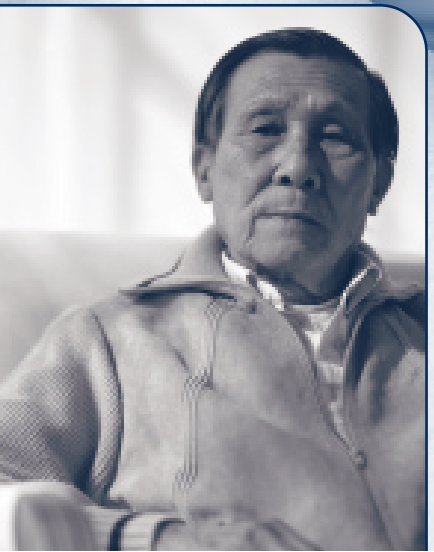
National Institute on Aging
National Institutes of Health



2001-2002
Alzheimer's Disease
Progress Report

The National Institute on Aging (NIA), part of the Federal Government's National Institutes of Health (NIH), has primary responsibility for research aimed at finding ways to prevent, treat, and cure Alzheimer's disease (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 2001-2002 Progress Report on Alzheimer's Disease summarizes recent AD research conducted or supported by NIA and other components of NIH, including:

- National Institute of Neurological Disorders and Stroke (pages 21, 27)
- National Institute of Mental Health (pages 10, 12, 15, 21, 30, 31, 39, 40)
- National Center for Research Resources (pages 11, 29, 38)
- National Human Genome Research Institute (pages 30, 31)
- National Institute of Environmental Health Sciences (pages 16, 19)
- National Institute of Child Health and Human Development (pages 21, 26)

Modest AD research efforts also are supported by the National Cancer Institute, National Institute of Nursing Research, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute on Alcohol Abuse and Alcoholism, National Institute on Deafness and Other Communication Disorders, National Center for Complementary and Alternative Medicine, National Center on Minority Health and Health Disparities, and the John E. Fogarty International Center.

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Part 1
Introduction

Alzheimer's disease (AD) is an age-related and irreversible brain disorder that develops gradually and results in memory loss, behavior and personality changes, and a decline in thinking abilities. These losses are related to the breakdown of the connections between nerve cells in the brain and the eventual death of many of these cells.

The course of this disease varies from person to person, as does the rate of decline. On average, patients with AD live for 8 to 10 years after they are diagnosed, though the disease can last for up to 20 years. AD advances progressively, from mild forgetfulness to a severe loss of mental function. In most people with AD, symptoms first appear after age 60. 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 Alzheimer's Disease

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 up to 4 million people currently have the disease, and the prevalence (the number of people with the disease at any one time) doubles every 5 years beyond age 65.

These numbers are significant now and will become even more so in the future because of dramatic increases in life expectancies since the turn of the century. Furthermore, the group over 85 – the group with the highest risk of AD – is the fastest growing group in the population. Researchers estimate that by 2050, 14 million Americans will have Alzheimer's disease if current population trends continue and no preventive treatments become available (Hebert et al., 2001).

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 are estimated to be as much as $100 billion (Ernst and Hay, 1994; Ernst et al., 1997; Huang et al., 1988).

GIVEN OUR AGING POPULATION, THE MAGNITUDE OF AD AS A NATIONAL HEALTH PROBLEM IS STEADILY INCREASING.

Alzheimer's Disease: An Urgent National Health and 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 reduce the number of people with the disease. This in turn would ease 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 communicate with each other and the reasons why some nerve cells die and others do not is a central element of scientific efforts to discover what causes AD.

Many researchers also are looking for better ways to diagnose AD in the early stages and to identify the earliest brain changes that eventually result in AD. Investigators are striving to identify markers of dementia, improve ways to test patient function, determine causes and assess risk factors, and improve case-finding and sampling methods for population studies.

Other researchers are working hard to discover and develop drugs that may help treat symptoms or slow the progress of the disease, and eventually delay the onset of and prevent AD. Many of these drugs are now being tested in clinical trials. Finally, scientists and many health care professionals are seeking better

ways to help patients and caregivers cope with the decline in mental and physical abilities and the problem behaviors that accompany the disease and to support those who care for people with AD.

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) has recently revised and updated its booklet *Alzheimer's Disease: Unraveling the Mystery*, which uses illustrations and text to explain Alzheimer's disease. Designed for a lay audience, *Unraveling* also describes ongoing research in the cause, diagnosis, and treatment of AD and in ways to support caregivers of people with AD. This booklet is available from NIA's Alzheimer's Disease Education and Referral (ADEAR) Center (www.alzheimers.org or 1-800-438-4380). The ADEAR Center provides a variety of information materials on AD, including booklets on caregiving, fact sheets, and reports on research findings (many of which were developed by NIA-funded investigators). ADEAR also maintains a database of AD clinical trials and studies, develops recommended reading lists, and provides referrals to local AD resources.

Part 2
2001-2002 Research Advances: Opening Doors to New Discoveries

During the last year, scientists supported by NIA and other NIH Institutes made advances in a number of areas important to Alzheimer's disease. This report focuses on new research that is attempting to answer three key questions:

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

These questions are important because they get to the heart of this complex disease – what happens during the very first steps of the disease process, what might we be able to do to prevent AD, and what can be done once the disease takes hold. They can be asked only because of the knowledge that has accumulated through research over the last 25 years. The answers are slowly emerging, and they hold the key to future prevention, treatment, and caregiving strategies.

What Causes the Transformation from Healthy Aging to Alzheimer's Disease?

As a person gets older, 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. In certain brain regions, chemical and electrical changes occur in neurons and their connections to lower their efficiency and ability to communicate with other cells. These changes may make neurons more vulnerable to damage.

- Neurofibrillary tangles develop in neurons and beta-amyloid plaques develop in surrounding areas, though in much smaller numbers than in AD.

- Damage by free radicals increases (a free radical is a kind of molecule that reacts easily with other molecules; too many of these molecules can damage neurons).

- Inflammation (the complex process that occurs when the body responds to an injury or abnormal situation) also increases.

