in collaboration with researchers at the California National Primate Research Center, conducted neuroimaging studies in older monkeys and rats to distinguish the effects of healthy aging and AD on the structure of the brain (Small et al., 2004). The selection of the animals for this study was important because neither monkeys nor rats naturally develop AD. They found that the brain region known as the dentate gyrus (a region within the hippocampus) was changed by aging in both species. However, AD predominantly affected a different region of the hippocampus, thus indicating that some processes affecting normal aging and AD may be distinct.

New Thinking About Cognitive Reserve

Two questions have fascinated investigators for years:

- Why do some people remain cognitively healthy all their lives while others develop dementia?
- Why do some people remain cognitively healthy even though examination of their brain tissue after death shows significant deposits of plaques and tangles?



hemispheres of the brain in 150 people aged 18 to 93 years (Head et al., 2005). They found that early-stage AD did not make age-associated reductions in the white matter region worse. They also found that

One possible explanation revolves around the concept of “cognitive reserve.” Reserve refers to the brain’s ability to operate effectively even when function is disrupted and to the amount of damage that the brain can sustain before the damage is clinically apparent. Individual variability in reserve may reflect genetic differences or differences in life experiences, such as education, occupational experience, or leisure activities.

Lifelong engagement in activities that help to build and maintain cognitive reserve is generally beneficial to health and may even help keep people cognitively healthy as they age. A number of research teams are looking intensively at these activities. For example, new information from the Religious Orders Study, a long-term study of aging among members of 40 religious communities, has revealed that years of formal education may modify the relationship between level of cognitive functioning and AD pathology (Bennett et al., 2003). After comparing participants’ brain tissue after their deaths and the results of earlier cognitive function tests, study investigators at the Rush University Medical Center ADC in Chicago, found that the density of plaques in the brain tissue was linked to cognitive function. This relationship was modified by the number of years of education the person had received, such that a person with a higher level of education retained a higher level of cognitive function even in the presence of AD damage to the brain.

In another study, scientists from Columbia University periodically tested the memory performance of 136 cognitively healthy older people over the course of 5 years (Manly et al., 2003). The scientists accounted for the participants’ age at the beginning of the study and their years



of education. They found that participants with low levels of literacy (a proxy for quality of education) had a steeper decline in their ability to remember a word list immediately after seeing it, as well as after a delay, as compared to those with a higher literacy level. These findings suggest that literacy may be an important measure of cognitive reserve, or even that literacy itself builds cognitive reserve, protecting against memory decline in older people without dementia.

Rush ADC investigators from the Chicago Health and Aging Project (CHAP), an epidemiologic study of AD risk factors in a racially diverse urban population, looked at the issue of cognitive reserve from a slightly different angle (Barnes et al., 2004). They wondered whether an important life experience, such as the level

of engagement in social networks of family and friends, could be related to changes in cognitive function. The 6,102 African-Americans and whites in the study participated in up to three interviews over the course of about 5 years. The researchers found that more social networks and a higher level of social engagement were associated with a higher initial level of cognitive function. These factors also were related

to a reduced rate of cognitive decline over time. Additional research is clearly necessary to sort out cause and effect. Does increased involvement with social networks increase cognitive reserve, or are people who later develop dementia less involved because they are already in the early stages of AD, before symptoms are evident?

Findings from recent studies suggest that the brain has an inherent ability to cope with age- and disease-associated changes.

Use of Neuroimaging, Biomarkers, and Other Indicators to

Recent advances continue to demonstrate the current and potential value of neuroimaging techniques, biological markers, and sensitive oral and written tests of changes in memory, language skills, and cognitive function. These techniques help investigators understand the events unfolding in specific regions of the brain in the very early stages of AD. They also can be used to identify people who are at risk of AD even before they develop the symptoms of the disease. They may even become a valuable means for assessing the effectiveness of potential therapeutic strategies. Two recent developments demonstrate the growing importance of all these efforts to AD research:

- NIA has launched a multi-year effort that will combine data from serial MRI and PET scans with clinical, neuropsychological, and biomarker data to examine how brains change as mild cognitive impairment (MCI) and AD progress. See p. 18 for more information on MCI and p. 68 for more on the NIA AD Neuroimaging Initiative.

- In September 2004, the Centers for Medicare and Medicaid Services (CMS) approved Medicare coverage for PET scans for some beneficiaries whose clinical exams cannot distinguish between possible AD and

another cause of dementia. For more information on Medicare coverage, see www.cms.hhs.gov.

Investigators are using these techniques in a variety of ways. For example, a recent study attempted to develop a more precise diagnostic marker for the progression of AD. Investigators from the New York University School of Medicine used serial MRIs in cognitively healthy and AD participants to calculate the rate of volume loss within the entire brain and within the medial temporal lobe, the region that is particularly affected early in the course of AD (Rusinek et al., 2004). The investigators found that the rate of atrophy within the medial temporal lobe derived from the serial MRIs was indeed a useful marker because it allowed them to classify the two groups of participants correctly more than 90 percent of the time.

Researchers from Rush University Medical Center in Chicago used MRIs to assess the predictive value of volume changes on an even more detailed level (deToledo-Morrell et al., 2004). Twenty-seven participants with MCI received an MRI scan at the beginning of the study and an annual scan for 3 years after that. During that time, 10 of the participants developed AD. The volumes of two brain structures within the medial temporal lobe

that are known to be involved very early on in the course of AD—the entorhinal cortex and the hippocampus—were compared to determine which region could best differentiate those who would convert to AD from those who would not. Although changes in both regions independently predicted conversion, changes in the entorhinal cortex more accurately predicted the change to AD.

Scientists also are developing highly sophisticated computer and analytic tools to help them understand what neuroimaging observations mean. Investigators from the University of California at Los Angeles funded by the NCR and the National Institute of Mental Health (NIMH) have developed a series of computer algorithms that they used to compare AD brain images across individuals and over time (Thompson et al., 2003). These algorithms allowed the scientists to describe more fully the loss of neurons that is typical of AD and the characteristic manner in which this loss spreads through the brain.

Other investigators are trying to discover whether certain substances in the blood or cerebrospinal fluid (CSF) could reflect early changes in the brain associated with AD. Understanding these “biomarkers”—what they are, how they function,

It may attempt to compensate for these changes through various mechanisms, such as the use of alternate brain networks to bypass those that are not functioning or the use of new cognitive strategies (Buckner, 2004). A number of scientists are exploring these compensatory mechanisms. For example, researchers at Columbia University examined whether engaging in various intellectual, social, and physical activities, such as gardening, reading, traveling, and going to

the movies, might enhance cognitive reserve (Scarmeas et al., 2003). Cognitively healthy older people and people with early AD were scanned for blood flow in the brain using PET. The researchers found that study participants with AD who had a higher leisure activity score also had prominent deficits in cerebral blood flow, despite being at the same level of clinical disease. Those participants who had engaged in more lifestyle activities before disease onset were able to

Define and Understand Early Brain Changes

and how and when their levels change—will help investigators answer questions about the cause and early development of AD and may lead one day to the identification of targets for treatments to delay or prevent the onset of the disease. For example, scientists at the University of Pennsylvania ADC in Philadelphia assessed levels of *tau* and beta-amyloid in the CSF of 106 people with dementia, 4 people diagnosed with AD but without dementia, and 69 cognitively healthy people (Clark et al., 2003). The study team found that the elevated levels of *tau* and beta-amyloid in the CSF were associated in many participants with AD pathology and were helpful in distinguishing AD from other types of dementia.

A second biomarker study, conducted at the New York University School of Medicine Center for Brain Health, used MRIs as well as CSF levels of *tau* to identify the earliest clinically detectable evidence for AD brain changes in cognitively healthy people and those with MCI (de Leon et al., 2004). The researchers found that levels of one specific form of *tau* were highly correlated with reductions in hippocampal volume measured by MRI, and that using CSF and MRI measures together improved their

ability to distinguish between normal cognition and MCI. They also found that it was not possible to use the *tau* level to measure AD progression, but that these changes could be tracked with another biomarker, isoprostane. It may be that a panel of biomarkers will prove to be the most useful for accurate diagnosis and tracking over time.

Finally, recent developments in neuropsychological tests are demonstrating their utility as a valuable and complementary tool that clinicians can use to define and understand early changes in AD. For example, University of Pittsburgh researchers were interested in seeing whether individuals who were ultimately diagnosed with AD showed evidence of cognitive impairment in the years before dementia symptoms began (Saxton et al., 2004). The study, part of the longstanding Cardiovascular Health Study, included 693 people living in the community (see p. 50 for more AD-related studies from the Cardiovascular Health Study). The participants completed a series of neuropsychological tests in 1991 and 1992 and then were tested every year for the next 8 years. Seventy-two people were ultimately diagnosed with AD. Of these, 24 were diagnosed 1.5 to 3.4 years after the initial round of testing, 20 were diagnosed 3.5 to

5 years after testing, and 28 were diagnosed 5.1 to 8.1 years after testing. The research team found that participants who were ultimately diagnosed with AD had poorer scores on the initial neuropsychological tests than did participants who remained cognitively healthy. Although individuals who were diagnosed after the shortest period of time performed the most poorly on the initial tests, cognitive impairment was detected even in those who did not develop AD until 5 to 8 years later.

NIA researchers have pursued this idea even more specifically by comparing the predictive value of scores on two different neuropsychological tests—the Benton Visual Retention Test (BVRT), which measures visual memory, and the WAIS-vocabulary test, which measures verbal memory (Kawas et al., 2003). The study, which involved participants in the Baltimore Longitudinal Study of Aging, revealed that those who scored six or more errors on the BVRT had approximately twice the risk of developing AD than did subjects with zero to five errors. More importantly, BVRT results even as many as 15 years before AD diagnosis were still predictive. In contrast, scores on the vocabulary test were not associated with the risk of AD.

sustain more pathology, as shown by greater cerebral blood flow deficits.

Another approach to understanding compensatory mechanisms comes from Down syndrome (DS) and AD PET scan studies. National Institute of Child Health and Human Development (NICHD)-funded researchers at the University of California at Irvine tested a hypothesis that dementia starts in the same places in the brain in both DS and AD and progresses through similar patterns of change. Data from the scans, which track glucose use by cells in particular brain regions, allowed the researchers to measure and compare brain activity in adults with DS who did not have dementia, adults with AD, and cognitively healthy adults (Haier et al., 2003). The researchers found that, compared to the healthy adults, both those with DS and those with AD exhibited lower brain activity in one particular region of the brain (the posterior cingulate). However, when the researchers looked at another area of the brain—the inferior temporal/entorhinal cortex (the area known to be the site of the earliest brain damage in AD)—the participants with DS had higher brain activity while those with AD had lower activity compared to the healthy participants. The researchers believe that those with DS were in the very early stages of developing dementia and that their elevated brain activity levels represent an attempt by damaged neurons to work harder to maintain function. They also suggest that this compensatory response may eventually fail



and the brain activity rates decrease, leading to degeneration of the neurons and the first clinical signs of dementia.

Understanding that AD is a process that develops over many years and is the result of many factors creates opportunities for early interventions that may prevent or delay the onset of the disease. It may be that because of the physical properties of a person's brain and his or her genetic makeup and life experiences, the person is able to tolerate and adapt to a certain amount of change and damage that occurs to the brain during aging. This tolerance level differs from person to person depending on cognitive reserve and other factors. At some point in the life of some people, the balance may tip in favor of a disease process. For others, the balance may remain in favor of healthy aging. Learning about the earliest developments in the disease process will help researchers understand this complex, lifelong balancing act.

Mild Cognitive Impairment

As some people grow older, they develop memory problems greater than those expected for their age. However, these problems do not necessarily meet all the accepted criteria for AD. These people have a condition called mild cognitive impairment.

Because many, but not all, people with MCI progress to AD, scientists debate whether MCI is an early stage of AD, an entirely distinct condition, or a multifaceted condition in which AD is one of several potential causes. To help settle this question, scientists hope to learn more about the underlying causes and courses of MCI. They have defined subtypes of MCI based on cause (for example, degenerative, vascular, psychiatric [especially depression], and medical), and on which aspects of cognition are predominantly affected.

Using Different Kinds of MCI Studies to Full Advantage

Scientists conduct clinic-based and community-based studies of MCI, knowing that the goals and the constraints of both are different. Clinic-based studies can use a greater number and array of assessment tools, including specialized imaging techniques, and they can gather rich data on potential causes based on expert clinical judgment. However, they typically involve smaller numbers of highly selected participants who volunteer or are selected for the studies.

Community-based epidemiological studies provide valuable complementary information because they involve large numbers of participants who exhibit the variety of health conditions that are typical of the general population. For example, the Monongahela Valley Independent Elders Survey (MoVIES) study, conducted by a University of Pittsburgh School of Medicine team, revealed that the prevalence of MCI in this community-based sample was 3 to 4 percent among persons who were, on average, about 75 years old. The study also found that many people with MCI did not progress to dementia and some even reverted to normal cognitive functioning. The researchers concluded that MCI may be much more heterogeneous than previously thought and suggested that the condition represents more than just a precursor to AD (Ganguli et al., 2004).

Understanding the multiple, potentially overlapping, causes of MCI and its relationship to dementia and AD will require clear, reliable definitions and reliable long-term data that come from both of these types of studies—the community-based studies of “regular folks” as well as the carefully controlled studies of selected participants.

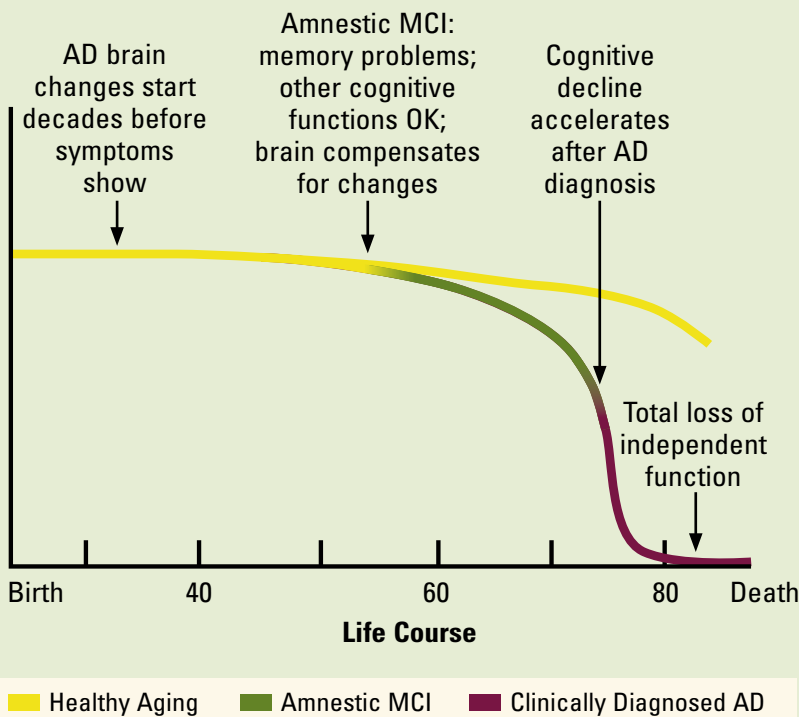
The subtype that features memory impairment most prominently is called MCI with memory loss, or “amnesic MCI,” and is the subtype likely to lead to AD. Individuals with other MCI subtypes may have prominent deficits in other cognitive functions, such as language skills or visuospatial ability. These types of dementia can be caused by other degenerative diseases, such as frontotemporal dementia and dementia with Lewy bodies, or by other conditions such as vascular dementia (Petersen, 2005a).

Being able to describe the essential characteristics of MCI is another important step in understanding this condition. Investigators at the Alzheimer’s Disease Cooperative Study (ADCS; see p. 57 for more information) have done just that in a recent study (Grundman et al., 2004). The research team compared participants with amnesic MCI to individuals with AD and determined that the people with this type of MCI had impaired memory but that other elements of cognitive function were not affected. The people with amnesic MCI achieved test scores between healthy people and those with AD on cognitive and functional tests. Of the 214 participants with this type of MCI who progressed to dementia, 212 were classified as having AD after 3 years of follow-up (Petersen et al., 2005b). By so clearly describing this population in terms of the elements and extent of cognitive function affected by amnesic MCI, the study team has made a major contribution to a vital component of AD research—clinical trials. Their definition of amnesic MCI has already been widely used by other research teams working on AD treatment strategies.

In an effort to understand the effects of memory problems on cognitive function, researchers have examined what happens in specific brain regions of individuals with memory complaints when these regions are activated during memory tasks. A group of investigators from Massachusetts General Hospital conducted a type of MRI called “functional MRI” (fMRI), which measures brain activity, in 32 older individuals with memory complaints who did not have dementia (Dickerson et al., 2004). Participants performed several cognitive tasks during and after the fMRI. Several activated regions within the medial temporal lobe of each participant were identified, and the investigators measured the

degree of activation in those regions during the tests. They found that greater activation of the hippocampal regions was correlated with better memory performance. They suggest increased activation in people with memory complaints could predict impending clinical decline. Paradoxically, participants who had a greater degree of cognitive impairment recruited a larger extent of particular portions of the hippocampal region during the successful cognitive tasks than did less impaired participants. This was also true for those whose cognitive abilities declined over the 2.5 years of the study. The researchers hypothesize that the increased activation of these brain regions reflects a compensatory response to accumulating neuronal damage and is itself a marker of that damage.

Charting the Course of Healthy Aging, MCI, and AD



The Journey from Healthy Aging to AD: Damage in the Brain

Since the earliest days of AD research, investigators have focused on the basic disease process in the brain—on trying to understand exactly what happens in neurons to damage and ultimately kill them. In the last several years, scientists have made enormous progress in characterizing the individual players in this process, describing their activities, and determining the exact steps in the disease process. These advances mean that scientists are increasingly able to move away from studies of these players in isolation and focus on their complex relationships and how their effects on each other affect the development of AD. This section of the *Progress Report* describes a number of significant advances in this area.

New Discoveries About Beta-amyloid and Plaque Formation

Recent studies have dramatically improved scientists’ understanding of how beta-amyloid plaques are formed. These

discoveries have fundamentally changed how scientists think about this critical component of AD pathology.

APP, the starting point for beta-amyloid plaques, is one of many proteins associated with cell membranes, the lipid barrier that encloses the cell. As it is being made inside the cell, APP becomes embedded in the neuron's membrane, 4/5 on the outside and 1/5 on the inside, like a toothpick stuck in an orange. While APP is embedded in the cell membrane, certain enzymes (proteins that cause or speed up a chemical reaction) cleave it into discrete fragments. Several years ago, scientists identified the enzymes responsible for cleaving APP into these peptides. These enzymes are called alpha-secretase (α -secretase), beta-secretase (β -secretase), and gamma-secretase (γ -secretase). In a major breakthrough, scientists then discovered that, depending on which enzyme does the cleaving and the segment of APP within which the cleaving occurs, APP processing can follow one of two pathways that have very different consequences (see illustration on p. 22).