Many investigators are now focused on understanding more fully these changes in normal aging and their effects on memory and thinking. For example, scientists have examined whether older adults differ from younger adults in the types of information they use to make decisions and their actual decision-making processes. NIA intramural scientists found that older adults' memory and decision accuracy improved when they perceived the task to be personally relevant or when they were held accountable for their performance (Hess et al., 2001). Other studies comparing the performance of older and younger adults on memory tasks also showed that when older adults were given materials that engaged their emotional interest, their performance on memory tests equaled that of young adults (Rahhal et al., 2001). Other work shows that older adults perform better on most memory tasks at their optimal time of day. This time is determined by a biological clock that appears to shift toward the morning as a person ages (West et al., 2002). These results further reinforce the growing understanding that many factors besides age influence memory and cognitive ability.

By identifying the changes that occur in normal aging, investigators hope to be able to understand the transformation from healthy aging to Alzheimer's disease. In addition, learning more about the very earliest stages of the disease process may open doors to treatments that may delay the onset of the disease or prevent its progression. In the past year, scientists have examined this early stage from several perspectives: mild cognitive impairment, biological markers and oxidative stress, and beta-amyloid.

Mild Cognitive Impairment

As they get older, some people develop memory problems greater than those expected for their age. However, these problems do not necessarily meet all the accepted criteria for AD. For example, a person with memory problems might not experience the personality changes or difficulties in making decisions experienced by those with AD. These people are thought to have mild cognitive impairment (MCI) with memory loss. In certain studies, about 40 percent of these individuals develop AD within 3 years. Other people with MCI, however, have not progressed to AD, even after 8 years.

Some scientists think MCI with memory loss is often a very early stage of AD. One recent study provided some support for this notion (Morris et al., 2001). In this study, researchers at the Washington University School of Medicine in St. Louis, Missouri, examined 404 people who had either mild memory loss

AS THEY GET OLDER, SOME PEOPLE DEVELOP MEMORY PROBLEMS GREATER THAN THOSE EXPECTED FOR THEIR AGE.

(classified as MCI) or no memory problems. These participants agreed to have annual memory assessments, and 42 agreed to donate their brains to the study after death. The 227 people with MCI were placed into one of three categories that reflected the researchers' degree of confidence that the subtle signs of memory loss might indicate the onset of AD. The categories were: "fairly confident" of dementia, "suspicious" of dementia, and "uncertain" of dementia. The volunteers were reassessed annually for up to 9½ years. After 5 years, AD symptoms had developed in 7 percent of the healthy volunteers, 20 percent of the individuals in the "uncertain" group, 36 percent of those in the "suspicious" group, and 60 percent of those in the "fairly confident" group. By 9½ years, all the volunteers with the most severe form of MCI had developed the clinical symptoms of AD. In studying the donated brain tissue of those who died, investigators also found that 21 of the 25 volunteers who originally were diagnosed with MCI had damage to brain tissue that was characteristic of AD.

The investigators interpreted these findings to mean that MCI is an early stage of AD.

It must be noted that most of the participants in the MCI studies done thus far have been recruited from clinics that specialize in memory problems. The diagnosis of MCI in general populations may be less predictive of the development of AD. However, because it appears that many more of those with MCI develop AD than do cognitively healthy individuals, many scientists are intensely interested in this clinical state, and they are studying it using a number of approaches.

Neuropsychology

Several research teams have hypothesized that performance on specific cognitive tests might predict whether an individual will develop AD. For example, in one recent study, Boston University investigators gave 1,076 participants in the ongoing Framingham Heart Study a series of cognitive tests every 2 years for up to 22 years (Elias et al., 2000). At the time of the first tests, participants were at least 65 years old. None had had a stroke or dementia. The investigators found that lower scores in a number of areas – learning new things, recall, retention, and abstract reasoning – obtained during any time period that a participant did not have dementia were associated with the

later development of AD. The study team also found that a detectable lowering of cognitive functioning preceded the appearance of AD by many years. Changes in abstract reasoning ability and capacity to retain verbal information were the strongest predictors of AD when there was a long interval between the initial assessment and development of AD.

A smaller study of cognitively normal elders and people with mild memory difficulty, conducted by investigators at Massachusetts General Hospital and Harvard Medical School, also showed that neuropsychological tests can predict the development of AD to some extent (Albert et al., 2001). Of the 20 neuropsychological measures used in the initial tests given in this study, four were useful in discriminating those who converted to a diagnosis of probable AD from those who did not. Tests of memory and executive functions (such as the ability to reason and make decisions) had the most power to discriminate between those who were likely to develop AD and those who were not.

Although scientists know that a majority of people with dementia experience neuropsychiatric symptoms, such as depression, apathy, and irritability, it has not been clear whether those with MCI also suffer the same symptoms. Depression and other neuropsychiatric symptoms are a major source of added disability for patients and caregivers and contribute to the costs of care. Johns Hopkins University researchers supported by the National Institute of Mental Health (NIMH) and the NIA analyzed more than 10 years' worth of data from the Cardiovascular Health Study (CHS) Cognition Study, which was designed to evaluate the prevalence of neuropsychiatric symptoms in dementia and MCI (Lyketsos et al., 2002). A total of 824 study participants completed the Neuropsychiatric Inventory (NPI), a state-of-the-art rating of neuropsychiatric symptoms in dementia. Of these, 362 were classified with dementia and 320 with MCI. Forty-three percent of MCI participants exhibited neuropsychiatric symptoms in the previous month, with depression, apathy, and irritability being most common. These are the first population-based estimates for neuropsychiatric symptoms in MCI, indicating a high prevalence associated with this condition. The research team concluded that these types of symptoms should be asked about and treated as necessary, and called for further studies of possible treatments. Study of the causes of neuropsychiatric symptoms will not only help those with dementia and MCI, but will also improve our understanding of brain-behavior relationships and the development of neurodegenerative diseases like AD.