In one 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 from the neuron of a fragment called sAPP α . This fragment has 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 segment. The smaller of the resulting fragments also is released into the space outside the neuron, while the larger fragment remains within the neuron and interacts with factors in the nucleus.

In the second pathway, beta-secretase cleaves the APP molecule at one end of the beta-amyloid peptide, releasing a fragment called sAPP β from the cell. Gamma-secretase then cleaves the resulting fragment at the other end of the beta-amyloid peptide. Following its cleavage at both ends, the beta-amyloid peptide is released into the space outside the neuron and begins to stick to other peptides of beta-amyloid. These small, soluble clumps of two, three, four, or even up to a dozen beta-amyloid

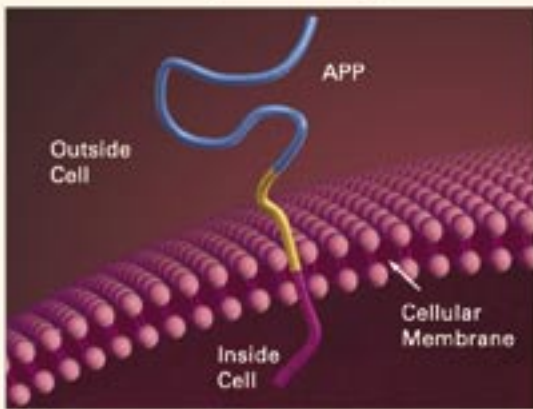
In a major breakthrough, scientists discovered that APP processing can follow one of two pathways that have very different consequences.

peptides are called ADDLs. The number of individual beta-amyloid peptides within ADDLs varies, but collectively, they are referred to as oligomers. It is likely that some oligomers may be cleared from the brain. Those that cannot be cleared clump together with more beta-amyloid peptides and other proteins and cellular material. As the process continues, these oligomers grow larger, becoming increasingly insoluble entities called protofibrils and fibrils. Eventually these entities coalesce into the well-known plaques that are characteristic of AD.

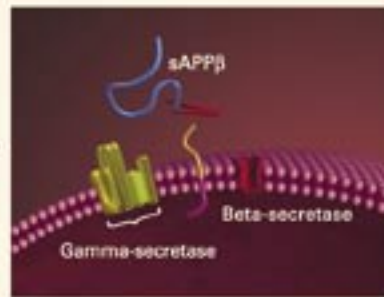
Until recently, scientists thought that fibrils and plaques were somehow responsible for all the neuronal damage and death in AD. Now, new evidence suggests that the formation of plaques may actually be a kind of clearance mechanism that the brain uses to get harmful beta-amyloid clumps away from neurons.

Two Pathways...Different Outcomes

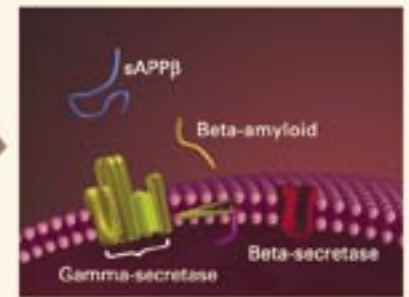
Pathway to Harm



As it is being made, APP sticks through the neuron's membrane, partly inside and partly outside the cell.

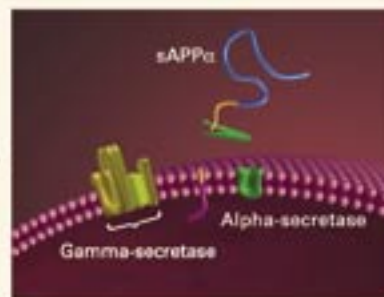


Beta-secretase cleaves APP at one end of the beta-amyloid peptide; sAPP β is released into the space outside the neuron.

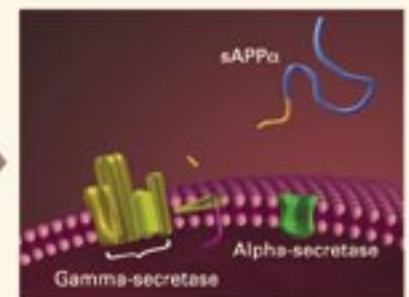


Gamma-secretase cleaves APP at the other end of the beta-amyloid peptide, releasing it into the space outside the neuron. The other fragment stays within the neuron.

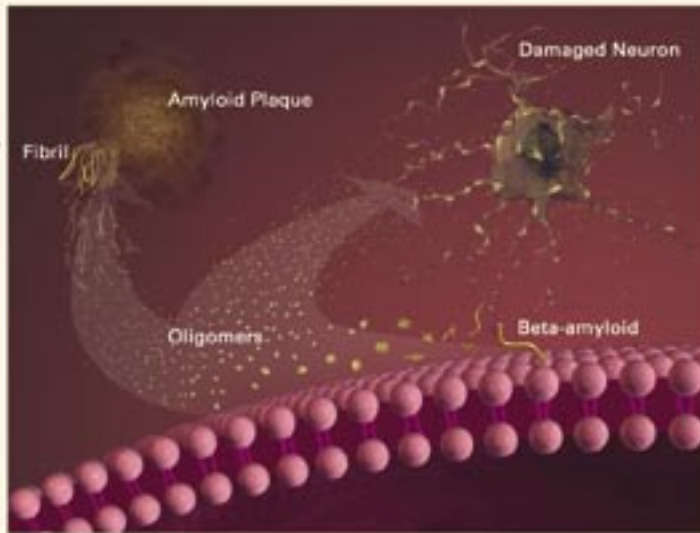
Pathway to Healthy Aging



Alpha-secretase cleaves the APP molecule within the portion that would have formed beta-amyloid. sAPP α is released into the space outside the neuron.



Gamma-secretase cleaves the remaining fragment. The smaller portion is released into the space outside the neuron; the larger stays within the neuron.



Single beta-amyloid peptides clump into soluble oligomers. Some oligomers attach to neurites, disrupting synapse function. Some oligomers clump together with other cellular material, forming increasingly insoluble fibrils. Eventually this clumping process leads to the insoluble plaques that are found in abundance in AD.

Key Questions Remain

Even though scientists have deciphered the steps in the APP cleaving process, they are still working to answer three key questions:

- Why is one pathway taken rather than the other in any single cleaving of APP?
- Why, in some people, is one pathway consistently favored over the other through the course of many years?
- What is the relative toxicity of oligomers, fibrils, and plaques?

Researchers also are increasingly convinced that oligomers that are not cleared from the brain and that do not become part of a plaque may be one of the neuron-damaging culprits. A research team at Northwestern University has even suggested how oligomers damage neurons and cause the memory loss that features so prominently in AD (Cleary et al., 2005; Lacor et al., 2004). Working with cell cultures and tissue extracts taken from AD and rat brains, the scientists found that some oligomers attach themselves to the synapses located on neurites (the structures that branch out from the cell body; see the Structure and Function of the Brain sidebar on p. 5). When this happens, the synapses are not able to function properly and therefore cannot receive messages from other neurons. Unable to communicate, the neuron ultimately ceases to function and dies. As this destructive process accelerates, essential cognitive operations, such as memory formation and retrieval, are disrupted.

University of California at San Francisco investigators funded by the National Institute of Neurological Disorders and Stroke (NINDS), NIA, and other research institutions are contributing to this understanding through their studies of an enzyme called fyn kinase, which is thought to increase the susceptibility of neurons to beta-amyloid toxicity. In their studies with transgenic mice, the investigators found that fyn kinases were necessary for the toxic effects of beta-amyloid on neuronal synapses and contributed to premature death in the mice, but they were not involved in all elements of the pathologic process in neurons (Chin et al., 2004).

This expanding knowledge about the stages of plaque formation and the toxicity of molecules formed at each stage is giving scientists new therapeutic targets. For example, because toxic forms of beta-amyloid build up most rapidly when they are at high

concentrations in the brain, one strategy is to investigate whether high levels of beta-amyloid in the brain might be partly due to how rapidly these molecules are removed from brain tissue into the blood stream through the blood-brain barrier. Several groups are trying to understand which receptors on the surface of cells at the blood-brain barrier are responsible for this transport and whether their ability to move beta-amyloid in and out of the brain might be related to AD pathology.

One research team based at the University of Rochester Medical Center is working on receptors that remove beta-amyloid from the brain (Deane et al., 2004). A receptor called low-density lipoprotein receptor-related protein (LRP) was previously found to be primarily responsible for this task. The new studies show that LRP binds to beta-amyloid at the blood-brain barrier. Interestingly, LRP's efficiency in clearing beta-amyloid from the brain into the blood was greatest for the most soluble form of normal beta-amyloid. In contrast, mutated forms (such as one found in a Dutch family where mutated beta-amyloid accumulated around blood vessels) and less soluble forms of normal beta-amyloid were cleared from the brain much less rapidly. However, at high concentrations, all forms of beta-amyloid directly caused an increased rate of LRP breakdown, reducing the ability of LRP to clear beta-amyloid from the brain. Together, these results indicate that preserving LRP activity at the blood-brain barrier may be an important component of strategies to remove beta-amyloid from the brain.

A receptor called $p75^{NTR}$ also is coming under scientific scrutiny. Among other actions, $p75^{NTR}$ makes many kinds of neurons more susceptible to beta-amyloid. In a recent study funded by NINDS and other organizations, a research team from the University of Rochester studied the effects of beta amyloid on $p75^{NTR}$ levels in cell cultures of human neurons. They expected that increasing $p75^{NTR}$ would make the neurons more susceptible to beta-amyloid. Instead, they found that exposure to beta-amyloid increased $p75^{NTR}$ activity in the neurons and that the increased activity actually protected the cells, even when cells were exposed to levels of beta-amyloid 2,500 times higher than those usually found in people with AD (Zhang et al., 2003). These findings open the door to future studies to examine the possibility that activating the $p75^{NTR}$ receptor may be a useful strategy for treating AD in humans.

Scientists funded by the National Institute of Environmental Health Sciences, NIA, and the Wisconsin Distinguished Rath Graduate Fellowship in Medicine have investigated another protein that may be protective because it binds beta-amyloid (Stein et al., 2004). This research team, from the University of Wisconsin at Madison, studied why transgenic mice that had defective genes from people with early-onset AD inserted into their DNA had high levels of beta-amyloid deposits but did not exhibit any neurodegenerative symptoms. Further investigations led the research team to discover that these mice were producing high levels of transthyretin, a carrier of the thyroid hormone thyroxine. When the mice were given antibodies that prevented transthyretin from interacting with the beta-amyloid protein, the mice showed an increased level of brain cell death. Cell culture studies of human brain cells treated

Building a Better Structural Model for Beta-amyloid

Researchers at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have used the latest in sophisticated microscopes and solid-state nuclear MRI technology to construct a molecular model of a beta-amyloid fibril (Antzutkin et al., 2002; Antzutkin et al., 2003; Petkova et al., 2004). This model has provided many insights into the molecular interactions that drive fibril formation. For example, beta-amyloid peptides of slightly different lengths appear to have the same physical structure even though one is associated with AD and the other is not. The researchers speculate that the difference in solubility and the speed of fibril formation, rather than the difference in structure, are responsible for the difference in toxicity.

The researchers also found that a specific segment of the full length beta-amyloid protein associated with early-onset AD mutations has a loop or bend in it. This structural feature may have some importance in the plaque formation process.

These studies point up the complexity of beta-amyloid and the importance of understanding its structure and the interactions of its various parts. Expanding knowledge in this area may reveal much about the mechanisms underlying the development of AD.

with transthyretin and beta-amyloid showed minimal amounts of cell death while beta-amyloid alone caused significant cell death. These studies indicated that transthyretin can block the progression of AD in this mouse model by inhibiting the effects of beta-amyloid protein. Although we do not yet know whether transthyretin protects against beta-amyloid in humans, this discovery suggests that it may be possible to

develop a drug that increases the production of transthyretin and thus protects people at risk of AD, possibly including those who are at higher genetic risk of developing the disease. The findings also may improve the detection of environmental agents that may play a role in the development of AD by allowing scientists to determine which of these agents upsets the balance between transthyretin and beta-amyloid proteins.

Avenues of beta-amyloid research involving new pathways are proving to be rich ground for discovery. The possibility that blocking the production of beta-amyloid in the brain might prevent the development of AD is one such avenue. NIMH- and NIA-funded scientists at the Howard Hughes Medical Institute and the University of Pennsylvania built on previous research suggesting that an enzyme called glycogen synthase kinase-3 alpha (GSK-3 α) may be crucial to the development of AD because inhibiting the action of GSK-3 α also inhibits the formation of beta-amyloid plaques and neurofibrillary tangles. In the new study, the investigators examined the potential of the mood-stabilizing medication lithium to inhibit GSK-3 α and minimize the biological changes leading to AD (Phiel et al., 2003). The researchers first showed that lithium inhibited GSK-3 α in cultured cells, reducing the production of beta-amyloid. Then, they demonstrated that administering therapeutic doses of lithium to transgenic mice markedly reduced the accumulation of beta-amyloid in the mouse brains. These results appear promising and are opening new lines of investigation about the association of lithium and AD.

For example, it may be useful to investigate whether patients who have taken lithium for bipolar disorder show a lower incidence of AD. However, even if lithium does prove to be useful as an AD intervention, its known side effects, such as nausea, fatigue, and hand tremor, particularly in older patients, may require the development of new agents that provide the therapeutic effects without the negative side effects.

New Discoveries About Presenilin

At the same time that researchers are making new discoveries about beta-amyloid oligomers, they are gaining insight into another crucial AD player—presenilin. Presenilin is an essential component of the

gamma-secretase enzyme responsible for cleaving APP to form beta-amyloid. Certain mutations in the presenilin genes (PS1 and PS2) cause the most common type of familial early-onset AD (FAD). Most of the research on the effect of presenilin mutations on AD has focused on their effects on the gamma-secretase enzyme complex.

Gamma-secretase is an example of an enzyme whose biological activity depends on several proteins working together in a complex. To understand how this important enzyme functions, we need to know what other proteins it contains besides presenilin. Knowing the additional protein components will allow us to answer important questions about how it works,

Building a Better Mouse Model for AD... and Better Imaging Equipment to See AD Pathology

Research in animals has always been a vital part of understanding any disease process, including AD, and mice and rats have been the mainstay of animal research for decades. Researchers have recently developed better small animal models for AD along with highly sophisticated imaging systems to look at brain changes.

University of California at Irvine researchers recently developed an entirely new breed of mice that exhibit the hallmarks of AD as they age (Oddo et al., 2003). These mice contain two mutated genes that cause early-onset AD and a mutated *tau* gene that causes another form of dementia. Using these “triple transgenic” mice, the scientists were able to demonstrate, for the first time, a chronology of cellular and functional impairments consistent with those seen in AD. They found that disruption of normal synaptic functions and the

presence of abnormal beta-amyloid in the spaces between neurons preceded the formation of plaques and tangles. This transgenic mouse model holds great promise as a means to understand the pathologic process in AD more completely and as a tool for testing future diagnostic and therapeutic strategies.

In complementary research, two teams of investigators funded by the National Institute of Biomedical Imaging and Bioengineering have made several advances in imaging systems that may alter the way scientists study and visualize biochemical processes in small animals. Imaging systems like these also help to lay the groundwork for future progress in human brain imaging.

■ Scientists at Washington University and Massachusetts General Hospital have refined a light microscope-based technique called multiphoton microscopy. Using this

technique over a period of months, they can image microscopic structures in the brains of living mice that develop AD-like plaques (Skoch et al., 2005). A subset of neurons in the brains of these mice has been engineered to express an imaging agent called yellow fluorescent protein. A near-infrared laser is used to excite this imaging agent. The resolution of this technique is several orders of magnitude higher than existing techniques, such as PET or MRI.

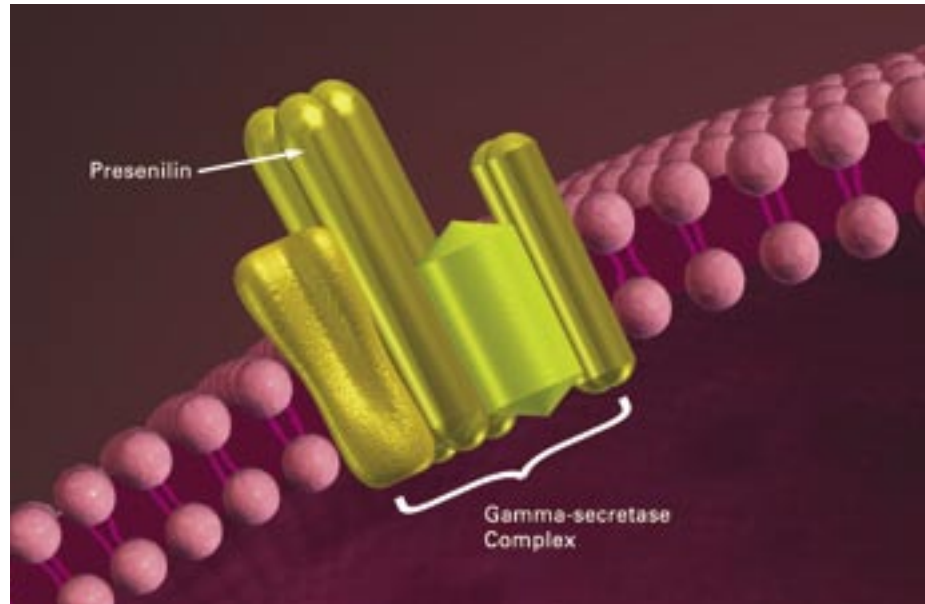
■ University of Pennsylvania researchers have developed methods to improve the speed, sensitivity, and resolution of another kind of imaging technology, called single photon emission computed tomography (SPECT) technology (Acton and Kung, 2003). These improvements allow investigators to take advantage of existing SPECT machines to better visualize biochemical processes in living mouse models of AD.

what proteins besides APP it may cleave, and how its activity can be altered. A group of Harvard Medical School investigators used mass spectroscopy, a highly sensitive analytical technique that can identify and quantify both known and unknown compounds, to isolate and characterize gamma-secretase (Fraering et al., 2004). Using this technique, the researchers determined that the gamma-secretase complex contains three other proteins in addition to presenilin—nicastrin, Aph-1, and Pen-2—and that all four proteins must be present for gamma-secretase activity. In addition, the researchers found that increased production of beta-amyloid, or production of a slightly longer form of beta-amyloid that was more prone to aggregate into toxic products, could be modified by several factors that influence the structure of the gamma-secretase components. These factors include the lipid composition of the cell membrane and a number of well-characterized gamma-secretase inhibitors. These results provide important clues to possible therapeutic strategies for lowering the production of toxic beta-amyloid by modulating gamma-secretase activity.

Researchers are now showing that the presenilin proteins appear to be involved in a number of other nervous system functions as well. Examples are clearance of proteins no longer required by the cell, neurogenesis (the generation of new neurons), and cell signaling. Some of these other functions of presenilins are likely to be important in brain aging and development of AD and perhaps in other neurodegenerative diseases as well.

A team of scientists from the Mt. Sinai School of Medicine, in New York, is exploring the possibility that presenilins normally play an important role in preventing other typical AD pathologies,

including changes to *tau* and cell death (Baki et al., 2004). Using cells taken from transgenic mice with both normal and mutated PS1 genes, the researchers found evidence suggesting that PS1 normally activates a cell signaling pathway called PI3K/Akt. This pathway blocks cell death



and inhibits *tau* phosphorylation. It also appears that AD mutations in PS1 may promote AD pathology by inhibiting the PI3K/Akt pathway. The researchers hypothesized that inadequate activation of PI3K/Akt signaling and impaired transmission of survival signals due to familial PS1 AD mutations (or the loss of normal presenilin function) could contribute to AD pathology independent of PS1's role in cleaving APP.

Other studies have focused on a newly-discovered effect of presenilin mutations on one of the two main “garbage disposal” systems of the cell, the lysosome. Neurons contain a large number of these structures, which eliminate most of the damaged or

Exploring Commonalities in the Transformation from Healthy Aging to Neurodegenerative Disease

For some time, scientists have realized that a number of devastating diseases—such as AD, dementia with Lewy bodies, frontotemporal dementia, Parkinson’s disease, Huntington’s disease, and prion diseases—are characterized by aggregations of abnormally folded proteins. In AD, the abnormal proteins are beta-amyloid and *tau*; in PD, it’s synuclein; and in frontotemporal dementia, it’s *tau*. Scientists think, therefore, that the pathological process in these diseases must share some characteristics, though these overlaps are not fully understood.

For example, research in the past 2 years on beta-amyloid aggregates has provided evidence that the actual structure of oligomers may help to explain the pathology seen in these diseases. In one series of experiments, scientists at the University of California at Irvine made an antibody in rabbits that specifically recognizes soluble beta-amyloid oligomers. The antibody

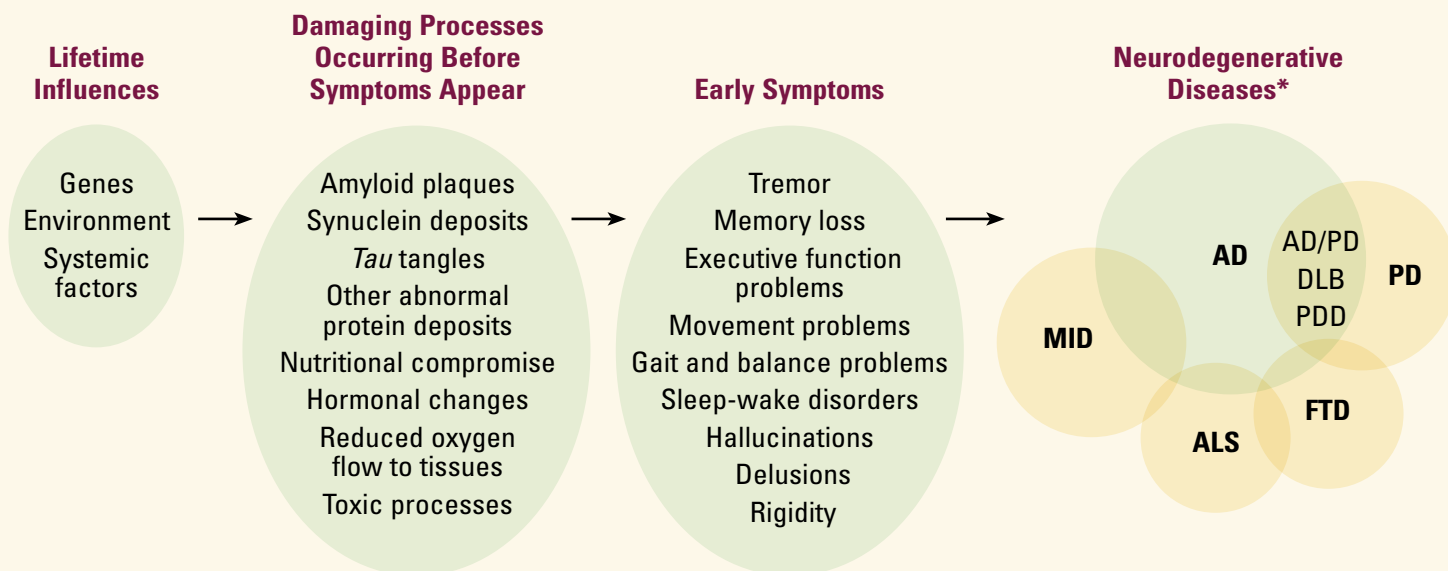
failed to recognize soluble lower-molecular weight and fibrillar forms of this peptide (Kayed et al., 2003). This antibody also reacted with a variety of soluble protein oligomers that are involved in other neurodegenerative diseases, regardless of their specific amino acid sequence. Importantly, this particular antibody blocked the toxicity of these oligomers on cells in culture, including that of beta-amyloid oligomers. These results suggest that many types of soluble oligomers contain a common structural feature, independent of their amino acid sequence, and that the toxicity and pathogenesis of these oligomers may be mediated by a common mechanism.

Scientists also know that many neurodegenerative diseases have some clinical characteristics in common. For example, some people with AD have trouble moving, the most obvious symptom of PD. Many of those with PD also have dementia. Sleep-wake disorders, delusions,

psychiatric disturbances, and memory loss occur in all of these diseases. Finally, it is clear that all of these diseases develop over many years and occur as a result of complex interactions of genes, lifestyle and environmental factors, and factors affecting all parts of the body (such as hormonal changes).

One way of looking at this constellation of disease pathologies, manifestations, and classifications is shown below. It recognizes that complex and interactive biological processes over time result in a group of early symptoms that signal that some kind of disease is beginning to manifest itself. The result may be any one of a number of diseases that has unique characteristics as well as shared characteristics with other diseases.

By investigating these diseases individually and together, scientists hope to shed light on their causes and, possibly, on future common treatment and prevention strategies.



*AD = Alzheimer’s disease, AD/PD = AD with parkinsonism, ALS = amyotrophic lateral sclerosis, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, MID = multi-infarct dementia (also known as vascular dementia), PD = Parkinson’s disease, PDD = Parkinson’s disease with dementia

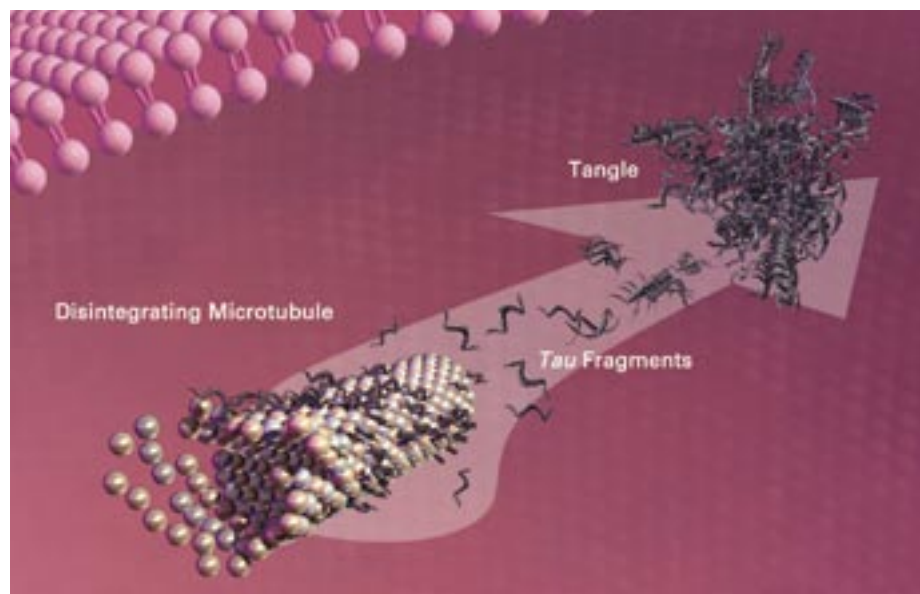
abnormal proteins that can accumulate in age-related neurodegenerative diseases. Researchers from the Mailman Research Center, McLean Hospital, Belmont, Massachusetts, found that presenilin gene mutations induce more severe damage to lysosomal systems in the brains of people dying with FAD than that seen in brains of individuals with the more common late-onset AD (Cataldo et al., 2004). This difference was also seen in PS1 transgenic mouse models of the disease. Some of the lysosomal pathology seemed to be in reaction to the presence of beta-amyloid, and some occurred independently. These results indicate that presenilin mutations can compromise the major garbage disposal systems of the cell and cause a loss of normal neuronal function.

In another twist to the garbage disposal story, a University of Pennsylvania team of scientists showed that removing the presenilin genes altogether in transgenic mice also interfered with the cell's lysosomes (Wilson et al., 2004). The investigators showed that the faulty lysosomes in these mice contained very high levels of two proteins, alpha- and beta-synuclein. This is an important finding because the abnormal accumulation and aggregation of alpha-synuclein has been implicated in several neurodegenerative diseases, including Parkinson's disease. The effects were not due to loss of the gamma-secretase activity itself, but seemed more likely to be due to an effect on calcium metabolism within the cells that lacked PS proteins. Thus, aberrant accumulation of alpha- and beta-synuclein in degradative organelles are novel features of neurons that lack PS1, and similar events may promote the formation of clumps of alpha-synuclein found in several neurodegenerative diseases.

New Discoveries About Tangles and *Tau*

Even though scientists have agreed for years that plaques and tangles are two of the major features of AD, they've disagreed about the relative importance of each. The development of the mouse model of AD that exhibits all the major characteristics of the disease (see p. 26 for more on this mouse model) has given scientists further insights into plaques and tangles, their interrelationships, and the roles that both beta-amyloid and abnormal *tau* play in damaging normal neuronal function.

When scientists at the University of California at Irvine placed a beta-amyloid antibody into the hippocampus of one side of the brains of a group of triple transgenic mice in an immunotherapy study, they were not surprised to see that beta-amyloid deposits were partially removed from the spaces outside the neurons (Oddo et al., 2004). Intriguingly, they also found that beta-amyloid levels inside neurons also appeared to be reduced. However, a most important lead for the further understanding of AD pathology



came from the unexpected finding that this beta-amyloid immunotherapy also resulted in the clearance of abnormal *tau* from the cell body and dendrites of hippocampal neurons of these animals. No *tau* was cleared from hippocampal neurons on the side of the brain without the antibody. Reduction of abnormal *tau* following anti-beta-amyloid treatment suggests a direct interaction between these two hallmarks of AD. Furthermore, it suggests that a hierarchy exists—the abnormal beta-amyloid appears first, followed by abnormal *tau*.

A recent study supported by NINDS, NIA, and other organizations also explored the association between beta-amyloid and *tau* (Gamblin et al., 2003). A team of Northwestern University researchers used test tube studies to demonstrate that certain enzymes called caspases can break the *tau* protein into segments when they are in neurons that have already been treated with beta-amyloid. The resulting segments have a greater tendency to form damaging tangles than does normal *tau*. These findings help expand our understanding of the functional relationship between beta-amyloid and *tau* and suggest that the caspases, which are well known for their involvement in cell death pathways, also may be involved.

Recent studies have examined other aspects of tangles and *tau*, and they also are helping to explain *tau*'s role in the AD process. For example, some scientists think that the misfolded shape of the highly phosphorylated *tau* in the neuron increases its tendency to form neurofibrillary tangles and encourages the loss of stabilization

of microtubules. Studies have shown that the molecular chaperones Hsp90 and Hsp70 (proteins that protect cells from the adverse effects of protein misfolding and aggregation), stabilize *tau*'s normal shape, reduce *tau*'s abnormal phosphorylation and aggregation, and restore its binding to microtubules (Dou et al., 2003). This research, which was funded by NIA, the Alzheimer's Association, and the Ellison Foundation, has implications not only for AD and diseases caused by *tau* mutations (such as FTD and parkinsonism linked to chromosome 17), but also for other neurodegenerative diseases, such as Huntington's disease and prion diseases that are characterized by abnormal aggregates of other types of protein.

Scientists have known for years that *tau* is important in maintaining microtubule integrity and, therefore, their ability to transport materials and organelles, such as mitochondria, between the cell body of the neuron and the synapse. However, only more recently has it become clear that the level of *tau* and normal phosphorylation might also regulate the actual transport of materials down intact microtubules. As with other neuronal systems, a delicate balance must be maintained for optimal function. A research team at the New York State Institute for Basic Research in Developmental Disabilities investigated how high levels of *tau* actually inhibit axonal transport from the cell body to the synapse (Tatebayashi et al., 2004). They found that the enzyme called GSK3 β , which is regulated by the PS1 gene, also phosphorylates *tau* under normal conditions. This phosphorylation does not alter *tau*'s ability to bind to microtubules, but it appears to be required for normal axonal transport in

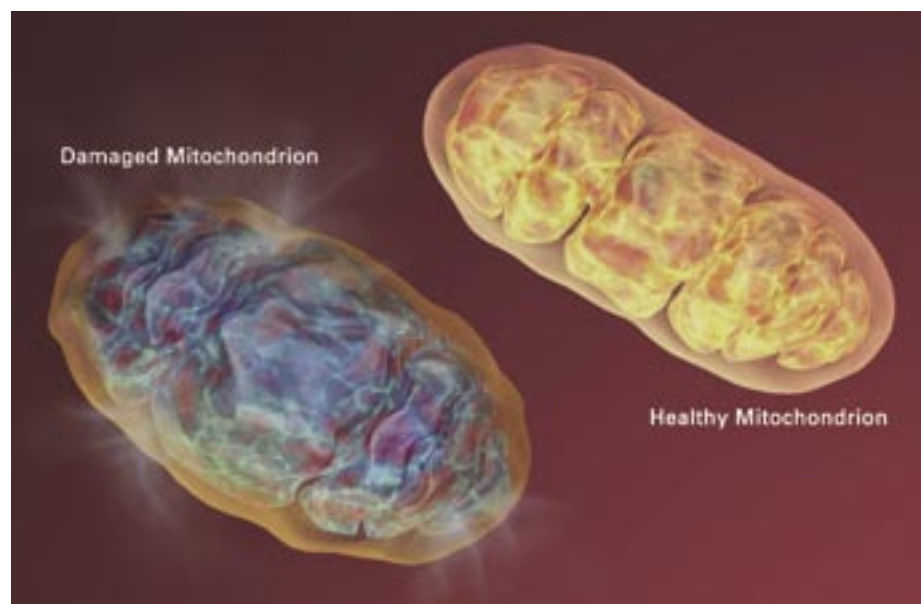
cells. These findings raise the possibility that the physiological phosphorylation of *tau* by GSK3 β also may be involved in regulating organelle transport. Supporting the idea that either too much or too little of a protein like GSK3 β might adversely affect neuronal function, NICHD-funded researchers from the University of Connecticut Health Center found that another function of PS1 is to maintain physiological levels of GSK3 β (Pigino et al., 2003). When the gene for PS1 was eliminated, GSK3 β activity increased. This caused a critical transport protein to fall off the microtubules, causing a decrease in axonal transport. The investigators then inserted a PS1 gene containing a mutation called M146V, which causes a very aggressive early-onset form of FAD and got the same effect.

In the last several years, researchers have actually begun to test a potential therapy for the loss of neuronal function that occurs when microtubules disintegrate and *tau* filaments begin to form tangles. In studies funded by NINDS, several other NIH Institutes, and the Institute for the Study of Aging, a research team at the University of Kansas showed that beta-amyloid toxicity can be reduced by pretreating tissue culture cells with agents that stabilize microtubules, such as taxol, a drug used in cancer treatment (Li et al., 2003a). These agents seem to work by indirectly inhibiting an enzyme that abnormally phosphorylates *tau*. The researchers then generated taxol-like compounds that, unlike taxol, can cross the blood-brain barrier and showed a likely positive effect of these drugs in combating beta-amyloid toxicity in adult mice. Working in the same area, a team of scientists from the University of Pennsylvania School of Medicine treated transgenic mice that develop AD-like tangles with

a drug that binds microtubules—in effect, substituting for the *tau* that should normally be there (Zhang et al., 2005). The investigators found that after 12 weekly treatments, the drug restored microtubule function, increased the number of stable microtubules, and lessened motor impairments in the mice. These findings open the way for additional studies to explore the therapeutic potential of drugs that offset the effects of beta-amyloid toxicity and loss of microtubules.

New Discoveries About Mitochondria

Mitochondria are critically important structures in all cells, including neurons. They are the power plants for the cell, providing the energy a cell needs to move, divide, and carry on its functions. A mitochondrion has a smooth outer membrane and an inner membrane that forms many folds. On these folds, glucose combines with oxygen to produce ATP, the cell's primary energy source.



AD researchers have thought for some time that damage to or mutations of mitochondria could play a role in the early development of AD because they lead in several ways to the death of the cell through a process called apoptosis (Beal, 2000; Melov, 2004). Damage to mitochondria also leads to a rapid increase in the formation of free radicals, which are highly reactive oxygen molecules that can build up in neurons over time. If unchecked, the build-up of these molecules can cause oxidative stress, which damages other cellular molecules such as proteins, lipids, and nucleic acids. Oxidative stress and mitochondrial dysfunction have been implicated in several neurodegenerative diseases, including AD.

Several research teams have recently expanded our understanding of mitochondria, free radicals, and oxidative stress. For example, Columbia University scientists observed that in AD brains, beta-amyloid is bound to a protein called A β -binding alcohol dehydrogenase (ABAD), which is an integral part of mitochondria (Lustbader et al., 2004). Studies in AD transgenic mice show that the binding of beta-amyloid peptides to ABAD prevents the normal function of ABAD and leads to enhanced production of free radicals followed by increased apoptosis. When the investigators developed transgenic mice that overproduced ABAD as well as developed plaques, they observed increased oxidative damage in their brains. Cognitive tests showed that these mice had impaired memory compared to AD transgenic littermates that had normal levels of ABAD. If these findings are borne out in additional studies, blocking

the interaction between ABAD and beta-amyloid could be a possible target for future therapeutic strategies in AD.

A research team from the Buck Institute for Age Research, in Novato, California, took advantage of the availability of genetic models of oxidative stress as well as other technologies to explore the impact of mitochondrial oxidative stress on the activity of individual mitochondrial enzymes (Hinerfeld et al., 2004). For this research, they used mice deficient in a key antioxidant enzyme known as superoxide dismutase type 2 (SOD2). These mice suffer a loss of neurons in particular brain regions. The investigators found that certain parts of the mitochondrial molecular machinery that produces energy are more vulnerable to oxidative stress than are others. Most important from a therapeutic standpoint was the finding that an antioxidant compound was able to prevent the damage of the mitochondrial enzymes, and in doing so, restored some of the neuronal loss caused by the oxidative stress.