Based on the results of these and similar neuropsychological studies, the Quality Standards Subcommittee of the American Academy of Neurology has developed clinical practice guidelines for clinicians who work with patients with memory complaints (Petersen et al., 2001). The guidelines recommend that clinicians use general cognitive screening instruments, such as the Mini-Mental State Examination, and neuropsychological tests to evaluate and monitor patients with MCI. These tests may help clinicians assess the degree of cognitive impairment and help them detect signs that might indicate the development of dementia. In addition, the Subcommittee suggested that clinicians consider using structured interviews of caregivers or relatives when screening patients for cognitive impairment. The investigators also recommended a number of avenues for future research, including better definition of the

course of cognitive function in normal aging, and studies to identify which screening instruments might be most practical and useful in busy clinical practices.

Neuroimaging

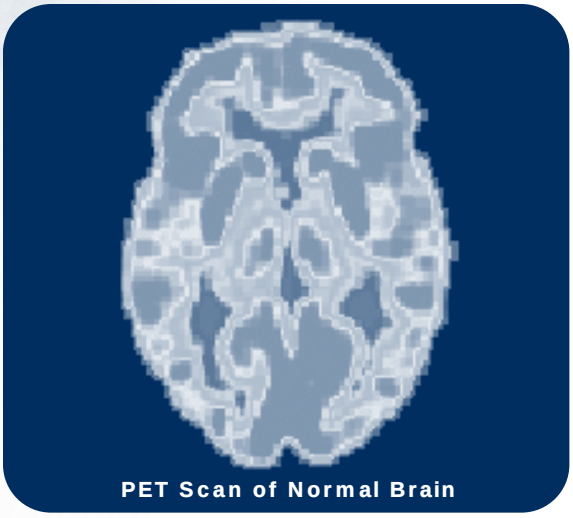
Investigators are continuing to use neuroimaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), to assess whether it is possible to measure aspects of brain structure or function that will identify those people who are at risk of AD before they develop the symptoms of the disease. Over the past year, results from a number of promising longitudinal neuroimaging studies have been published. These studies have expanded our understanding of the potential usefulness of imaging techniques for research and diagnostic purposes as well as increased our knowledge about early AD changes in the brain.

For example, it is well known that the hippocampus, a region of the brain important for learning and short-term memory, is affected early in the course of AD. Using a series of MRI scans, researchers at the Mayo Clinic documented for the first time the rate of hippocampal atrophy (shrinkage resulting in loss of function) in patients with MCI (Jack et al., 2000). In this study, the investigators grouped participants into those who were cognitively healthy, those who had MCI, and those who had probable AD. Each participant had an MRI at the beginning of the study and another one later during the course of the study. The percent change in hippocampal volume was measured for each participant. Within the cognitively healthy and MCI groups, those who declined clinically over time had a significantly greater volume loss than those who remained clinically stable. These results correlated the rate of change in hippocampal volume and change in cognitive status. The data also suggest that it should be possible to distinguish stable from declining members of a group, both in persons showing early symptoms and in those who have not yet shown symptoms. The research team concluded from this study that serial hippocampal volume measurements may be a useful tool to monitor the efficacy of therapeutic interventions in clinical trials for both progression and prevention of AD, and that they may also be a way to identify people with MCI who will not progress to AD.

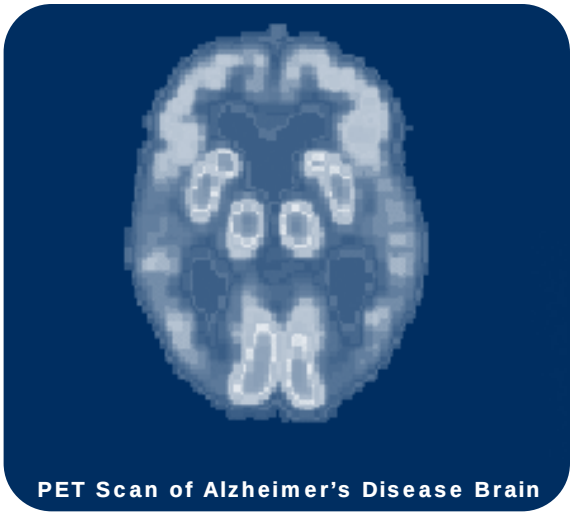
Neuropathological studies have shown that neurons die in the entorhinal cortex (EC), another brain region involved in memory function, even earlier than in the hippocampus (Kordower et al., 2001; Price et al., 2001). Several studies using MRI have shown that

Improvements in the Not-So-Simple Matter of Identifying Brain Structures

As particular areas of the brain are especially affected by AD atrophy over time, neuroimaging studies of brain volume are becoming an increasingly important research tool. In these brain volume studies, a trained anatomist or technician manually outlines brain structures shown on an MRI scan. This procedure is tedious and time-consuming. National Center for Research Resources (NCRR)-supported scientists at the Massachusetts General Hospital have now developed an automated procedure that is as accurate as the manual procedure and takes about 30 minutes on computer workstations. This improved technique enables scientists to process thousands of images per day (Fischl et al., 2002).



PET Scan of Normal Brain



PET Scan of Alzheimer's Disease Brain

patients with AD and MCI also have reduced EC volumes as compared with cognitively normal older adults. Some researchers have found that changes in EC volume are better than hippocampal volume for distinguishing individuals with AD from those with MCI (Du et al., 2001). Others have found that conversion to dementia from MCI is better predicted by volume of the EC, as opposed to the hippocampus (Dickerson et al., 2001). Further study of the time course of change in the hippocampus, EC, and other structures will help delineate which brain regions are best for diagnosing AD early and following its progression.

A research team from the New York University School of Medicine has recently published the first longitudinal PET imaging study of cognitively healthy elderly declining to MCI (deLeon et al., 2001). Unlike MRI, which uses powerful electromagnets to create the signals that are converted by computers into detailed images, PET scanning uses short-lived radio-labeled water or glucose to measure blood flow and glucose metabolism throughout the brain. The investigators in this study found that decreased glucose metabolism in the EC at baseline was the most accurate predictor of conversion from normal cognition to MCI. That is, changes in the EC were seen before cognitive decline and before changes in metabolism in other parts of the brain. Reduced glucose metabolism in the EC accurately predicted declining cognitive function in 83 percent of study participants who got worse, and accurately predicted non-decline in 85 percent of participants who remained cognitively healthy after 3 years. At the follow-up PET evaluation in those who had progressed to MCI, reduced glucose metabolism was also seen in the hippocampus and temporal neocortex, a development also seen in AD. In addition, those who experienced cognitive decline and were carriers of the APOE-ε4 allele (a genetic risk factor for AD) showed especially marked reductions over time in glucose metabolism in the temporal neocortex (see p. 26 for more on genetics and AD). This finding is consistent with earlier reports by other investigators that showed reductions in temporal cortex metabolism of APOE-ε4 carriers compared to persons without APOE-ε4.

In another study, supported by the NIMH, NIA, and other funders, Arizona State University researchers also investigated the potential of using PET in longitudinal studies.

Using Neuroimaging Techniques to See Deep Inside the Brain

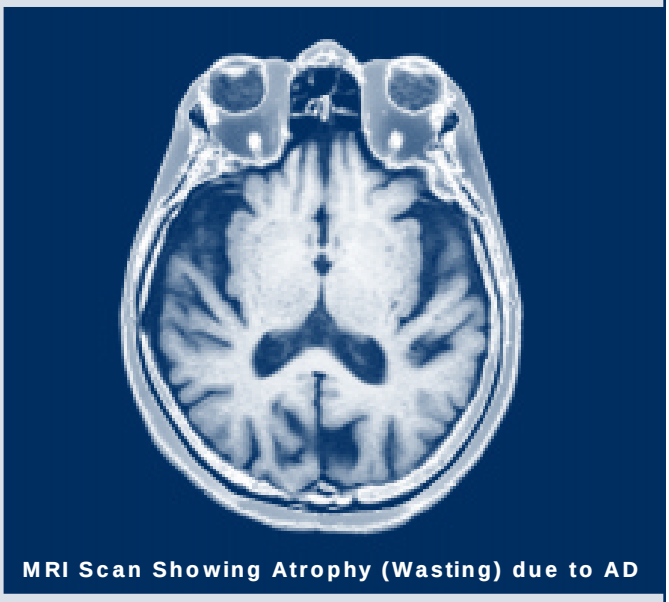
Magnetic resonance imaging (MRI) is a technique used to image internal structures of the body. Images are very clear and are particularly good for soft tissue, brain and spinal cord, joints, and the abdomen.

Functional magnetic resonance imaging (fMRI) is a variant of MRI that measures changes in the oxygenation level of the blood. This level depends on blood flow and is correlated with changes in the activity of nerve cells. Since its development in the early 1990s, nearly all studies using fMRI have focused on the changes in blood flow that occur while a person is performing an "activation" task, such as taking a memory test or looking at pictures. This presents a difficulty, however. Because individuals must perform an activation task, patients with moderate to severe dementia, who cannot understand the experimental instructions, cannot be scanned. Activation tasks also cannot be performed in small animals because they must be anesthetized to prevent them from moving while the scan is being conducted.

fMRI also has another important limitation: The images generated have a spatial resolution of a few millimeters, which is insufficient for evaluating many small brain structures such as the subregions of the hippocampus. The cells of the hippocampal subregions have unique patterns of gene expression that are reflected in their electrical properties and chemical profiles. These differences may account for the fact that cells of the different subregions are selectively vulnerable to different pathological processes. Thus, evaluating the hippocampus globally does not do full justice to its cellular complexity.

To overcome these limitations and enhance the resolution of the images, investigators needed a highly sensitive approach that was applicable to both mice and humans and that was based on fMRIs taken while the person or animal was not being asked to do anything. Because most causes of brain dysfunction produce changes not only in the active but also in the resting function of neurons, investigators reasoned that signals that could be obtained at rest might also indicate brain damage.

Investigators from Columbia University are in the process of developing such a method (Small et al., 2000). Using this technique, the investigators found that signals from the hippocampus were significantly lower in elderly people with memory decline than in cognitively healthy elderly individuals. They also found that different people showed dysfunction in different subregions of the hippocampus. Among healthy elders, signal intensity from one subregion called the subiculum was correlated selectively with memory performance. In tests with mice, the investigators found that the fMRI signal was sensitive enough to detect functional changes in hippocampal neurons even in the absence of underlying anatomical changes in animals with memory deficits.



MRI Scan Showing Atrophy (Wasting) due to AD

The new techniques introduced in this study are beginning to make it possible for researchers to conduct subregional analyses of the hippocampus, which eventually might allow precise mapping of existing dysfunction and a greatly enriched understanding of the earliest changes in the Alzheimer's disease process.