NIA researchers have tracked the declines in synapse activity and neuronal energy consumption that occurs during the evolution of the AD process (Rapoport, 2003). They found that changes in the structure and function of synapses resulting from AD pathology reduce neuronal energy demand and lead to potentially reversible decreases in energy production within the mitochondria. PET scans showed that, at this early stage in the disease process, the synapses can almost be normally activated in response to stimulation. As the disease progresses, however, tangles with abnormally phosphorylated *tau* accumulate within the neuron to the point that they disrupt microtubules and axonal transport. Mitochondria are prevented from traveling along the axon between the cell

body and the synapse. The resulting severe energy depletion at the synapse and other pathology leads to the death of the neuron. If these findings are confirmed by further research, strategies to maintain neuronal energy metabolism during the early stages of the disease process may be a potential therapeutic goal.

Other research teams have focused on genetic aspects of mitochondria's role in AD. Mitochondria possess their own DNA, distinct from the DNA in the cell's nucleus. Although the amount of DNA in a mitochondrion is very small compared to that in the nucleus, mutations in it can have deleterious effects. Researchers from Cornell University Medical College set out to test whether people with AD have mutations in mitochondrial DNA (Coskun et al., 2004). They found several mutations in the part of mitochondrial DNA that controls the activity of mitochondrial genes. These genetic changes could be found in more than half of the AD brains examined but in none of the brains from cognitively healthy individuals of the same age. These AD-specific mutations in mitochondrial DNA could underlie the mitochondrial failure to produce sufficient energy for proper functioning of neurons, which, in turn, can result in loss of communication between neurons. These investigators speculate that the accumulation of these mutations might be a significant and contributing factor to the development and progression of AD.

Finally, a research group from Oregon Health and Sciences University compared the expression of mitochondrial genes from the brains of cognitively healthy individuals and brains from people at early- or late-stage AD (Manczak et al., 2004). They found AD-related changes in the patterns by which certain genes are expressed. These

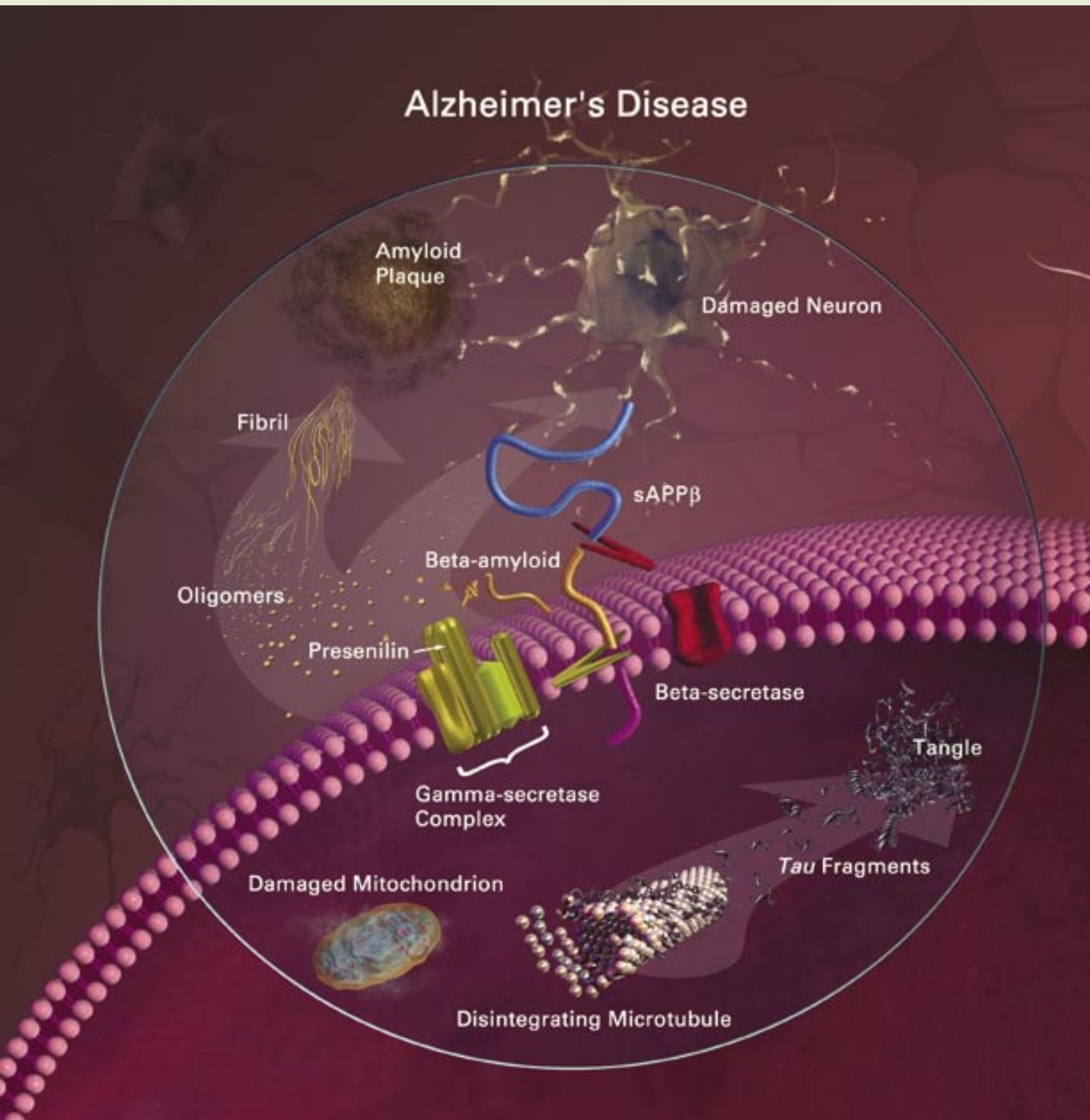
genes encode the proteins that make up the three major components of mitochondria's energy-producing machinery. These findings suggest that the ability of the mitochondria to produce energy is compromised in AD and that the mitochondria inside the surviving neurons are trying to compensate for the brain's loss of energy resources.

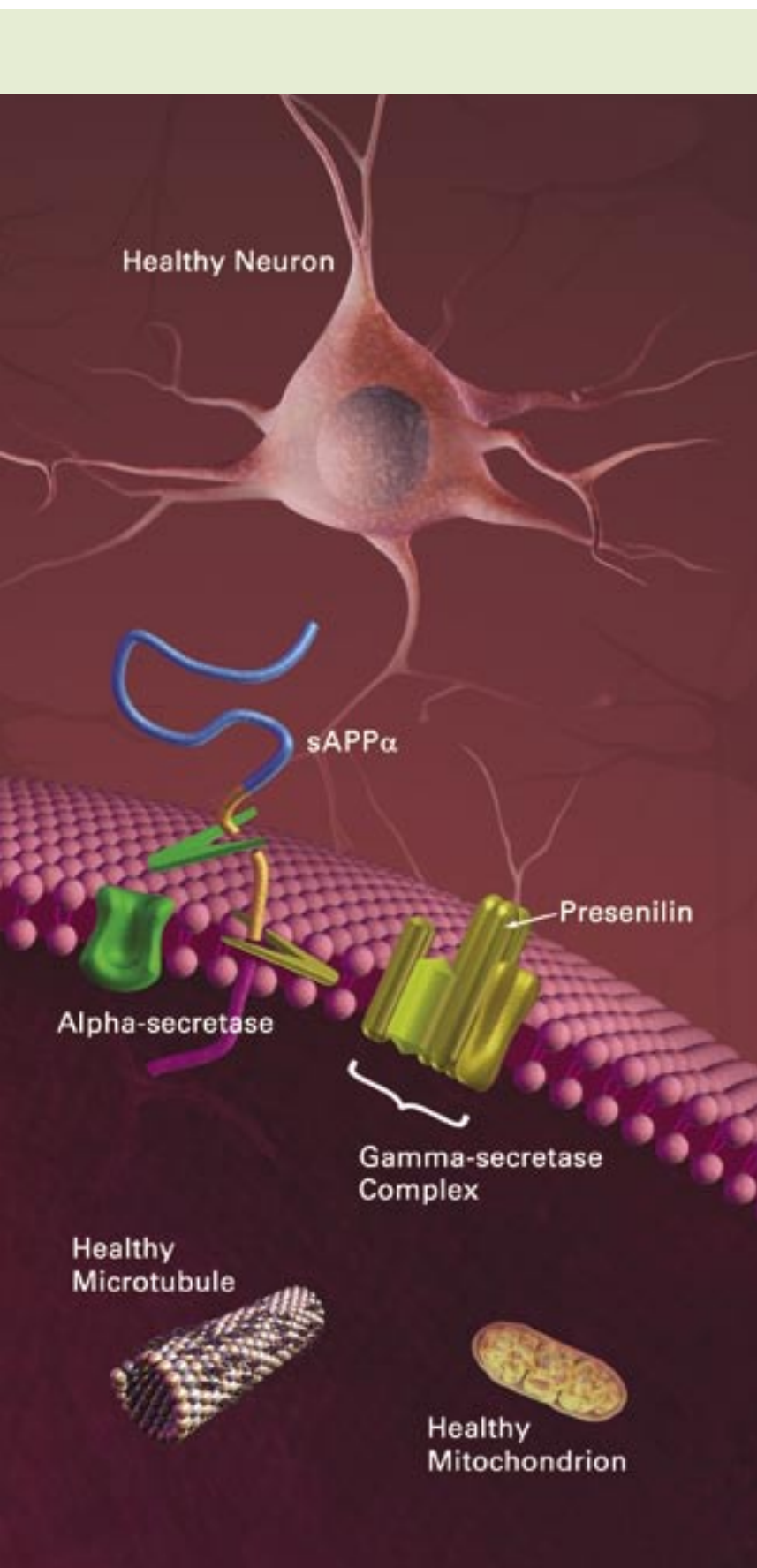
New Discoveries About Other Processes that Contribute to Neuronal Damage

Over the last several years, knowledge has grown about several other related areas that appear to play an important role in AD.

Cell Death. An area that is generating increasing scientific interest is abnormal cell death caused by disruptions in the normal function of key structures in neurons. For example, a proteasome is a large structure, which, along with lysosomes, is responsible for chopping up misfolded or damaged proteins so that the cell can dispose of them. This critical system protects cells from the toxicity of damaged proteins. Increasing evidence suggests that disruptions to proteasome activity occur in normal aging as well as in many neurodegenerative conditions, including AD, PD, and Huntington's disease. The inhibition of proteasome activity causes many and diverse effects on cells, including cell death, and recent studies suggest that proteasome inhibition may contribute to some disease-related mitochondrial changes. A research team from the University of Kentucky explored the effects of chronic, low-level proteasome inhibition on cell function by looking at changes in the activity of a large number of genes. These changes are called "gene expression" (Ding et al., 2004).

Players on the AD Stage: Putting It All Together





The researchers found that a limited number of genes changed their level of expression in cells in which proteasome action was inhibited, and the affected genes were those involved in cell cycle events, inflammatory processes, calcium control, and protein degradation. Alterations in these cell processes have been implicated in normal aging and neurodegenerative diseases.

Another type of cell death is the process called apoptosis. Some evidence suggests that cell death in AD occurs through this process. Sometimes, apoptosis involves mitochondria. Other times, the process can be activated by membrane receptors, such as tumor necrosis factor receptor (TNFR). Studies have shown that components of a TNFR-1 pathway were elevated in AD brain tissue, while cellular inhibitors of this pathway were decreased. One, called TRADD, binds to the TNFR-1 receptor, causing cell death. Another, called DENN/MADD, binds to the TNFR-1 receptor and prevents cell death. Researchers at the University of Southern California Keck School of Medicine recently found a reduction in DENN/MADD and an increase in TRADD in the hippocampus of brains from people with AD compared to tissue from cognitively healthy people (Del Villar and Miller, 2004). Similar changes were seen in neurons treated with beta-amyloid and in cortical tissue from transgenic mice that develop AD-like disease. These changes, which may be caused by inflammation or oxidative stress, may be responsible for increased apoptosis in the AD brain.

Inflammation. A dynamic and complex biological process, inflammation affects cells and tissues all through the body. This process occurs in response to many types of injuries or abnormal situations. In some cases, the inflammation reaction occurs as part of a healing process, such as when the body reacts to a simple scrape on the skin.

In other cases, inflammation is a central characteristic of a disease process, such as in rheumatoid arthritis. Inflammation occurs in the AD brain as well, and many scientists are examining its role in the development and progression of the disease. They don't necessarily agree on its significance—some scientists think that inflammation is part of a vicious cycle that is harmful to neurons. Others think that aspects of inflammation may be valuable to the brain by counteracting the detrimental aspects of the AD process.

Recent inflammation-related research has focused on two kinds of glial cells: astrocytes and microglia. These cells have the capacity to move toward and respond to sites of injury. Beta-amyloid plaques in the AD brain are surrounded by numerous activated astrocytes and microglia. In fact, the presence of large numbers of activated astrocytes surrounding sites of brain injury is one of the earliest manifestations of AD. Scientists speculate that this event could occur in response to degenerating synapses and neurons and to the accumulation of beta-amyloid plaques.

A collaborative team of researchers from Columbia University, Stanford University, and the Gladstone Institute of Neurological Disease in San Francisco demonstrated that astrocytes isolated from adult mouse brains can degrade and remove beta-amyloid peptides (Wyss-Coray et al., 2003). This finding from tissue culture was a surprise because in AD brains, astrocytes surrounding beta-amyloid deposits seem incapable of removing beta-amyloid. Discovering ways to stimulate the ability of astrocytes to clear beta-amyloid may be a fruitful strategy for reducing the toxicity and neurodegeneration associated with plaques and their earlier-stage aggregates.



Other investigators are exploring strategies for stimulating microglia. Like astrocytes, most of the evidence to date shows that microglia can engulf and remove beta-amyloid aggregates in tissue culture, but they fail to do so in living brains. Identifying the molecular details of this “phagocytic” activity is crucial if scientists are to develop microglia that will successfully engulf and remove beta-amyloid aggregates from the brain. Researchers from Cleveland’s Case Western Reserve University School of Medicine used both pharmacological and genetic approaches to discover in tissue culture that beta-amyloid fibrils are engulfed by a receptor composed of several proteins on the surface of microglia. This receptor is entirely different from the typical phagocytic receptors (Bamberger et al., 2003). When each of the receptor components was blocked, the microglia lost the capacity to degrade beta-amyloid (Koenigsnecht and Landreth, 2004). These findings pave the way for researchers to find out why the plaque-associated microglia in living brain tissue are unable to remove the beta-amyloid

deposits effectively, despite their physical association with the plaques.

Other scientists have found that microglia also may be responsible for some of the damaging processes that occur in the AD brain. Microglia are rapidly activated in the presence of aggregated beta-amyloid and are responsible for the strong inflammatory response that can encourage the neurodegenerative changes observed in AD. Deciphering the molecular mechanism by which fibrillar beta-amyloid activates this inflammatory response may suggest future therapeutic targets. In trying to address this problem, scientists from Massachusetts General Hospital put beta-amyloid into the brains of normal mice and mice that were deficient in a particular cell surface protein called CD36 (El Khoury et al., 2003). The researchers found that far fewer microglia were recruited to the beta-amyloid site in CD36-deficient mice compared to normal mice. In addition, microglia isolated from CD36 mice could not produce certain toxic molecules in response to aggregated beta-amyloid, which precluded the ability of these molecules to harm neurons.

In an effort to understand how to regulate the negative effects of microglia, Stanford University scientists found that a growth factor, TGF- β , which regulates cell survival and inflammation throughout the body, has a key role in maintaining neuronal integrity and regulating microglial activity (Brionne et al., 2003). The researchers found that the brains of mice that are deficient in TGF- β have widespread neuronal degeneration and microgliosis, a process characterized by the presence of numerous microglia that have the capacity to harm neurons. They also examined transgenic mice that over-produced TGF- β in their brains and found that overproduction of TGF- β protected

against various forms of brain injury. This finding is highly significant in light of the fact that humans have large variations in the levels of TGF- β in the brain.

Other researchers have been investigating additional factors that may influence brain injury caused by beta-amyloid. A team of scientists at the University of California at Irvine developed transgenic mice that lack a protein called C1q. This protein is involved in the complement cascade, a precise series of events that takes place during the body's immune response; inflammation is part of this response. The researchers bred these C1q-deficient mice with transgenic mice that develop amyloid plaques and found that the offspring that develop plaques in the absence of C1q do not exhibit the intense inflammatory response in the brain tissue as mice that have C1q (Fonesca et al., 2004). The C1q-deficient mice also showed a slower loss of markers of neuronal communication as the plaque pathology developed. These findings suggest that C1q is part of the molecular signaling that leads to the deterioration of neurons in the presence of beta-amyloid aggregates.

Epidemiologic studies have suggested that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), such as naproxen, ibuprofen, and indomethacin, are associated with a decreased risk of AD. These studies provide another avenue of research suggesting that an inflammatory process may be involved in AD. However, previous laboratory research by a group of scientists from the Mayo Clinic in Jacksonville, Florida, showed that some NSAIDs could lower beta-amyloid production, hinting that this mode of action,

rather than an inflammatory pathway, might be responsible for the possible protective effect of some NSAIDs. To further investigate this connection, the Mayo Clinic researchers used cell cultures and an AD transgenic mouse model to study the effects of a number of common NSAIDs on beta-amyloid production (Eriksen et al., 2003). After screening 20 widely-used NSAIDs, the scientists found that 8 effectively reduced beta-amyloid levels both in the cell cultures and in the mouse models. Moreover, this action occurred through a different mechanism than that usually associated with most NSAIDs. The investigators suggest that some NSAIDs could act to delay the development of AD by inhibiting gamma-secretase, and that it might be useful to screen other types of agents for their effect on this key process in AD neuropathology. So far, no clinical trial has shown a beneficial effect of NSAIDs on AD prevention or progression.

The Brain Protects Itself

Until recently, scientists thought that the brain's ability to repair itself after injury or neurodegeneration was limited or nonexistent. In the past several years, however, with new discoveries about brain anatomy and function and the emerging concept of cognitive reserve, scientists are changing that view.

One exciting recent development is the discovery that the brain can, in fact, generate new neurons in a process called neurogenesis. In the adult, this process occurs in two areas of the brain, the hippocampus and the subventricular zone, and possibly in others as well. These brain areas contain special cells called stem cells, which can divide and migrate to other areas of the brain under certain conditions. These adult neural stem cells can make

new neurons and glial cells. This discovery raises the prospect that neural stem cells could be harnessed to replace dying cells or to repair damaged cells and neural circuits in the aging or diseased brain.

Many researchers are studying the fundamental biology of neurogenesis and how it may be linked to AD. For example, NIA-funded researchers recently examined whether abnormalities in neural stem cells might contribute to human disorders of learning and memory, including AD (Haughey et al., 2002). If neurogenesis is impaired in AD, then it may be possible to develop therapeutic approaches that enhance neurogenesis. The investigators wanted to determine whether stem cell proliferation, survival, and differentiation were impaired in transgenic mice that developed a form of FAD. They also wanted to assess the effects of beta-amyloid on stem cell survival and neuronal differentiation. They found that proliferation and survival of the stem cells in a certain region of the hippocampus was reduced in the mice. They also found that beta-amyloid impaired proliferation and neuronal differentiation of human and mouse stem cells, and promoted apoptosis of the cells.

Presenilin mutations also have been shown to reduce neurogenesis from stem cells in the brain. Mt. Sinai School of Medicine scientists discovered that the PS1 mutation that causes the most severe and earliest form of FAD had a major inhibitory effect on the survival of newly-formed neuronal cells from stem cells in mutated PS1 transgenic mice compared with transgenic mice that contained the normal PS1 gene (Wen et al., 2004). This could have implications for the physiological functioning of the hippocampus in FAD. In contrast to the impaired neurogenesis caused by PS1 mutations in other transgenic mouse models of AD, the NINDS-

and NIA-supported work of researchers at the Buck Institute for Age Research showed that neurogenesis is actually enhanced in the hippocampus of people with AD as well as in a transgenic mouse model with two APP mutations that cause FAD (Jin et al., 2004). It is possible that different forms of AD mutations have different effects on brain neurogenesis and that neurogenesis may be an important mechanism the brain uses to try and repair the early effects of AD. Enhancing neurogenesis could be an effective therapeutic strategy.

Other basic science studies conducted by NIA-funded researchers have focused on a protein called Notch, which resides on the surface of neural stem cells. Previous studies have shown that Notch controls the process of neurogenesis. When the gene for Notch is disabled in mice, the development of their brains is severely abnormal and they die in the womb. A similar abnormality in brain development occurs when the PS1 gene is disabled. Mutations in PS1 cause FAD, suggesting a link between Notch and AD. NIA-funded scientists designed experiments using transgenic mice to determine whether Notch is involved in learning and memory (Wang et al., 2004). These mice, which had reduced levels of Notch, exhibited impaired communication at synapses between hippocampal neurons that are critical for learning and memory. When a protein that activated Notch was applied to the hippocampus, communication at the synapses was enhanced. These findings suggest an important role for Notch in synaptic function associated with learning and memory processes, and it may be a new target for therapeutic interventions to improve learning and memory.

Scientists also are beginning to look at other regulators of neural stem cell biology, especially as they influence aging and neurodegenerative diseases like AD. For example, NIMH- and NIA-funded investigators at the Washington University School of Medicine in St. Louis found that transgenic mice had a decreased capacity to generate new neurons in the hippocampus and this decrease was greatest when they were under stress from being housed in isolation (Dong et al., 2004). These deficits also were associated with deficits in

One exciting recent development is the discovery that the brain can generate new neurons in a process called neurogenesis.

contextual memory, which is the aspect of memory related to experiences such as recognizing physical surroundings. Greater amounts of plaques also were deposited in the stressed mice compared to unstressed mice. However, an antidepressant medication that increases cell proliferation in normal mice also increased cell proliferation and improved contextual memory in the stressed transgenic mice. These results suggest that this AD mouse model has an impaired ability to generate new cells in the hippocampus and that this impairment can be modulated by stress and certain drugs.

A number of important questions are being asked about the role of neurogenesis in counteracting the effects of neurodegenerative damage. In an effort to find answers, a Mt. Sinai School of Medicine

research team studied whether injuries to the entorhinal cortex, which has direct connections to the hippocampus, affected the ability of mice to generate new neurons from stem cells in the hippocampus (Gama Sosa et al., 2004). The development of new neurons and their survival was studied for several weeks after the injury. Results

showed that the number of new neurons that were formed in the days immediately after the injury did not increase. However, 6 weeks later, the number of new neurons had almost doubled. This transgenic mouse shows promise as a model for studying the molecular events affecting neurogenesis in the hippocampus.

system into brain areas containing beta-amyloid plaques in APP transgenic mice. The production of neprilysin appeared to increase degradation or reduce the growth of existing plaques. The amount of plaque was reduced to less than half that found in untreated areas. This study suggests that boosting normal, protective processes in the nervous system might help prevent or treat degenerative events associated with AD, and this strategy provides a new way of potentially interfering with the disease process.

Scientists are eager to understand how risk and protective factors balance each other over the course of a lifetime.

Researchers also continue to be very interested in examining the potential of neurotrophic factors, which are proteins that stimulate neuronal survival and growth, to prevent or treat neurodegenerative disorders. The problem has been how to deliver these proteins to the brain because they do not readily cross the blood-brain barrier. Another challenge is how to specifically target them to degenerating neurons to avoid unwanted side effects. Gene therapy offers one approach. Recently, a group of researchers from the Salk Institute for Biological Studies in La Jolla, California, developed a gene delivery system to carry the human neprilysin gene, which makes an enzyme that degrades beta-amyloid (Marr et al., 2003). The team put the neprilysin delivery

Can Certain Factors Protect Against or Increase Risk of AD?

We've known for some time that certain genetic and nongenetic factors can increase the risk of developing AD. Recent evidence has suggested that other factors may actually help to reduce AD risk (see p. 14 for more on one of these factors—cognitive reserve). The combined weight of these advances is making scientists eager to understand how these risk and protective factors balance each other over the course of a lifetime. They also want to know more about the types of interventions that may be useful in changing this balance in the direction of healthy aging and the times in the life cycle at which these interventions might be most effective.

Ideas about what these risk and protective factors might be are derived from a variety of different types of studies, including genetics studies, studies of individual lifestyles and behavioral patterns, and studies of large groups or populations. Findings from these studies are important because they point the way to potential therapeutic approaches that might be worth investigating in controlled clinical trials. If

confirmed in trials, they may suggest ways that people can change their lifestyles or environments to reduce risk. The genetics studies, in particular, will help identify pathways that affect the development or progression of AD. They also will help researchers develop new animal models to understand early events in the disease, as well as identify potential targets for treatment and prevention.

New Discoveries About AD Genetics

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 (“age at onset”). 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, or the PS2 gene on chromosome 1—are linked to the rare early-onset form of familial AD. The APP gene is responsible for making APP, the precursor to beta-amyloid. The presenilin genes code for proteins that are components of enzymes that play an important part in cleaving APP to form beta-amyloid. Presenilin gene mutations promote the breakdown of APP, leading to increased production of harmful beta-amyloid.

A fourth gene on chromosome 19 encodes a protein called apolipoprotein E (ApoE). ApoE carries lipids in the bloodstream and is important in clearing lipids from the blood. APOE, the gene that encodes ApoE, has three common forms, or alleles— $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The $\epsilon 4$ allele is a risk factor gene for the common late-onset AD. The $\epsilon 2$ allele may provide some

protection against AD and $\epsilon 3$ is thought to play a neutral role.

Scientists estimate that an additional four to seven risk factor genes exist for late-onset AD. A study from researchers at Massachusetts General Hospital, who are participating in NIMH’s Alzheimer Disease Genetics Initiative and who are also supported by NIA funding, is shedding light on these genes. The researchers screened the entire genomes of a large number of families with AD using 382 genetic markers and complex statistical analysis to identify regions of the genome that were associated with AD and might contain additional susceptibility genes (Blacker et al., 2003). The study identified 12 additional chromosomal regions that might be linked to AD. Some of these regions will probably be found not to contribute to AD. However, other regions may well harbor genuine AD susceptibility genes, particularly the regions that yielded strong statistical evidence during the genome analysis. Even though it will be difficult to identify and characterize the genes in these chromosomal regions, the results will greatly facilitate the development of strategies for AD treatment, early intervention, and prevention.

Another team of researchers examined genetic associations with AD in a different population. This Boston University School of Medicine team worked with a population in Wadi Ara, an Arab community in northern Israel that has an unusually high prevalence of AD (Farrer et al., 2003). A genomic scan conducted on people from this community with and without AD revealed markers with significant AD allelic association on chromosomes 2, 9, 10, and 12. The researchers then analyzed the distribution of allele frequencies to narrow

the potential regions on these chromosomes where the genes might be found. The unique characteristics of the Wadi Ara populations and the fact that findings from this analysis replicate those from other genome scans may help scientists more rapidly identify AD risk factor genes on these chromosomes.

Other studies have shown that a region on chromosome 10 is likely to harbor at least one AD risk factor gene and several research teams have made advances in this area. For example, scientists from the Karolinska Institute in Stockholm, Sweden, examined a stretch of genetic material on chromosome 10 that contains the insulin degrading enzyme (IDE) gene (Prince et al., 2003). This enzyme is of interest because it also degrades beta-amyloid. Genetically engineered mice that do not have the IDE gene develop high insulin levels, glucose intolerance, and increased brain levels of beta-amyloid (see p. 52 for more on the links between AD, insulin, and diabetes). The scientists compared genetic material from people with and without AD to assess the IDE gene and two other close-by genes. They were interested in finding differences between individuals at a single point in the genetic code (these points are called SNPs) and in stretches of DNA that are inherited in common among groups of people (these stretches of DNA are called haplotypes). Results strongly indicated that this region contains alleles and haplotypes that confer AD risk. These findings provide substantial evidence that genetic variation within or extremely close to IDE affects both disease risk and traits related to the severity of the disease. The study also indicated that an analysis of this type can be an effective way

to assess genetic variation in complex diseases like AD.

Investigators from the Veterans Affairs Puget Sound Health Care System, in Seattle, explored the connection between IDE and APOE status in a study with cognitively healthy older people and those with AD (Craft et al., 2003). The scientists gave participants infusions of insulin at five different levels and then measured cognitive performance and APP levels in the blood 2 hours later. The results supported a role for insulin in normal memory function and on APP levels and suggested that the APOE- ϵ 4 allele interacts with insulin to affect APP levels. This team of investigators explored these relationships further in a second study (Cook et al., 2003). In light of the possible association of IDE with late-onset AD and the evidence that APOE status may affect insulin metabolism, they hypothesized that the expression of the IDE gene may be altered in people with AD. To test this hypothesis, they measured the expression of IDE in hippocampal tissue from the brains of individuals who were cognitively healthy and others who had AD. They found that the hippocampal IDE protein was reduced by about half in those with AD who carried the APOE- ϵ 4 allele compared to the participants with AD who did not carry the APOE- ϵ 4 allele or to cognitively healthy participants. These findings show that reduced IDE expression is associated with APOE- ϵ 4 and suggest that IDE may interact with APOE- ϵ 4 status to affect beta-amyloid metabolism. Consistent with these findings, scientists at the University of California at Los Angeles found that deficient insulin signaling correlated with reduced IDE in the brains of people with AD, as well as in the brains of a mouse model of AD. The authors hypothesize that enhancing the effects of

insulin in the brain may reduce amyloid accumulation and is a promising strategy to pursue against AD (Zhao et al., 2004).

Studies of chromosome 10 also are allowing scientists to explore another intriguing aspect of AD—age of onset. A research team at Duke University Medical Center began their study by focusing on a region of chromosome 10 that earlier



studies suggested contained an area that influenced age of onset for both AD and Parkinson's disease (Li et al., 2003b). This chromosomal region contains a large number of genes, however, so the investigators established a novel approach called "genomic convergence," which allowed them to reduce and prioritize the number of candidate genes in the chromosome 10 region. By combining three independent but complementary lines of evidence, the team found four genes that mapped to a region of chromosome 10 that appeared to be important to the age of onset. These genes were expressed differently in people with and without AD. Though these findings are potentially valuable, additional studies must be conducted to determine whether, in fact, these genes do affect age of onset.

Other scientists have focused on chromosomes 12 and 19. In one study, conducted collaboratively by scientists from NIA and Celera Diagnostics of Alameda, California, the researchers examined regions of chromosomes 12 and 19 from three separate sample sets that included people with and without AD (Li et al., 2004). The researchers found that SNPs in the glyceraldehyde 3 phosphate dehydrogenase (GAPD) gene family were significantly associated with AD risk in all three sample sets. They also found that some GAPD SNPs on chromosome 12 were associated with an age of onset of 75 years and older, whereas some GAPD SNPs on chromosome 19 were associated with an age of onset of less than 75 years. Individually, the GAPD SNPs made different contributions to AD risk in each of the sample sets, and the investigators speculate that variants in functionally similar genes may account for this heterogeneity of AD risk.

Finally, knowledge gained from studying Down syndrome is revealing much about chromosome 21 and its possible role in AD. Most people have two copies of chromosome 21, but people with DS have three. Therefore, they have an extra copy of the APP gene. Every individual with DS who survives into his or her third decade develops the signature brain pathology of AD, although the location and distribution of these features are much more variable than in traditional AD. Research conducted by National Cancer Institute (NCI)-funded scientists demonstrates that those who survive into adulthood with DS also have a substantially increased risk of death from a number of causes, including cancer (Hill et al., 2003).

In recent years, DS has become a “natural model” for studying how AD develops and progresses. For example, several teams of scientists funded by the NICHD have attempted to find the genes on chromosome 21 that contribute to the development of dementia in individuals with DS and to understand the implications of these changes for the level of gene expression on normal brain development and maturation. At least 10 genes on chromosome 21 are involved in brain structure or function, but investigators have implicated only three of these genes to date in DS. Researchers at the University of Arkansas for Medical Sciences, Little Rock; the University of Connecticut, Farmington; and the Instituto de Médica in Córdoba, Argentina, are studying various aspects of these alterations in gene expression and the pathways these genes influence. Findings from these studies will help them understand why dendrites develop abnormally in infants with DS and will help them learn more about amyloid plaque formation and neuronal decline and death in middle-aged people with DS.

The University of Arkansas researchers discovered that in adults with DS, neuronal loss is dramatic and the plaques that develop are consistent with those found in AD (Mrak and Griffin, 2004). The researchers were able to demonstrate that two chromosome 21-based gene products—APP and S100B—are involved in these neuronal changes. S100B, which is over-expressed throughout the lifetime of people with DS, has been implicated in beta-amyloid plaque formation and correlates with the AD pathology that people with DS begin to experience as young adults. They also found that a protein called IL-1 (an inflammatory protein),

which is not found on chromosome 21, is also over-expressed throughout life in people with DS. IL-1 increases expression of APP and S100B and drives numerous processes that contribute to the development of late-onset and DS-related AD.

Another genetics area of great interest to investigators is APOE- ϵ 4, the risk factor gene found on chromosome 19. A number of recent studies have shed additional light on the role of this APOE allele in AD. For example, studies using PET scans have found that people with AD have abnormally low rates of glucose metabolism in certain areas of the cerebral cortex (the outer layer of neurons in the brain that controls conscious thought, mental activity, and voluntary movement, and that processes sensory information from the outside world). Building on earlier PET studies that showed that cognitively healthy older carriers of the APOE- ϵ 4 allele had abnormally low rates of glucose metabolism in those same brain regions, investigators at the Banner Good Samaritan Medical Center in Phoenix, Arizona, examined whether this was true for relatively young adults as well (Reiman et al., 2004). The investigators performed PET and MRI scans and conducted neuropsychological tests on 24 healthy participants, 12 of whom were APOE- ϵ 4 carriers and 12 were not. The two groups did not differ significantly in gender, age, educational level, neuropsychological test scores, or other characteristics. Results of this study were consistent with previous studies in that the researchers found that APOE- ϵ 4 carriers had abnormally low rates of glucose metabolism in the selected brain regions. This study is important because it documents the earliest brain changes yet seen in living persons at risk of AD. These results also provide evidence that AD-like changes in the brains of APOE- ϵ 4 carriers can occur in cognitively

healthy young adults. Tracking brain and cognitive changes over time will be necessary to determine how this pattern of AD-like brain changes relates to the likelihood that APOE- ϵ 4 carriers will develop AD at a later age. If these functional brain changes are eventually validated as an early predictor of AD, very early intervention and treatment will become a possibility.

Another study from the same group compared memory decline and new learning in APOE- ϵ 4 carriers and noncarriers aged 48 to 77 over a 2-year period. These investigators and colleagues from several other research

sites in Arizona found that APOE- ϵ 4 carriers aged 60 and older showed a decline in new learning as compared with noncarriers (Baxter et al., 2003). No difference in cognitive performance was seen in those younger than 60 years old. These findings suggest that repeat testing of new learning over time may be a sensitive measure for detecting early cognitive changes in older people who are at increased risk of AD.

In a follow-up study with a larger group of participants and a longer study period, the Arizona researchers examined whether

Gene Analysis Provides a Window on Very Early Brain Changes That Could Signal AD Development

Identifying changes in the activity level of genes in the brain over an organism's lifespan may implicate genes that protect brain health, as well as those that contribute to age-related brain disorders. Similarly, gene expression related to critical behaviors, such as learning and memory, which change with normal aging and age-related disorders, might point to sites for possible therapeutic interventions. One way to look for gene expression that changes with age and with cognitive impairment is to use a powerful new technology called a gene microarray analysis. In this type of analysis, thousands of genes are quickly screened to detect expression changes in cells or pieces of tissue. Two recent gene microarray studies show the potential of this technology.

In the first study, Harvard Medical School investigators conducted a gene microarray analysis of one brain region—the frontal cortex—from individuals ranging in age from 26 to 106 (Lu et al., 2004). The profile

showed that a set of genes with reduced expression after age 40 could be identified. These genes play key roles in the healthy functioning of synapses, neuronal transport, and mitochondrial function. In the older individuals, the investigators also found increased expression of genes that mediate stress responses, inflammatory or immune responses, antioxidants, and DNA repair. In particular, they found that DNA damage to the regulatory regions of certain genes was markedly increased in the cortex by age 40 and was prominent by age 70. The regulatory regions of the same genes were selectively damaged by oxidative stress in human neurons in tissue culture.

In the second study, scientists at the University of Kentucky College of Medicine grappled with a fundamental challenge posed by gene microarray studies—how to analyze the enormous amounts of data gathered in order to obtain useful and reliable information. The investigators used a sophisticated, statistical approach to validate data on gene

expression patterns in rat hippocampal tissue (Blalock et al., 2004).

Based on the pattern of changes in gene activity related to aging and cognition revealed by the microarray analysis, the investigators were able to suggest a model of brain aging in which loss of neuronal processes and other changes in nerve cells fuel brain inflammation, eventually leading to impaired neuronal function and cognition. Again, most of the gene expression changes became apparent in mid-life, at a time when cognition was not impaired, suggesting that changes in gene activity in the brain in early adulthood might initiate cellular or biological changes that could lead to functional changes later in life.

As more microarray studies of aging and AD are published, common features of gene expression changes will be found. Insights from these studies will advance our understanding of the molecular basis of normal brain aging and may point to ways in which people can make the most of their brain function to enhance healthy aging.

memory loss could be detected in carriers of APOE- ϵ 4 before the onset of amnesic MCI (Caselli et al., 2004). The cognitive abilities of a group of 212 cognitively healthy middle-aged to older adults were evaluated over approximately 33 months. In this study, the investigators did find that APOE- ϵ 4 carriers older than age 50 showed a modest decline in a number of memory skills compared to noncarriers of the same age, but they detected no differences in language, spatial skills, or executive functioning. As with the other studies,

A group of investigators from the Cache County Study has reported on recent genetic findings about whether AD is an inevitable consequence of aging (Khachaturian et al., 2004). The Cache County Study, a long-term study of 5,000 people in Cache County, Utah, provides a unique perspective on AD because the participating population is one of the longest lived in the United States. It includes about 700 individuals older than 85 and almost 250 who are 90 years old and older. This aspect of the study allowed the investigators

Discovering the genetic or environmental factors responsible for AD is clearly a high priority for future research.

to explore one AD puzzle: We know that the risk of AD increases with age, but we don't know much about the proportion of people who would be likely to get AD over an extended life-

the authors emphasize that more work is needed before the relationship, if any, between memory decline and MCI or AD can be determined.