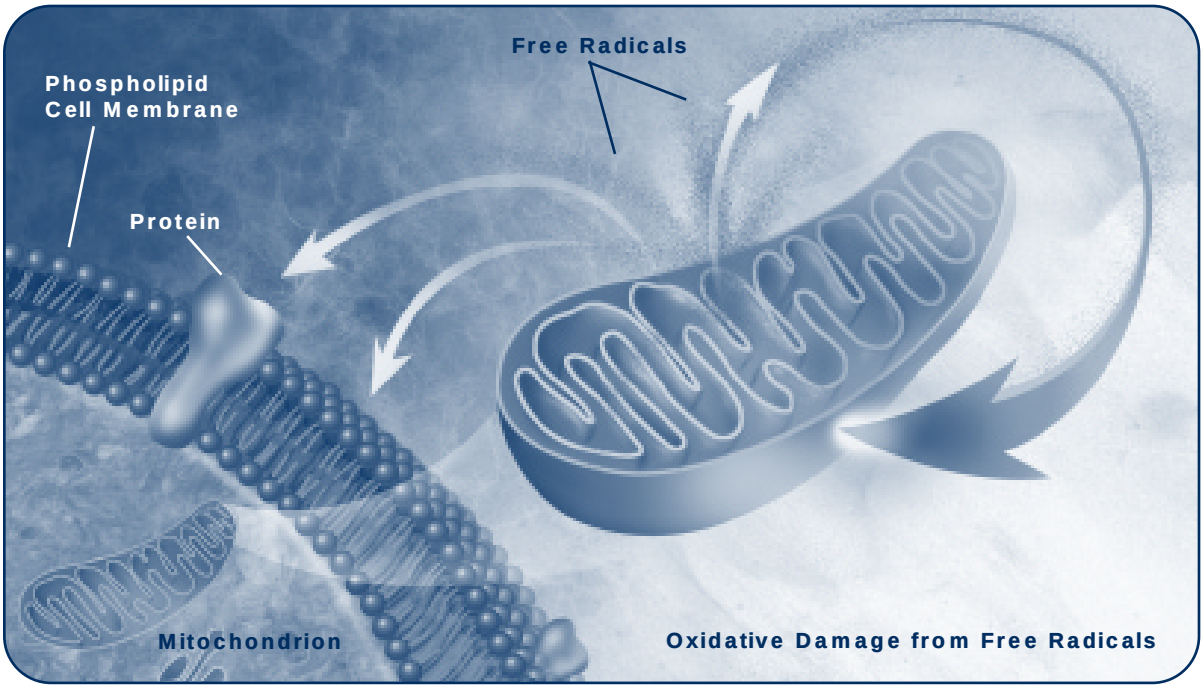
In this study, the research team used PET to track changes in brain activity that precede the onset of memory and thinking problems in a group of individuals of late middle-age (Reiman et al., 2001). The group was divided into those who were APOE-ε4 carriers and those who were not. The scientists found that the cognitively normal APOE-ε4 carriers had significant declines in regional brain activity over a 2-year period, and that these declines were significantly greater than those found in non-APOE-ε4 carriers. Findings from this study suggest that PET could be a useful future tool to test, in a relatively small number of people (APOE-ε4 carriers), the potential of AD prevention and treatment strategies that might benefit many thousands.

It is important to note that using PET to identify persons at risk of developing MCI and AD is still at the experimental stage, and a number of longitudinal studies will need to be completed and analyzed before its potential can be usefully evaluated.

Biological Markers and Oxidative Stress

Scientists are also trying to discover whether biological markers exist that could indicate early changes in the brain associated with AD. Understanding more about these markers – what they are, how they function, and how and when their levels change – will help investigators answer questions about the cause and development of AD and may lead one day to treatments to delay or prevent the onset of the disease.

One long-standing theory of aging and neurodegeneration is that damage from highly reactive molecules called oxygen free radicals can build up in neurons over time. If unchecked, this oxidative stress can modify or damage cellular molecules such as proteins, lipids, and nucleic acids. Oxidative stress may play a role in the pathogenesis of neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis. In the AD brain, in particular, such



OXIDATIVE STRESS MAY PLAY A ROLE IN THE PATHOGENESIS OF NEURODEGENERATIVE DISORDERS.

damage has been observed, especially in the late stages, when both beta-amyloid plaques and neurofibrillary tangles (the two main neuropathological features of AD) are present. However, scientists do not know whether the oxidative stress causes or results from the process of beta-amyloid plaque formation. A number of markers of oxidative stress have been measured in the cerebrospinal fluid (CSF) of people with AD, but for most of these markers, the amounts found in those with AD and in cognitively healthy individuals overlap substantially.

Scientists have suggested that the extent to which lipids in the central nervous system have been affected by free radical oxidative stress can be assessed by measuring body levels of a newly described class of lipids – the isoprostanes (iP). Isoprostanes are formed by the addition of oxygen to particular lipids. In a new study, researchers at the University of Pennsylvania School of Medicine worked with transgenic mice (mice that have been specially bred to develop beta-amyloid plaques in the brain) to see whether iP accumulation might be a useful biomarker of plaque pathology (Praticò et al., 2001). Over 14 months, these investigators compared the amount of a particular iP in urine, blood, CSF, and brain from transgenic mice and a control group of mice at different ages. Results showed that after the age of 6 months, the amounts of iP in the two groups began to diverge, and differences in all the fluids and tissues increased in parallel with age. The levels of iP began to increase just before a surge in beta-amyloid levels in the transgenic mice and well before the appearance of amyloid plaques at 8-12 months. High iP levels in the transgenic mice were observed only in the cortex and hippocampus, brain regions that are heavily affected by plaque accumulation. Results from this study suggest that oxidative stress in the brains of these transgenic mice is a very early event, occurring just before the rise in amyloid peptide levels and before amyloid plaque deposition. Because iP is chemically stable and can be measured in plasma, urine, or CSF, it may have utility as a diagnostic tool and to monitor development of pathology in AD or other neurodegenerative diseases in which oxidative stress has been implicated.

Cornell University investigators supported by NIMH also used CSF to hunt for biological markers of AD. These researchers used state-of-the-art protein analysis tools to identify changes in the composition of CSF that correlate with Alzheimer's disease (Choe et al., 2002). Using this approach, the investigators identified a panel of nine proteins that demonstrate altered expression in patients with Alzheimer's disease. When taken together, these proteins suggest the clinical state of Alzheimer's disease. This study is one of the

first to use a multiple-marker assay for the presence of Alzheimer's disease based on changes in CSF composition. In the future, a biomarker assay like this may help to improve the accuracy of AD diagnosis.

A study from a research team at the University of Kentucky Sanders-Brown Center on Aging examined the possibility that a marker of oxidative stress in DNA may identify persons with neurodegenerative disorders such as Alzheimer's disease (Lovell and Markesbery, 2001). This marker of DNA oxidative stress is called 8-hydroxy-2'-deoxyguanosine (8-OHG). It is formed by oxidation of one of the four building blocks (bases) that make up DNA strands. In normal cells, not very much oxidation of this base takes place, and the cell is able to repair the DNA by removing the 8-OHG. The 8-OHG is then found free in the cell. In AD, two changes to this process seem to take place. First, a high level of oxidative stress causes more of the 8-OHG to be formed in the DNA. Second, the repair process is much less efficient, so less of the oxidized base is removed from the DNA and found free in the cell. After comparing people with AD and cognitively healthy individuals, the University of Kentucky investigators found that the ratio of DNA-bound 8-OHG to free 8-OHG increased 100-fold in the patients with AD. The investigators suggest that this marker of DNA oxidation mirrors brain degeneration and might be a useful indicator of disease progression.