Other investigators have looked at the occurrence of APOE- ϵ 4 across a number of neurodegenerative diseases. A research team from the Mayo Clinic in Rochester, Minnesota, and Jacksonville, Florida, and the London School of Hygiene, assessed whether the presence of the APOE- ϵ 4 allele influenced the frequency of AD-like pathology in dementia with Lewy bodies, frontotemporal degeneration, progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy (Josephs et al., 2004). They found that this allele strongly influenced the occurrence of AD-like damage in these diseases, particularly in dementia with Lewy bodies and multiple system atrophy. Further study is needed to find out why APOE- ϵ 4 appears to have a larger effect in these diseases than in others.

time, say 100 years, or about the effect of APOE- ϵ 4 over that time period. Using several types of analytic models, these investigators set out to estimate the risk of developing AD as a function of age and number of APOE- ϵ 4 alleles. The models estimated that 28 percent of individuals would not develop AD over any reasonable life expectancy. They confirmed that AD onset is accelerated in individuals with one, and especially two, APOE- ϵ 4 alleles, but did not see any meaningful difference in lifetime risk of developing AD related to number of APOE- ϵ 4 alleles. The authors concluded that this population contains individuals who are not susceptible to developing AD at an advanced age, regardless of which APOE allele they may carry. Discovering the genetic or environmental factors that are responsible for this resilience is clearly a high priority for future research.

Finally, scientists have used a genetics approach to examine late-life depression, a condition that is often associated with cognitive impairment and is a risk factor for

the development of dementia and AD. To determine whether the presence of APOE- ϵ 4 could explain the linkage of this form of depression with dementia, University of Pittsburgh investigators funded by NIMH and NIA analyzed how frequently the different forms of APOE occurred in patients with depression compared to healthy older adults and people with AD (Butters et al., 2003). As expected, APOE- ϵ 4 occurred more frequently in individuals with AD. However, the frequency of APOE- ϵ 4 was not higher in those with depression compared to the healthy study participants. APOE- ϵ 4 frequency also did not differ among depressed participants with and without accompanying cognitive impairment. Unexpectedly, the onset of depression occurred at a younger age for APOE- ϵ 4 carriers compared to noncarriers. These results indicate that APOE- ϵ 4 is associated with the age of onset of late-life depression, but not cognitive functioning in that condition. Further studies will be required to elucidate the avenues through which late-life depression may contribute to the onset of AD.

Lifestyle and Dietary Patterns

The possible impact of environmental and lifestyle factors, such as intellectually stimulating activities, physical activity, and diet, on AD risk is becoming an increased focus of research. A number of studies over the past few years have provided intriguing hints that these factors may be linked to a reduced risk of AD, and they are consistent with what we know about other benefits associated with health-promoting behaviors throughout life. It is important to note, however, that these factors have been identified in observational and animal studies, and at present, they are only associated with changes in AD risk. Only further research, including clinical trials, will reveal whether, in fact, these factors can help prevent AD.

Recent studies have looked at these environmental and lifestyle issues from various aspects. For example, researchers from the Rush ADC found reduced AD risk among participants in a Chicago Health and Aging Project study who consumed fish frequently and whose diet was high in unsaturated, unhydrogenated fats (Morris et al., 2003a; Morris et al., 2003b). In this CHAP study, complete dietary intake and disease diagnosis data were available on 815 people, and the length of follow-up between dietary assessment and clinical evaluation was about 2.3 years. CHAP investigators found that participants who consumed one or more fish meals per week had a 60 percent reduced risk of AD compared to participants who seldom or never ate fish. People whose diets were higher in polyunsaturated and vegetable fats also had a reduced AD risk compared to those whose fat intake was predominantly saturated fats. Though these studies support other research showing health benefits related to fish and unsaturated fat consumption and provide some intriguing hints about AD, the authors caution that further studies are needed before dietary recommendations can be made based on a relationship to AD risk.

In another study, NIA-funded researchers used data from the Honolulu-Asia Aging Study to find out whether certain dietary antioxidant intakes could reduce oxidative stress and thereby reduce dementia risk (Laurin et al., 2004). This study of approximately 3,700 Japanese-Americans focused on possible relationships between vascular factors—such as blood





pressure, blood cholesterol, and inflammation—and the later development of dementias such as AD. The team found no association between risk of dementia and mid-life intakes of antioxidants such as vitamins E and C and beta-carotene.

A considerable amount of research also has been devoted to examining the role of educational attainment on AD risk. One recent study, conducted by investigators at Harvard Medical School, used data from the long-term Nurses' Health Study of 16,596 older female registered nurses to assess the relationship of educational attainment, husband's education, household income, and childhood socioeconomic status to cognitive function and decline (Lee et al., 2003). The study participants had an initial cognitive assessment in the

late 1990s and a second assessment about 2 years later. The investigators found that women with a graduate degree had substantially decreased odds of a low initial cognitive score and of cognitive decline over the 2 years compared to women with less education. The other measures of socioeconomic status considered in this study had little, if any, relation to cognitive function or decline in later life.

In the past few years, several research groups have attempted to link participation in leisure activities with a lower risk of dementia. However, the exact relationship remains unclear. Scientists do not know whether increased participation in leisure activities lowers the risk of dementia or whether people who later develop dementia participate less in leisure activities because they are already in the early phase of dementia, before symptoms are evident. Investigators from the Albert Einstein College of Medicine in New York City explored this issue in a group of 469 cognitively healthy people who were older than age 75 and still living in the community (Verghese et al., 2003). Over a period of about 5 years, 124 people developed dementia. Based on a statistical analysis, the investigators concluded that participation in leisure activities was associated with a reduced risk of dementia, even after adjusting for participants' initial cognitive status and after excluding participants with possible preclinical dementia. Controlled clinical trials are needed to explore this issue further and assess the protective effect of leisure activities on the risk of dementia.

In addition to these studies, which suggest an association between particular lifestyle factors and actual AD risk reduction, other research provides indirect indications that lifestyle factors may be related in some way to AD risk. For example, a recent collaborative study by investigators at the

University of Toronto and the University of California at Irvine 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, including vitamins E and C, and fruit and vegetable extracts could reduce age-related cognitive decline in dogs (Milgram et al., 2004). Dogs are a good model for studying AD because they can perform sophisticated and complex cognitive behaviors, their brains accumulate beta-amyloid plaques with age, and the degree of beta-amyloid deposition is related to the severity of cognitive decline. This study included both old and young dogs. Some received the fortified food and the enriched environment, some received one or the other enrichment, and some received neither. At the end of a year, the researchers tested the dogs on two learning tasks. Not surprisingly, the researchers found that the old dogs performed less well than the young dogs. However, the performance of the old dogs was improved by the fortified food and behavioral enrichment. The effects of the treatments were most evident in the dogs who received both interventions.

Accumulating evidence also suggests that being physically active may benefit more than just our hearts and waistlines. Research in animals has shown that aspects of both brain function and cognitive function improve with physical exercise. Several studies in aging adults have shown similar results. One study, conducted by researchers at the University of Illinois at Urbana-Champaign, used a form of MRI to measure changes in brain activity in healthy adults aged 58 to 78 before and after a 6-month program of brisk walking

(Colcombe et al., 2004). The researchers found that the function of neurons in key parts of the brain increased along with improvements in the participants’ cardiovascular fitness. Compared to a physically inactive group, the walkers were able to pay attention better and focus more clearly on goals while disregarding unimportant information. Scientists working in this area speculate that physical activity may be beneficial because it may improve blood flow to the brain. Another possibility under investigation is that physical activity triggers cellular mechanisms that protect the brain from damage and promote its repair.

Vascular Disease and AD

In recent years, a number of studies have suggested that vascular diseases—heart disease and stroke—may contribute to the development of AD, the severity of AD dementia, or the development of multi-infarct dementia (a type of dementia that

Accumulating evidence suggests that being physically active may benefit more than just our hearts and waistlines.

results from multiple strokes). If this is true, it may have great scientific importance for two reasons. First, it may help investigators understand the origins of AD by encouraging them to focus attention on particular aspects of damage to the brain, such as microscopic strokes. Second, new avenues for preventive or delaying strategies may be possible if it becomes clear that modifiable risk factors for vascular disease (such as high cholesterol and high blood pressure) also are risk factors of AD or of degree of dementia.

Recently, five research teams working in separate large-scale epidemiologic studies explored whether vascular disease affects the likelihood of developing AD:

- Using data from the Washington Heights-Inwood Columbia Aging Project, a study of aging and dementia in New York City that includes 1,766 Medicare recipients, investigators found that the risk of AD was 60 percent higher in individuals with a history of stroke compared with individuals without such a history (Honig et al., 2003). The risk of AD was particularly great if hypertension, type II diabetes, or heart disease also was present.

- Boston University School of Medicine researchers working on the long-standing Framingham Study studied a group that had not had a stroke and did not have dementia (Ivan et al., 2004). The researchers found that those participants who went on to have a nonfatal stroke were twice as likely to develop dementia as those who did not experience a stroke. This finding underscores the importance of stroke prevention in reducing the possible risk of dementia.

- A group of scientists analyzed data from the University of Washington/Group Health Cooperative Alzheimer's Disease Patient Registry and found that people with the same level of cognitive decline in AD who also had vascular damage had less severe AD pathology in brain tissue than those with AD alone (Riekse et al., 2004). These findings suggest that cerebrovascular disease may act to increase the severity of the cognitive impairment in people with AD.

- An analysis of data from the Honolulu-Asia Aging Study showed that high blood pressure during mid-life increased the risk of dementia later in life.

Study participants who had high diastolic blood pressure, but who were never treated for hypertension, had an increased risk of atrophy in the hippocampal region of the brain (Korf et al., 2004). The authors suggest that early treatment of hypertension may reduce this risk.

- Finally, researchers at the Rush ADC and Rush Institute for Healthy Aging in Chicago, conducted a long-term clinical and pathology study as part of the ongoing Religious Orders Study (Schneider et al., 2004). These scientists found that brain infarction (a stroke occurring in blood vessels in the brain) and AD pathology each contributed to an increased likelihood of dementia. In particular, the odds of developing dementia increased nearly three-fold if evidence of one or more brain infarctions was present. Brain infarctions and AD pathology contributed jointly to a greater risk of developing dementia than would be indicated by either condition alone.

Since 1988, the National Heart, Lung, and Blood Institute has funded the Cardiovascular Health Study (CHS), a long-term study of risk factors for the development and progression of coronary heart disease (CHD) and stroke in elderly adults. This study has provided valuable data about the relationships between cardiovascular risk factors and AD, and it includes cognitive decline and dementia related to vascular disease as a key element of its design. One of the distinguishing features of the study has been add-on components funded by other NIH Institutes, including NIA. These add-ons have provided a cost-effective opportunity for investigators to use existing study populations to explore issues that were not part of the original study design. In the past 2 years, CHS study investigators from the University of Washington and the University of Pittsburgh have made several advances important to AD research. These

studies have laid the groundwork for future examinations of the interactions between cerebrovascular risk factors, AD, MCI, and dementia:

- The researchers have developed a methodology for conducting long-term dementia evaluations (Lopez et al., 2003a). In 1991, they conducted MRIs on approximately 3,600 CHS participants. This large and diverse study population is a particular strength of the CHS. This same group of participants received cognitive function evaluations every year thereafter, and, from 1998 to 2000, they also were evaluated for dementia through detailed neurological and neuropsychological exams. Not only was this the largest-ever study of dementia to include cognitive testing, MRI, and examination of genetic markers, but it provides a methodology that other researchers can use to study dementia in large groups.

- The investigators assessed the incidence of dementia, vascular dementia, and AD across the CHS population who had received the MRIs (Fitzpatrick et al., 2004). There was no indication of sex or racial differences, but strong associations with education and APOE- ϵ 4 status were apparent. Compared with results from other studies, the incidence of vascular dementia was higher than expected.

- Investigators found that particular measures of cognitive function, APOE- ϵ 4 status, and brain tissue characteristics as seen on MRI were strong predictors of both dementia and AD in the CHS population (Kuller et al., 2003).

- The research team found that 22 percent of the participants aged 75 or older had amnesic MCI. Most of these people

had other health problems as well, which affected their cognitive function (Lopez et al., 2003b). The research team also discovered that the people who developed this form of MCI were more likely to suffer from depression, be African-American, have a relatively low educational level, carry the APOE- ϵ 4 allele, or have cerebrovascular disease (Lopez et al., 2003c). Presence of the APOE- ϵ 4 allele was linked only to amnesic MCI. Though these findings are

The Cardiovascular Health Study has provided valuable data about the relationships between cardiovascular risk factors and AD.

intriguing, additional research is necessary to determine exactly how these factors are associated with MCI risk.

In collaboration with NIA researchers, a group of scientists at the University of California at San Francisco took a somewhat different look at vascular risk factors and the risk of cognitive decline (Yaffe et al., 2004a). These researchers wanted to determine whether an earlier stage of the cardiovascular disease process—metabolic syndrome—increased the risk of cognitive decline. Metabolic syndrome, a constellation of factors that increases heart disease risk, includes abdominal obesity, high triglyceride levels, low HDL (“good cholesterol”) levels, high blood pressure, and insulin resistance (an impaired ability to use insulin). The researchers also wanted to see whether vascular inflammation—another heart disease risk factor—modified possible associations between metabolic syndrome and cognitive decline. The investigators worked with participants of

the Health, Aging, and Body Composition study, a 1997 to 2002 study of 3,075 older adults living in Memphis and Pittsburgh. The researchers found that those participants with metabolic syndrome had an increased risk of cognitive impairment and decline, even adjusting for other demographic and lifestyle factors. The increased risk of cognitive impairment was seen primarily in participants who had high levels of inflammation markers in their blood. This suggests that at least some of the increased risk associated with metabolic syndrome is caused by inflammation. Though these results are consistent with the findings of other studies, further research is clearly needed to determine whether reducing risk factors for cardiovascular disease or lowering inflammation can reduce the risk of cognitive impairment in older adults.

Another aspect of heart disease risk that has been of continuing interest to both heart disease and AD researchers is homocysteine. Previous epidemiologic studies have shown that elevated levels of this amino acid, which is a risk factor for heart disease, are associated with an increased risk of developing AD. Basic science studies have shown that high homocysteine levels make some neurons vulnerable to dysfunction and death and that an enzyme called betaine-homocysteine methyltransferase (BHMT) may play a major role in regulating homocysteine levels in the blood. However, little is known about the properties of BHMT and the extent to which genetic variations in the enzyme might contribute to abnormally high levels of homocysteine. University of Illinois scientists funded by NIDDK have been trying to fill these knowledge gaps and recently found that BHMT functions only when it is in a certain structural form

(Szegeedi and Garrow, 2004). Additional studies will help to clarify the relationship between BHMT structure and function.

Diabetes and AD

The possible association of diabetes, insulin, and AD also is garnering increasing attention. Type II diabetes mellitus is a serious public health problem in the U.S. The condition affects about one in five people over age 65 and has been associated with a variety of adverse health effects. Evidence from a number of epidemiologic studies suggests a possible link between diabetes and cognitive impairment, and this has spurred researchers to examine this link on many levels, from test tube investigations to population studies. The idea behind this area of research is to determine whether or not diabetes is a risk factor for cognitive decline, and if so, whether therapies for diabetes may help lower risk of cognitive decline or AD.

One way that researchers are looking at the association between diabetes, cognitive problems, and AD is through epidemiologic studies. Recent long-term studies have linked diabetes to cognitive function in four distinct populations: Catholic nuns, priests, and brothers older than 55; female registered nurses aged 70 to 81; postmenopausal women with osteoporosis; and whites aged 42 to 89 years old and living in the community. In the first of these studies, conducted by investigators at the Rush ADC, participants of the Religious Orders Study underwent annual assessments of five cognitive “systems” that are commonly affected by aging, dementia, and AD (Arvanitakis et al., 2004). Over the 5.5-year study period, 151 people were diagnosed with AD, including 31 who had diabetes. An analysis of the study data revealed that the risk of developing AD was 65 percent higher in people with diabetes than in those who did

not have diabetes. The study also showed that diabetes appears to affect different cognitive systems differently, with the area of perceptual speed (the speed with which simple comparisons can be made) being most affected.

In the second study, investigators from the Harvard School of Public Health, working with participants in the Nurses' Health Study, found that women with diabetes performed worse on a range of

cognitive tests than did women without diabetes (Logroscino et al., 2004). The odds of cognitive difficulties were particularly high for those women who had had diabetes for a long time. Interestingly, women who were taking oral diabetes medications performed as well on the cognitive performance tests as did women without diabetes.

Researchers from the University of California at San Francisco investigated

Intriguing New Evidence about Lipids, Cholesterol, and AD

As we now know, the gamma-secretase enzyme complex is essential to APP metabolism and the formation of beta-amyloid (see p. 26 for more on gamma-secretase). However, new studies are showing that the milieu and place where the gamma-secretase functions may be just as important.

APP is cleaved in cholesterol-rich domains, also called "lipid rafts," which are found in the cell membrane of the neuron (Vetrivel et al., 2004). This fact is central to the thesis that cholesterol and ApoE (the principal cholesterol carrier in the brain and major risk factor for early- and late-onset AD) have direct roles in AD pathology.

Scientists are now speculating about whether disturbances in brain cholesterol could contribute to AD development and progression. Though knowledge in this area is growing, many questions remain about how cholesterol affects the processing of APP and formation of beta-amyloid.

Research in this area began with a study that showed that beta-amyloid deposits increased in the hippocampal neurons of rabbits fed a cholesterol-rich diet for

2 months. Since then, other studies using cells in culture and transgenic mice and guinea pigs, have confirmed and extended those experiments. Complementing this work, other studies showed that when AD transgenic mice were given a certain statin drug, not only did their blood cholesterol levels decrease, but levels of toxic beta-amyloid in the brain were significantly reduced (Petanceska et al., 2003). Importantly, two other studies pointed to a decreased incidence of AD and dementia in individuals with coronary artery disease who were treated with statins. Clinical trials testing statins in AD progression are underway, and those results should allow for definitive recommendations concerning the use of statins against AD (see p. 57 for more about one such trial).

Basic research is being conducted to answer a key question: How does cholesterol alter beta-amyloid production? Recent work by a team of NIA investigators may provide some clues. These experiments measured amounts of different lipids in brain cells from people with AD and healthy older people. The investigators found much higher

levels of cholesterol in the brain cells from the people with AD. They also found a lipid called ceramide specifically in brain regions important for learning and memory. These lipid abnormalities were associated with increased damage to nerve cells caused by free radicals (Cutler et al., 2004).

When the investigators exposed other neurons to beta-amyloid, similar increases in cholesterol and ceramide occurred. The lipid abnormalities were prevented, and the neurons were protected from beta-amyloid toxicity when they were treated with the antioxidant vitamin E or a drug called ISP-1, which prevents the accumulation of ceramide.

These findings suggest a sequence of events that causes degeneration of nerve cells in AD: Beta-amyloid induces oxidative stress, resulting in disturbed ceramide and cholesterol metabolism. This disturbance, in turn, triggers a neurodegenerative cascade that leads to clinical disease. Although additional studies are clearly needed, these findings also suggest that diets and drugs that target lipid abnormalities may someday help in preventing and treating AD.

whether diabetes and impaired fasting glucose (IFG, an indicator of increased diabetes risk) were linked to cognitive function (Yaffe et al., 2004b). The data for the study came from the Multiple Outcomes of Raloxifene Evaluation (MORE), a long-term osteoporosis study of more than 7,000 women between the ages of 31 and 80 (see p. 61 for information on MORE). The investigators found that the cognitive abilities of women with IFG were lower than those of women with normal blood glucose levels but higher than those with diabetes. They also found a higher risk of developing cognitive impairment among the women with IFG or diabetes than among the women with normal blood glucose levels.

Another University of California at San Francisco team of researchers examined the change in cognitive performance over a 4-year period among older adults participating in a study called the Rancho Bernardo Study (Kanaya et al., 2004). Participants, who were divided into three groups—normal glucose tolerance, impaired glucose tolerance, and diabetic—were given three different cognitive tests at the beginning of the study and again 4 years later. The researchers found that scores on all three cognitive function tests did not differ across the groups at the beginning of the study, but that the women with diabetes had a more rapid decline in performance on the verbal fluency test over the study period compared with women in either of the other two groups.

These findings are complemented by additional epidemiologic research conducted by researchers from the Mt. Sinai School of Medicine and Israel's Tel Aviv University and Sheba Medical Center (Schneider Beer et al., 2004). These investigators, working with more than 10,000 male participants in



the Israeli Ischemic Heart Disease study, also found evidence of diabetes as a risk factor for dementia. In contrast to other studies, however, these researchers linked diabetes in midlife to dementia that emerged more than 35 years later in very old members of the study group.

An analysis of data from the Honolulu-Asia Aging Study provides intriguing evidence about the possible associations between insulin levels and dementia risk (Peila et al., 2004). These data showed that increasing levels of insulin in the blood were associated with an increased risk of dementia. Too-high insulin levels can be controlled through dietary changes and increased physical activity, so this may be a modifiable risk factor if future research confirms these findings.

Other researchers, such as one team from New York University School of Medicine, are studying diabetes and cognition through studies with animals and small numbers of individuals (Convit et al., 2003). We know that age is a risk factor for both impaired cognition and impaired glucose metabolism, and a relationship between these deficits is suspected. It is not clear, however, how poor glucose metabolism may exert its effect on memory function. One

possibility is through the hippocampus, the brain structure that is important for learning and memory and is one of the earliest regions damaged by AD. Rodent studies have shown that during performance of a memory task, the hippocampus is activated, and hippocampal glucose levels drop in specific locations depending on the difficulty of the task. In older rodents, the drop in hippocampal glucose levels is more profound and lasts longer, perhaps forming a basis for impairments in memory performance seen in some older animals. Because of this vulnerability, subtle metabolic insults may lead to damage and volume loss. Using these findings as a starting point, the New York University investigators conducted memory tests with 30 nondiabetic middle-aged and older individuals who did not have dementia. Simultaneously, they administered a glucose tolerance test to measure the participants' ability to regulate glucose. The size of the hippocampus and other brain regions was measured with MRI. A decreased ability to regulate glucose was associated with decreased general cognitive performance, memory impairments, and atrophy of the hippocampus. This association was not related to the participants' ages. The investigators also found no association between the volume of other brain regions and glucose regulation. They concluded that a decreased ability to regulate glucose is associated with modest impairments of memory and that the impairments may be the result of a direct impact of poor glucose metabolism on brain structures important for memory. Based on these findings, the researchers suggest that memory deficits among older people with poorer glucose tolerance may be caused by an inability to compensate for the drops in hippocampal glucose levels that normally occur with activation of brain circuits during performance of a memory task. Perhaps better lifetime management of blood sugar

may help maintain memory function in old age and perhaps even reduce the risk of hippocampal damage.

What Can be Done to Slow the Progression of AD or Lessen its Effects?

The research advances described in the two previous sections of this report have vastly increased our understanding of brain function, the transformation from healthy aging to AD, and the factors that influence the development of AD. These findings have opened doors to a range of potential therapeutic approaches being investigated in various ways by NIA, other NIH Institutes, other research institutions, and private industry. Studies are underway on dozens of compounds and strategies to:

- Help people with AD maintain cognitive function over the short-term;
- Treat AD-associated behavioral and neuropsychiatric symptoms;
- Slow the progression of the disease; and
- Prevent AD.

As this report has shown, AD research has progressed to a point where scientists are increasingly able to think about how they can intervene to treat AD or perhaps even to prevent it. They think about the importance of timing—when is it best to intervene and what interventions are most appropriate at what time? For example, a physician would certainly provide different treatments to a patient who is having a stroke than to a patient who is seemingly healthy but at higher risk of having a stroke at some point in the future. AD develops over the course of years or decades, and a person's brain is affected well before any symptoms are evident. It may be that one

Recent Findings About Reproductive Hormones, Cognitive Health, and AD: An Illustration of the Scientific Process at Work

AD research advances over the past three decades would not have been possible without the various threads of scientific inquiry supported by NIH. These threads include population studies, basic research in laboratories, and studies in animals. Findings from these types of studies lay the foundation for clinical trials, in which interventions are tested for safety and effectiveness.

Sometimes, the process is straightforward—observations from population studies prompt researchers to investigate further in laboratory studies with tissue samples and laboratory animals. Positive findings from these studies lead to several rounds of testing in humans. At the end, an effective drug may come on the market.

Other times, the process is less straightforward—scientists experience setbacks at one stage or another and have to “return to the drawing board” to rethink their hypotheses or methods. Though these setbacks can be discouraging, they also are useful because they often raise issues that ultimately lead researchers down entirely new and fruitful scientific paths. Recent research that has explored associations between reproductive hormones and AD provides a good illustration of the scientific process at work.

Estrogen is a hormone produced by a woman’s ovaries during her childbearing years. It has widespread effects in the brain and affects neurotransmitter systems and brain regions involved in learning and memory. Over the past 25 years,

laboratory and animal studies and observational studies in populations have suggested that estrogen has positive effects on cognitive function. These findings led to two large clinical trials. The Women’s Health Initiative Memory Study (WHIMS) began in 1995 and was designed to study whether hormone therapy would decrease the risk of developing dementia in older women, years after menopause. As a sub-study of the Women’s Health Initiative (WHI), it was stopped when scientists found that WHI participants on hormone therapy were at increased risk of heart attacks, breast cancer, strokes, and blood clots, compared to participants on placebo. Women taking the hormone treatments also had twice the risk of dementia, rather than a decreased risk, as hoped.

Despite this setback, a number of NIA studies continue to support the idea that estrogen may have a positive effect on the brain and is one avenue for maintaining healthy cognitive function. As scientists plan research to explore this issue further, they are asking many questions to guide their new thinking:

- **Timing:** When in a woman’s life is it best to begin hormone therapy? How long should it be used?
- **Administration:** Should it be taken continuously over time or in ways that more closely mirror natural hormone fluctuations? Should high or low doses be taken? What is the best way to deliver the hormones—a pill or a patch?
- **Type:** Can equine estrogen formulations be used in future studies or

should only human estrogen be used?

Researchers at NIA and others funded by NIA also have been exploring some preliminary findings about possible associations between testosterone levels in older men and AD risk. In the first observational study of its kind, investigators assessed the testosterone levels of 574 men, ages 32 to 87, who were participating in the Baltimore Longitudinal Study of Aging. Based on physical, neurological, and neuropsychological exams, 54 of the 574 men were diagnosed with AD (Moffat et al., 2004).

The research team found that for every 50 percent increase in the levels of testosterone freely circulating in the bloodstream, there was about a 26 percent decrease in the risk of developing AD. Although overall free testosterone levels fell over time, these levels dropped more precipitously in those men who later developed AD. In fact, at the end of the study, men who were diagnosed with AD, on average, had about half the levels of circulating free testosterone as men who didn’t develop the disease. In some cases, the drop-offs in free testosterone levels associated with AD were detected up to a decade before diagnosis.

Study authors speculate that circulating free testosterone may have a broad range of influences on the aging brain, but they also emphasize that these are early days yet. Considerable additional study is necessary before firm conclusions can be drawn about any possible role of testosterone in the development of certain types of memory loss and AD.

kind of intervention with a particular compound or approach may be most effective if it is applied well before any symptoms are evident. Other interventions may be most appropriate for use after AD is established.

Investigators are working to develop an array of options from which clinicians can choose. For example, developing new and better drugs and broadening the range of nondrug therapeutic approaches are critically important for those who already have AD because of the long-term nature of the disease and its high emotional and physical toll. Slowing the progress of the disease and alleviating psychiatric and behavioral problems could do much to delay or prevent institutionalization, maintain the dignity of people with AD, reduce physical and emotional stress on caregivers, and reduce the financial costs associated with the disease. Finding ways to prevent the disease altogether is an increasingly urgent priority because of the enormous impact of AD on our society. Scientists use clinical trials to pursue all of these goals.

Clinical Trials

Clinical trials, which compare a potential new treatment with a standard treatment or with a placebo, are the only way to determine whether a drug, other compound, or nondrug approach is effective. These complex and expensive studies involve hundreds or even thousands of people and are often conducted over a long period of time. Some clinical trials are focused 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 are focused on **prevention** strategies—using specific compounds to help people reduce the risk of developing AD in the future. The sections that follow

describe some of NIH's AD treatment and prevention clinical trials. Recruitment is ongoing for a number of these trials. For more information about the clinical trials described here and other trials, visit NIA's ADEAR Center website.

AD Treatment Clinical Trials

The NIH is currently supporting 22 clinical trials of treatments for people who already have AD. Many of these are conducted as part of the Alzheimer's Disease Cooperative Study, an NIA-supported national consortium of more than 50 research sites that conduct clinical trials for both cognitive and behavioral symptoms of AD. Here are highlights of just a few of these trials.

Divalproex sodium and agitation. An ADCS clinical trial of divalproex sodium (Valproate), conducted among 150 nursing home residents, was designed to see whether this medication could ease agitation in people with severe AD. Data from this study are being analyzed and results should be available before the end of 2005. A second trial that has recently begun will examine whether divalproex sodium can delay or prevent agitation and psychosis in individuals with mild to moderate AD. Researchers are also interested in seeing whether its possible neuroprotective properties have any effect on slowing the rate of cognitive decline.

Simvastatin and AD progression. This 18-month ADCS trial, which began in 2003, is testing whether simvastatin (Zocor), a commonly prescribed cholesterol-lowering drug, can safely and effectively slow the rate of disease progression in people with mild to moderate AD. Data from epidemiologic and animal studies indicate that high cholesterol levels increase the risk of AD and that statin

drugs specifically may help reduce this risk. The trial, which is being conducted in about 40 sites nationwide, will enroll 400 participants. To date, 350 people have been enrolled and recruitment of participants continues. Some participants will receive 20 mg of simvastatin for 6 weeks and then 40 mg of the statin for the rest of the study period. Others will receive a placebo during the entire study. Clinical trial staff are tracking changes in participants' cognitive health by measuring a number of indicators, including mental status, functional ability, behavioral disturbances, and quality of life.

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 performed better on memory tests than those on placebo. Investigators also are interested in huperzine because it has antioxidant and neuroprotective properties that suggest it may be useful in treating AD. The study, which will enroll 150 participants, is taking place at about 20 sites nationwide, and recruitment is ongoing. Participants will be 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. All participants will receive huperzine A during the last 8 weeks of the 24-week trial.

Supplements to reduce homocysteine and slow the rate of cognitive decline.

High homocysteine levels are associated with increased AD risk. Levels of this

amino acid can be reduced by high-dose supplements of folate and vitamins B6 and B12. This ADCS clinical trial, which began in 2003, is designed 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 were divided into two groups: 60 percent of participants will receive daily high-dose supplements (5 mg of folate, 25 mg of vitamin B6, 1 mg of vitamin B12) and 40 percent will receive a placebo. Enrollment of the 400 participants has been completed.

Sertraline to treat 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. NIMH-funded researchers at Johns Hopkins University are conducting a clinical trial to assess the efficacy and safety of the antidepressant medication sertraline (Zoloft) for the treatment of major depression in AD (Lyketsos et al., 2003). The trial is still ongoing, but preliminary results from 44 participants indicate that sertraline reduced depressive symptoms in 84 percent of those treated. In contrast, depressive symptoms were reduced in 35 percent of those treated with a placebo. Participants taking sertraline also experienced a lessening of behavioral disturbances, such as apathy, anxiety, or irritability, and improvements in activities of daily living, such as bathing, dressing, and feeding. Their cognitive functions did not improve, however. The research team is continuing this trial with other groups of people with AD in hopes that similar treatment with antidepressant medication can benefit those with milder depression or with differing profiles of depressive symptoms.

Atypical antipsychotics to treat psychosis in AD. NIMH-funded investigators at the University of Southern California Keck School of Medicine have recently completed a clinical trial called the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Schneider et al., 2003). This trial was designed to assess the effectiveness of atypical antipsychotic drugs for use in people with AD who experience hallucinations, delusions, or agitation. These symptoms are very common in people with AD, and they can be very distressing to caregivers. The trial ended in October 2004, and publication of results is underway.

AD Pilot Treatment Trials

Before beginning a full-scale clinical trial, NIH Institutes often conduct pilot clinical trials to collect initial data on the safety, effectiveness, and best dosage of a potential treatment. These data help the Institutes determine which interventions should go to the next step. Here are highlights of a few current pilot clinical trials in AD:

Combination vitamin supplement in the treatment of AD in Down syndrome. This high-potency supplement consists of two cellular antioxidants (vitamins E and C) and a mitochondrial antioxidant (alpha-lipoic acid). The aims of this 24-month intervention trial are to determine whether cognitive function improves with antioxidant supplementation and to determine its safety and tolerability.

Nicotine skin patch and amnesic MCI. Some of the 60 participants in this study will be given the nicotine patch and others a placebo patch. Research has suggested that one of the causes of memory disorders may be a reduction in the neurotransmitter acetylcholine. Acetylcholine is critically important in the process of forming memories, and 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 to the non-smoking amnesic MCI participants over a 1-year period. Study investigators also hope to determine whether nicotine can improve memory loss symptoms over the longer term and whether it can help delay the progression of memory loss symptoms.

Rosiglitazone and amnesic MCI. This 18-month clinical trial will test whether rosiglitazone (Avandia), a drug that has anti-inflammatory properties and that improves sensitivity to insulin, can improve memory in people who have amnesic MCI. Epidemiologic studies indicate that people with insulin resistance are at increased risk for both MCI and AD. Insulin resistance also is associated with inflammation, which

may increase AD risk through several mechanisms. These findings provide the rationale for this novel treatment strategy. Study participants will be divided into two groups—one group will receive the 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 biomarkers in MCI with memory loss.

AD Prevention Trials

NIH is currently conducting seven AD prevention clinical trials. Although two of these trials have been suspended, investigators are still periodically assessing the participants' health.

People With Early AD Can Still Learn

The extent to which people with early-stage AD can learn new information and use it to perform daily tasks is not clear, and this is an area of vital importance to people with AD and their families.

Cognitive rehabilitation strategies have been shown to improve performance on memory and other cognitive measures in other brain disorders, such as traumatic brain injury and stroke, and some of these same techniques have shown promise in their ability to enhance learning in people with AD. However, until now, no systematically applied cognitive rehabilitation program for people with AD has incorporated all the techniques available.

In a clinical trial at the University of Miami Medical Center/Mt. Sinai Medical Center, in Miami Beach, 44 people with AD were randomly assigned into two groups (Loewenstein et al., 2004). All participants in the study were taking donepezil (Aricept) or similar medications. The 25 people in a "cognitive rehabilitation" (CR) group participated in two 45-minute sessions weekly for a total of 24 sessions. During these sessions, they learned face-name recognition techniques, such as associating a

prominent facial feature with a name. To enhance time and place orientation, CR participants were given memory notebooks and encouraged to record appointments, medication schedules, and contact information for relatives, friends, and doctors. They also were taught effective ways to make change for a purchase and were asked to use a calculator to balance a checkbook after paying three bills. In addition, they learned to click a mouse button in response to yellow boxes that randomly appeared on a computer screen. This technique was designed to improve attention span and cognitive processing speed. Finally, the CR group was asked to manipulate objects, such as a key, as though they were using them. Participants and their caregivers were encouraged to practice all of these techniques at home.

The 19 participants in a control "mental stimulation" (MS) group played computer games that required memory, concentration, and problem-solving skills. In addition, participants in this group were asked to discuss various topics, such as describing the neighborhood in which they grew up. They also were asked to do crossword puzzles, word scrambles, and other "homework" assignments.

At the end of the study, those in the CR group showed, on average, significantly improved ability to associate faces and names, had faster mental processing speeds, were better oriented to time and place, and were better able to make correct change for purchases than those in the MS group. However, neither group showed memory improvement for manipulating objects or balancing a checkbook. The improvements were still evident 3 months after the cognitive training ended.

This promising study suggests that some people with early cognitive impairment can still be taught to recall important information and to perform daily tasks better. It is the first trial to combine several specific cognitive memory techniques into a single rehabilitation program for those who are mildly impaired with AD. The study shows that people with early AD can learn, and that learning can be enhanced by using specific cognitive rehabilitation strategies. Thus, people with AD can be helped to remain engaged in daily activities and retain a connection to family, friends, and the world around them for a longer period of time.

Some prevention trials are exploring the potential of drugs and other compounds that already have been tested as treatments in people with established AD. Even when results have indicated that the compounds are not effective treatments for people who already have AD, enough laboratory, animal, and epidemiologic evidence exists to suggest that they may still have a potentially useful preventive function. Here are highlights from a few AD prevention studies.

The Multiple Outcomes of Raloxifene Evaluation. This clinical trial, conducted with nearly 5,400 postmenopausal women with osteoporosis, was designed to determine whether treatment with raloxifene (Evista), a selective estrogen receptor modulator (SERM) that is used to treat osteoporosis, affects the risk of developing AD and cognitive impairment (Yaffe et al., 2005). The women were divided into three groups: one group received a placebo, one group received 60 mg of the drug every day, and the third group received 120 mg daily. After 3 years of treatment, the 60 mg group and the placebo group did not differ. However, women who took 120 mg had a statistically significantly lower risk of developing MCI and a somewhat lower risk of developing AD and any cognitive impairment than did the women who took the placebo. Additional clinical trials are needed to confirm these results.