A University of Wisconsin research team funded by the National Institute of Environmental Health Sciences (NIEHS) studied the relationship between free radicals, oxidative stress, and programmed cell death. Programmed cell death, a process that occurs naturally in all cells, appears to be accelerated in Alzheimer's disease, perhaps because of increased oxidative stress caused by the accumulation of beta-amyloid. These researchers focused on ways to increase defense mechanisms in the brain by activating multiple antioxidant defense genes simultaneously, a process they refer to as programmed cell life (Li et al., 2002a). A small molecule, tert-butylhydroquinone (tBHQ) is known to activate the antioxidant response element and protect against cell death induced by oxidative stress. The researchers used tBHQ and cell culture models as a simple system to help them understand the genetic regulation of antioxidant defenses (Lee et al., 2001). Their work led recently to the identification of a factor that binds to the antioxidant response element and helps activate a number of antioxidant-related genes. Scientists hope that these and other similar studies may help elucidate the complex regulation of the many programmed cell life genes and may lead to improved drug targets and strategies in the future.

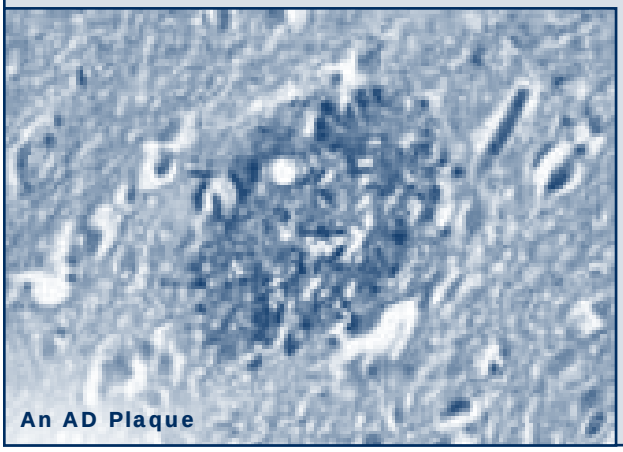
Beta-Amyloid

The study of beta-amyloid, the primary component of AD plaques, continues to be a vitally important part of the quest to discover what happens in the brain to cause the transformation from healthy aging to AD. Investigators continue to work intensely to understand the process by which amyloid precursor protein (APP) is cleaved by enzymes to release beta-amyloid fragments, how the fragments accumulate in the brain to form plaques, and whether the plaques themselves cause AD or whether they are a by-product of the production of beta-amyloid fragments. In studies during the past year, investigators examined several different issues related to beta-amyloid.

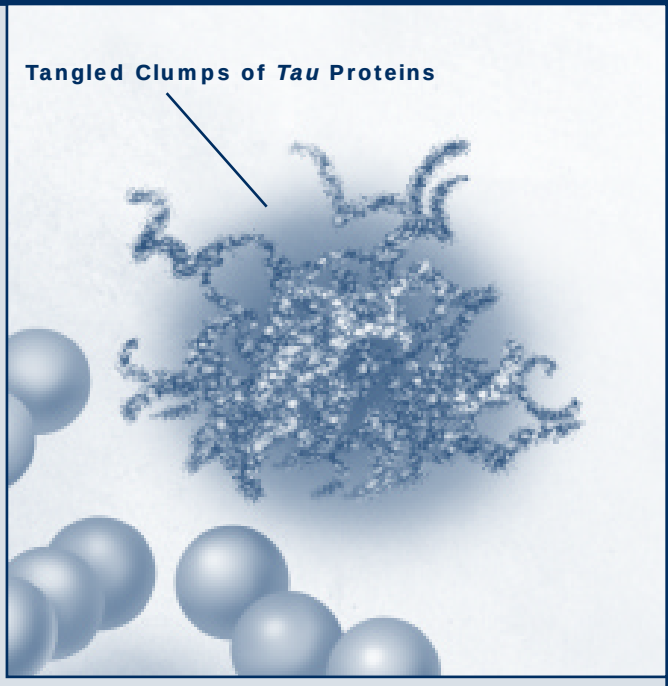
Beta-amyloid and Neurofibrillary Tangles: the Hallmarks of AD

The brains of people with AD have an abundance of two abnormal structures – beta-amyloid plaques and neurofibrillary tangles. This is especially true in certain regions of the brain that are important in memory.

● Plaques are dense, mostly insoluble deposits of protein and cellular material outside and around the neurons. They are made partly of a protein called beta-amyloid, which is a fragment snipped from a larger protein called amyloid precursor protein (APP). We don't yet know whether plaques themselves cause AD or are a by-product of the disease process.



An AD Plaque



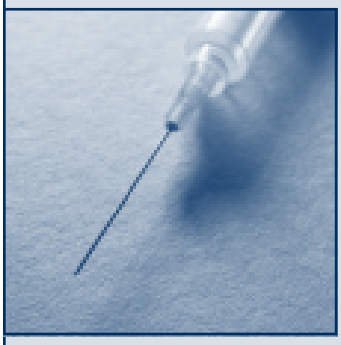
● Tangles are insoluble clumps of twisted fibers that build up inside neurons. These fibers are made of a protein called *tau*, which helps to stabilize the neuron's internal support structure. In AD, *tau* is changed chemically, causing it to pair with other threads of *tau* and become tangled up. This may result in malfunctions in communications between neurons and later in the death of the cells.

Scientists know that cleavage of APP by two kinds of enzymes – beta-secretases and gamma-secretases – generates the toxic beta-amyloid fragments. Two very similar beta-secretases, BACE1 and BACE2, can generate beta-amyloid. Previous studies demonstrated that the BACE1 enzyme is likely responsible for cleaving one end of the beta-amyloid fragment from APP. However, investigators thought that BACE2 might also be involved. A new study was designed to determine which of the beta-secretases is more important for the production of the toxic beta-amyloid (Cai et al., 2001). In this study, investigators at the Johns Hopkins University School of Medicine developed a transgenic "knockout" mouse in which the gene for the BACE1 enzyme was eliminated. This allowed the team to see whether removing the enzyme would interfere with the production of beta-amyloid. With the enzyme eliminated, beta-amyloid protein fragments no longer were produced in neuronal cultures from the knockout mice. These results suggested that BACE1 was involved in the amyloid-producing activity, and that BACE2 appeared to play a much smaller role

Update: Progress on the Immunization Front

Immunization is a common practice that protects people against a wide variety of diseases. Scientists questioned whether this might be a useful strategy for AD as well, and the results of their intense work over the last several years illustrate both the promise and the difficulties of this type of research.

In early studies conducted at Elan Pharmaceuticals, scientists worked with transgenic mice that gradually develop beta-amyloid plaques in the brain, injecting them with a vaccine composed of very small amounts of the beta-amyloid peptide, or protein fragment, mixed with another substance known to stimulate the immune system (Schenk et al., 1999). They found that the injections resulted in much less beta-amyloid being deposited in the brains of the mice and better performance on memory tests.



The success of these studies in mice led to preliminary trials in humans, conducted by Elan investigators and teams supported by NIH and other funders. These trials tested the vaccine's safety and assessed its effectiveness. In both trials, investigators also measured the immune response in those who received the vaccine. These human trials were halted prematurely in early 2002 because inflammation developed in the brains of some of the participants. The researchers' disappointment was tempered by the fact that the study still provided a wealth of important clinical and pathology data on hundreds of participants and by the recognition that cutting-edge research like this can suffer setbacks.

Simultaneously, other teams of investigators made additional progress in this area by continuing work with several strains of transgenic mice. One research team, from Washington University School of Medicine in St. Louis, used a strain of transgenic mice that carries a mutation for the APP gene. These mice develop beta-amyloid plaques as they get older. The scientists found that passively immunizing these mice (administering an antibody itself rather than stimulating the host's immune system to make an antibody) decreased the deposition of beta-amyloid in the brain and reduced the overall number of plaques (DeMattos, et al., 2001). In other studies, they also found that prolonged administration of anti-beta-amyloid antibody decreased the accumulation of beta-amyloid in plaques and rapidly increased the amount of beta-amyloid in the blood, effectively removing it from the brain (DeMattos et al., 2002a; DeMattos et al., 2002b). This is an important finding because it suggests that there may be ways to remove beta-amyloid from the brain without producing adverse side effects.

In conjunction with the researchers at Washington University, scientists with Lilly Research Laboratories in Indianapolis, showed that the antibody therapy rapidly reversed the impairment shown by the transgenic mice in certain learning and memory tasks (Dodart et al., 2002).

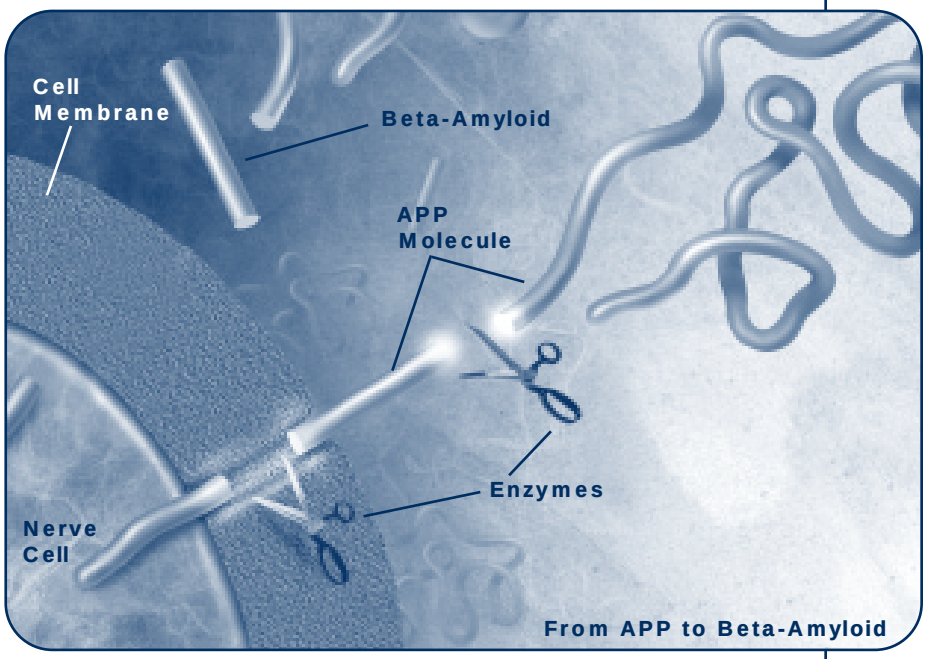
A group of Johns Hopkins University School of Medicine investigators replicated these results in another strain of transgenic mice that carries a human presenilin gene mutation as well as the APP mutation (Vehmas et al., 2001). This replication is significant because the AD-related damage in the brain of the double mutant occurs sooner and the amount of beta-amyloid deposited is greater than in mice with either mutation alone. As with the Washington University studies, this research suggests that binding antibodies to beta-amyloid clears it from the brain and deposits it into the blood where it can be degraded further.

Although scientists still have much to learn, this exciting research is helping them understand more fully the steps involved in the metabolism of APP and beta-amyloid, and how beta-amyloid is distributed among body compartments – including blood, cerebrospinal fluid, and brain. This improved understanding may prove central to more effective AD diagnosis and treatment in the future.

in the cleavage of APP in neurons. To further support this conclusion, the investigators also compared the roles of BACE1 and alpha secretase, an enzyme involved in normal, non-pathological processing of APP into soluble products. They found that the two enzymes appear to compete with each other in the processing of APP, further demonstrating that BACE1 is the primary enzyme in the production of beta-amyloid. Many scientists believe that interfering with the deposition of beta-amyloid may prevent AD or slow its progression. Because they play key roles in the processing of APP and the resulting deposition of beta-amyloid, both beta- and gamma-secretase activities represent potential targets for drug therapies. The finding that BACE1 is the principal beta-secretase in neurons suggests that scientists might want to focus on the design of therapeutics to inhibit BACE1 activity.