The Memory Impairment Study. Over the course of 3 years, this study compared the effectiveness of vitamin E, donepezil (Aricept), and a placebo in delaying the onset of a diagnosis of AD in 769 people with amnesic MCI. Results indicated that participants taking donepezil were at reduced risk of progressing to AD during the first 12 months of the study, but this benefit disappeared by 18 months

(Petersen et al., 2005b). However, in the subset of patients who carried the APOE- ϵ 4 allele, donepezil appeared to decrease the risk of progression to a diagnosis of AD for the full 36 months of the study. Vitamin E did not appear to slow the progression to AD. The investigators are conducting additional analyses to determine why donepezil's effect dropped off over time and to assess the practical and clinical implications of this complex study.

This landmark MCI trial, which took place in 69 sites in the U.S. and Canada, represents a major advance in clinical trial methodology, as it demonstrated that investigators could use standardized criteria in a multi-center trial to define and differentiate individuals with amnesic MCI, healthy people, and those with AD. Future clinical trials in people with this type of MCI should be instrumental in research to detect, treat, and delay AD (Grundman et al., 2004).

NSAIDs and inflammation. Some epidemiologic studies have suggested that NSAIDs might help slow the progression of AD, but clinical trials thus far have not demonstrated a benefit from these drugs. A clinical trial studying two of these drugs, rofecoxib (Vioxx) and naproxen (Aleve) showed that they did not delay the progression of AD in people who already have the disease. Treatment in another trial, testing whether the NSAIDs celecoxib (Celebrex) and naproxen could prevent AD in healthy older people at risk of the disease, was suspended after some participants showed indications of increased cardiovascular risk with long-term use of these drugs. Investigators are examining data about possible cardiovascular risk and continue to assess the participants' health periodically. However,

researchers are continuing to look for ways to test how other anti-inflammatory drugs might affect the development or progression of AD.

The Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADVISE) trial. This trial is NIA's add-on to NCI's Selenium and Vitamin E Cancer Prevention Trial (SELECT), which is evaluating whether taking selenium and/or vitamin E supplements can prevent prostate cancer in healthy men older than 60. PREADVISE is evaluating whether these agents can help prevent memory loss and dementia, such as that found in AD. Studies show that increased oxidative stress may damage brain cells and is linked with AD. Animal and tissue culture studies of vitamin E and selenium suggest that they can protect brain cells from oxidative damage.

Ginkgo biloba. Extracts of leaves from the ginkgo tree are thought to have beneficial effects on brain function, especially those related to dementia and AD. NIA is co-funding a National Center for Complementary and Alternative Medicine prevention trial comparing ginkgo to placebo in more than 3,000 people older than 70 who are cognitively healthy at the beginning of the trial. The study's results should indicate whether ginkgo is helpful in preventing or delaying the onset of dementia. As part of this trial, University of Pittsburgh investigators have used brain imaging techniques to determine whether cognitively healthy individuals and those with amnesic MCI show any differences in activation in specific parts of the brain that are normally related to an aspect of cognitive function called attentional control (Rosano et al., 2005). They have been able to detect

differences in activation in these brain regions between the two groups, and these changes are likely to be related to early changes in cognitive impairment.

Improving Support for Caregivers

Although much of NIH's AD research effort is focused on the causes, characteristics, diagnosis, and treatment of AD, researchers never lose sight of the enormous personal and emotional toll exacted by AD on those with the disease as well as their families, friends, and caregivers. Investigators supported by several Institutes, including NIA, NIMH, and the National Institute of Nursing Research (NINR) are exploring the emotional, psychological, and physical costs of caregiving, and they are investigating ways to ease the burden.

For example, it is well established that AD caregivers often experience stress, anxiety, depression, and other mental health problems as a result of the continuing and demanding nature of AD care. This chronic stress is known to have detrimental effects on caregivers' physical health. A research team at the University of California at San Diego explored this issue by assessing whether different emotional symptoms had different physical effects (von Kanel et al., 2004).

Working with a group of 48 older participants, the researchers found that although stress-associated depression and anxiety both raised the level of certain molecules in the blood that are associated with increased coronary risk, anxiety appeared to have a stronger effect than depressive symptoms. Having a more nuanced understanding of the effects of caregiving stress may inform the development of interventions to help caregivers cope with the daily stresses of caring for a loved one with AD.



study devoted to interventions that improve the mental health and well-being of AD caregivers. The Caregiver Core of the New York University ADC provided the infrastructure for this study. A total of 406 caregivers were enrolled in the study over its 17-year duration, and were divided into two groups. Half the caregivers, the control group, received counseling upon request. The other half, the enhanced treatment group,

A recent study, conducted by NINR-funded researchers at the University of Texas Health Science Center in San Antonio explored another aspect of caregiving stress by examining how male and female caregivers respond differently to the emotional and biological stresses of caregiving (Thompson et al., 2004). The researchers found that although the two groups of caregivers did not differ in the number of distressing caregiving experiences, men reported a lower sense of burden and a lower level of perceived stress than women. In addition, men had lower scores for depression, anxiety, anger, and physical symptoms, and higher scores for relaxation, social functioning, mental health, role performance, and sense of coherence. These findings point out the need for tailored caregiving support interventions that take caregivers' individual characteristics into account.

The emotional and psychological costs of caregiving are amenable to interventions, according to a recent study conducted by New York University School of Medicine scientists funded by NIA and NIMH (Mittelman et al., 2004). This study was conducted as part of the NYU-Spouse Caregiver Intervention Study, the longest

were given three additional types of counseling: two sessions of individual counseling, four sessions of family counseling, and weekly meetings with a support group of fellow caregivers. A key feature of the enhanced group was that each member was served by a single counselor for the duration of the study. After one year, nearly 30 percent of caregivers in the enhanced treatment group had symptoms of clinical depression, compared with more than 45 percent of those in the control group. Three years later, caregivers who received the enhanced care still had fewer symptoms of depression, on average, than those in the control group. This was true even for caregivers whose spouses moved to a nursing home or died, both of which are known to be highly stressful events for caregivers. Interestingly, many of the effects of the enhanced treatment were not felt immediately. The two groups of caregivers did not begin to show significant differences in their depression symptoms until a year after they enrolled in the study. The effects appeared to last for about 5 years; after that time, the level of depression in the control

and intervention groups became the same. The researchers note that the use of multiple types of coordinated therapy was one of the most important factors in decreasing depression among caregivers. Another important aspect of the study was that the counseling was tailored to the particular coping challenges that each caregiver and family were dealing with. These findings have important clinical implications because they offer evidence that the distress and depression experienced by family caregivers can be effectively eased and that the benefits can be sustained over a long period of time.

Up to now, research on family caregiving has generally focused on assessing the demands of providing care at home and developing interventions to reduce those burdens. Recently, an NIA/NINR-funded team of nurse researchers at the Rush University College of Nursing interviewed more than 170 caregivers to explore their concerns and identify best caregiving practices (Farran et al., 2003; Farran et al., 2004). Most caregivers said that they

felt stressed as they responded to changes, reevaluated their life goals and lifestyle, adapted to new roles, and faced competing demands from other family members, work, and outside responsibilities. Many caregivers admitted frustration about the limitations that caregiving placed on their own lives. The most sensitive and skillful caregivers learned to read the emotional and physical cues of the person with AD and understand the sequences that often led to inappropriate behaviors, and they responded to the needs of the person in a variety of creative ways. They also maintained their flexibility in the face of many demands, educated themselves about the disease and practical strategies, used their available resources, involved other family members and friends, and balanced the needs of the patient with their own needs. These findings could lead to the development of interventions to help caregivers cope with their stress and develop new caregiving skills.

In an effort to reduce the overall stress levels of caring for a person with AD at home, University of Minnesota researchers funded by NINR developed an innovative intervention that focused on changes in the home environment (Gerdner et al., 2002). Nurses taught care plans that emphasized changes in the home environment that would enhance safety, compensate for the cognitive decline of the person with AD, and reduce confusing stimuli. The impact of the intervention on the frequency of problem behaviors in care recipients and the home caregivers' reactions to these behaviors were then assessed. This psychoeducational intervention improved responses to the care recipient's memory and behavioral problems by both spouse and nonspouse caregivers.

More recently, some researchers have begun to focus on learning about transitions into and out of the caregiving role. A study conducted by University of Pittsburgh



scientists explored this issue by examining the experiences of caregivers when they place a relative into a nursing home or other care institution (Schulz et al., 2004). In particular, this study looked at the forces leading to the institutionalization, the frequency and types of contact among caregivers and their relatives, and the psychiatric and physical health status of caregivers after placement. Caregivers included in this study were enrolled in the NIA/NINR jointly-funded Resources for Enhancing Alzheimer's Caregiver Health (REACH) study, a multi-site clinical trial that is testing the feasibility of various psychosocial interventions and their impact on the health and well-being of family caregivers. The study found that many caregivers who placed their relative in care reported depressive symptoms and anxiety to be as high as when they were in-home caregivers. In addition, caregivers who said that providing help to their relative made them feel useful, needed, appreciated, and important were less likely to institutionalize their relative than were caregivers who did not report these feelings. The authors note that bereavement studies have shown that caregivers do recover after the death of their loved one, but the benefits to the caregiver of placing a relative into a care setting appear to be less positive, possibly because the caregiving role is not wholly relinquished after placement. Clearly, it is important to remember that caregivers are at risk for adverse health outcomes not only while providing care at home, but also after their loved one has been placed into a care setting.

REACH has recently published findings from a number of other caregiver studies as well:

- An assessment of the burdens of end-of-life AD care and the caregivers' response to the death showed how time-consuming and difficult this phase of caregiving can

be (Schulz et al., 2003). University of Pittsburgh investigators found that many participating caregivers were assessed as being at risk of clinical depression before the person's death, but that these numbers dropped significantly within a year after the death.

- An exploration of caregiving practices among African-American and white caregivers by scientists at the University of Alabama revealed that a majority of African-American caregivers were caring for a parent or other nonspouse family member, whereas most white participants were caring for their spouses (Roff et al., 2004). African-American caregivers also were younger and had a lower family income than the whites. Interestingly, the African-American caregivers reported finding more positive aspects to caregiving, had lower anxiety, a higher degree of religious faith, and were less bothered by the behavior of the person with AD than were whites. Examining the positive aspects of caregiving may provide useful lessons and new strategies for all caregivers.

- A 6-month follow-up evaluation of nine different REACH interventions involving more than 1,000 caregivers showed that the interventions were successful in helping lessen the perceived burden felt by caregivers, though only one intervention significantly reduced caregiver depression (Gitlin et al., 2003). One clear lesson from this evaluation, conducted by investigators at Thomas Jefferson University in Philadelphia, is that caregiver interventions need to target multiple aspects of caregiving and be tailored to the characteristics and circumstances of the caregiver.



Research in AD continues to move forward rapidly, bringing us ever closer to a full understanding of the causes of this devastating disease and to effective prevention and treatment strategies. Findings from basic science are unlocking the secrets of the disease process at a molecular level, involving beta-amyloid, presenilins, *tau*, and mitochondria, to name just a few. Findings from other types of studies are providing insights about possible risk and protective factors and ways to help caregivers cope as the disease takes hold in a loved one. Knowledge from these studies is giving scientists and clinicians increasing hope about the potential for new therapeutic agents and strategies.

Realizing these hopes for the future, however, requires action on a number of complementary fronts. In the past several years, the NIA, along with other NIH Institutes and Centers, the Alzheimer's Association, the Institute for the Study of Aging, and additional organizations, have launched several major initiatives to create and nurture the essential research infrastructure that will help NIH move from basic science to fully developed drugs and therapeutic approaches that can be tested in clinical trials and ultimately used to help people with AD.

Providing a Planning Framework

Two of these initiatives provide a critical framework for overall planning and support for AD and broader neurosciences research.

- NIA has partnered 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 methods of early detection and diagnosis, and advance basic science to understand AD. The Initiative also endeavors to improve patient care strategies and alleviate caregiver burden.

- NIA is an active member of the newly-established multi-institute **NIH Blueprint for Neurosciences Research**. This effort provides a framework to enhance cooperative activities among 15 NIH Institutes and Centers to reduce the burden of nervous system disorders, including AD.

Supporting a Collaborative Research Infrastructure

Two other initiatives provide venues and mechanisms for interdisciplinary and collaborative research on AD development and progression.

■ Many milestones in AD research in the U.S. since 1984 stem from resources provided by the **Alzheimer's Disease Centers**. NIA currently funds 32 ADCs around the country. Imaging, pathology, and clinical studies conducted in the ADCs are allowing investigators to correlate changes in brain structure and function with clinical evidence of disease. In recent



years, the Centers have placed increasing emphasis on evaluating cognitive function in healthy aging and the transition to 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 1999, NIA established the **National Alzheimer's Coordinating Center (NACC)** to provide a mechanism whereby data on patients from all of the ADCs could be pooled and shared. Eleven collaborative multi-Center studies have been funded by NACC and seven other collaborative investigator-initiated grants have been funded and are linked to NACC. The NACC now has information on more than 73,000 ADC study participants enrolled since 1984 and neuropathological data on 9,400 brains from participants autopsied in the ADCs. The data are accessible to Center scientists through NACC's website. NACC is now including more long-term data on ADC study participants and is working to define and standardize the clinical data elements that will be collected. This uniform data set became operational in September 2005. It is hoped that this effort will lead to better and more extensive research projects using standardized data collected from all Centers. New procedures have been adopted for widening access to the NACC database by non-Center scientists wishing to use the data.

Facilitating Innovation for the Future

An additional five efforts focus on particular aspects of AD or brain research, including neuroimaging, genetics, drug development and clinical trials, techniques for evaluating change over time in cognitive functioning, and healthy brain aging:

■ NIA has launched a multi-year **AD Neuroimaging Initiative**, which will use serial MRI and PET scans to examine how brains change as amnesic MCI and AD progress. The scans and other data and

biological samples from the Neuroimaging Initiative will be collected at about 60 clinical sites based in universities throughout the U.S. and Canada. The project will follow approximately 200 cognitively healthy individuals for 3 years, 400 people with amnesic MCI for 3 years, and 200 people with early AD for 2 years. Planning for the many interrelated facets of this initiative has been moving forward rapidly and enrollment has begun. 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 and neuropsychological assessments, and biomarkers 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. NIA hopes the Neuroimaging Initiative will help create rigorous imaging and biomarker standards that will aid in early diagnosis and provide the yardstick by which the success of future treatments can be measured. This would substantially increase the pace and decrease the cost of developing new treatments.

This landmark Initiative is a public-private partnership among government, industry, foundations, voluntary organizations, and academia. An important aspect of this Initiative is that the clinical, imaging, and biological data collected will be made available to qualified scientific investigators for further analysis. This emphasis on sharing data and resources

across research institutions will have an important beneficial impact on future research because it means that larger databases of information and samples of participants will be available. This expanded data will help increase the statistical power of studies and allow for analyses of small subpopulations and infrequent outcomes that wouldn't be possible otherwise.

■ Through the Alzheimer's Disease Cooperative Study—the Federal government's major mechanism for funding AD

Sharing data and resources across research institutions will have an important beneficial impact on future research.

clinical trials—another NIA initiative is focused on a critical “nuts and bolts” aspect of prevention clinical trials. **The Prevention Instrument Project** is developing sensitive and more effective methods for evaluating change over time in cognitively healthy elderly. Investigators involved in this project are focused on designing, developing, and testing new questionnaires and other instruments that can be used to test individuals in a number of areas, such as overall cognitive functioning, memory, ability to carry out activities of daily life, and quality of life. This study is comparing the results of evaluation instruments filled out by participants at home versus those done in the clinic to determine whether the home evaluations are equivalent to the clinic evaluations. If this proves to be the case, this innovation could

go far to reduce clinic visits and burden on participants and families, simplify and reduce the cost of clinical trials, and make recruitment and retention easier.

■ As AD genetics research has intensified, it has become increasingly clear that scientists need many more samples of genetic material if they are to continue making progress. NIA's **Genetics Initiative** is aiming to identify at least 1,000 families with members who have late-onset AD as well as unaffected family members, and is encouraging these individuals to provide blood samples and clinical data. The blood samples will allow investigators to create and maintain "immortalized" cell lines—cells that are continuously regenerated in

Shorter trials with fewer participants will allow investigators to be more effective in identifying and testing promising treatments emerging from basic science and translational studies.

the laboratory. These cell lines are crucial for the exhaustive DNA analysis studies needed to identify additional risk factor genes. The National Cell Repository for AD (NCRAD), located at Indiana University, serves as the centralized DNA and cell line repository for the Initiative.

Many families already have been recruited but more are needed. NIA has provided funding to the ADCs to help recruit additional study participants, and the ADEAR Center is collaborating with the Alzheimer's Association to develop media and community outreach programs to foster participation in this Initiative. Results will allow scientists to find new pathways affected in AD and help clinicians accurately identify and counsel people at high risk of developing the disease. Results also will help investigators recruit susceptible individuals into clinical trials, which will reduce the number of participants necessary and the cost and complexity of trials. Shorter trials with fewer participants will allow investigators to be more effective

in identifying and testing promising treatments emerging from basic science and translational studies. It also will contribute to future prevention strategies.

■ NIA's new **Translational and Drug Testing Initiative** aims to encourage researchers to move from purely basic research on AD and associated disorders into translational research and drug testing in clinical trials. This program is intended to expand the potential range of therapies that can be tested against AD and other aging-related diseases and age-related cognitive decline. The initiative provides small grants for research early in the drug development process and larger cooperative grants to move drugs through development up to approval by the FDA for clinical testing. Another component of the Translational

Initiative is the longstanding Investigational New Drug Toxicology program, which provides toxicology services to academic and small business investigators who believe they have promising compounds to treat or prevent AD but lack the resources to perform the required toxicology studies. This initiative also funds pilot clinical trials (see p. 59 for more on pilot clinical trials) as well as the ADCS and other clinical trials.

■ NIA, NINDS, and NIMH have joined efforts to launch the **Cognitive and Emotional Health Project: The Healthy Brain**, a new trans-NIH initiative. 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 are yielding promising results in animal and human studies, much remains to be discovered. Advances in understanding the positive and negative changes in cognition and emotion in adulthood, and what can be done to preserve and enhance positive outcomes, is central to the missions of the participating Institutes. The goal of the Healthy Brain 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.

As this report has shown, our knowledge about the many dimensions of AD is advancing rapidly, and the results of the initiatives described here will certainly accelerate new scientific discoveries. As we celebrate our scientific successes, however, we do not forget that AD remains an urgent problem for our Nation. Our challenge is to continue building upon the events and experiences of the past and present to create a brighter future in which the potential for successfully managing AD or even preventing it can become a reality for our older loved ones.





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