In other studies, intramural NIEHS researchers found that beta-amyloid blocks the function of the nicotinic acetylcholine receptor, a key nerve cell signaling receptor in the hippocampus (Pettit et al., 2001). These results suggest that beta-amyloid may exert its effects independently of plaque formation, and they may provide an explanation for early cognitive problems experienced by those with AD long before plaques begin to form. Potentially, better drug therapies could result from finding compounds that can prevent beta-amyloid from interacting with this receptor, thus maintaining communication between nerve cells in the brain.

In other work on beta-amyloid, scientists at NIA followed up on earlier research showing that, contrary to previous belief, the adult brain can form new neurons. These investigators wanted to see whether beta-amyloid had any effect on the formation of these new neurons (Haughey et al., 2002). They discovered that the ability of new nerve cells to form from stem cells is impaired in the brains of transgenic AD mice. They further showed that beta-amyloid has a direct adverse effect on neural stem cells, inhibiting their ability to form nerve cells. These findings suggest that an impaired ability of stem cells to form nerve cells may occur in AD, and might contribute to the progressive depletion of nerve cells and cognitive impairment in this disease. Taken together with other studies that have shown that dietary factors and nerve cell growth factors can stimulate the production of new neurons from stem cells, the present findings suggest that it might be possible to increase formation of stem cells in persons with AD, perhaps preventing or slowing down the depletion of neurons that causes the memory impairment.



From APP to Beta-Amyloid

Other research in this area has looked to vascular diseases, such as stroke, to provide clues about the formation of beta-amyloid and the pathogenesis of both early- and late-onset forms of AD. AD and vascular diseases share common risk factors, and stroke may be a risk factor for AD; this has increased the interest in the possible relationship of cerebrovascular pathology, neurodegeneration, and dementia (see p. 22 for a description of epidemiological research examining possible links between vascular diseases and AD). We know that production of transforming growth factor-beta1 (TGF- beta1), a protein that is part of the inflammatory response to injury, is increased immediately following brain injury. Previous work has shown that high levels of this protein increase the deposition of beta-amyloid in cerebral blood vessels. In this study, scientists at the Gladstone Institute of Neurological Disease at the University of California, San Francisco, developed a double transgenic mouse by mating mice carrying the gene for a mutated form of APP responsible for one form of early-onset AD with other mice carrying the gene for an active form of TGF-beta1 (Wyss-Coray et al., 2001). This transgenic mouse allowed the researchers to examine directly the effect of TGF-beta1 on deposition of human beta-amyloid plaques in the brain and its blood vessels. The study showed that TGF-beta1 significantly influenced the extent and localization of the beta-amyloid plaque deposition in the mice. Cerebral blood vessels showed a significant accumulation of beta-amyloid plaques while, at the same time, the formation of neuritic plaques in brain tissue was dramatically reduced. Overall levels of brain beta-amyloid also were markedly reduced in the double transgenics. This reduction was associated with activation of microglial cells and an increase in inflammatory molecules. In contrast to results from epidemiologic and other studies that suggest that an increase in brain inflammation might increase the risk of developing AD, this study's findings suggest that particular components of the inflammatory response in the brain might act to reduce, not elevate, plaque levels in brain tissue.

AD AND VASCULAR DISEASE SHARE COMMON RISK FACTORS.

Additional work in beta-amyloid has built on earlier studies indicating that the amount of copper and zinc is increased in the cortex of brains from individuals who have died of AD. These metals are concentrated in beta-amyloid plaques. Although controversial, some scientists believe that beta-amyloid possesses binding sites for copper and zinc that enhance the resistance of beta-amyloid to breakdown by enzymes and encourage its tendency to clump together to form plaques. In a new study, investigators in Australia, Sweden, Germany, and the U.S., led by scientists at the Massachusetts General Hospital, treated

Down Syndrome Research May Shed Light on Alzheimer's Disease

Many older adults with Down syndrome develop dementia similar to that seen in Alzheimer's disease, and results from several recent studies in Down syndrome may contribute to a better understanding of AD. For example, University of Colorado School of Medicine scientists funded by the National Institute of Child Health and Human Development (NICHD), NIMH, and NIA have found that a particular strain of transgenic mice have learning deficits that may be related to problems with nerve fibers that send impulses to the hippocampus (Hyde et al., 2001). These mice are helping scientists understand Down syndrome, but because the hippocampus is a critical brain region that is damaged in AD, these mice provide a potentially useful animal model for researchers interested in examining changing patterns of cognitive function in AD.

In another study, a University of Connecticut Health Sciences Center research team funded by NICHD, the National Institute of Neurological Disorders and Stroke (NINDS), and the Alzheimer's Association, examined whether mitochondrial dysfunction associated with Down syndrome affects APP and beta-amyloid plaque formation (Busciglio et al., 2002). Mitochondria are structures inside a cell that provide energy to the cell and play a role in synthesizing some cellular proteins. The researchers found that the mitochondrial problems not only disrupted the normal functions of the APP, but also contributed to the rapid accumulation of plaques.

Other research has indicated that vitamin E may be protective against AD because of its antioxidant properties. The NIA is currently funding a study of vitamin E treatment in people with Down syndrome, to explore whether treatment may slow progression to dementia. Results may offer insights into how some of the damage to nerve cells occurs in both illnesses.

12-month-old transgenic mice with orally administered clioquinol for 12 weeks (Cherny et al., 2001). Clioquinol is a chemical that binds metals such as copper and zinc and removes them from body tissues. The team found that treatment with clioquinol reversed the deposition of beta-amyloid in the brain of the transgenic mice with AD. The amyloid plaque surface area was significantly reduced and membrane-associated (sedimentable) beta-amyloid in brain tissue decreased by 65 percent. In fact, two of the six animals treated with clioquinol had no sedimentable beta-amyloid, and no beta-amyloid could be detected using very specific and sensitive immunological techniques. Twenty older transgenic mice (21 months of age) treated at a higher dose for just 9 weeks also were examined. After this treatment, sedimentable brain beta-amyloid decreased by 49 percent and the study team found an overall clearance of beta-amyloid from the brain. Clioquinol did not cause decreased levels of APP nor did it result in decreased levels of a protein involved in neuron-neuron communication, suggesting that it was not toxic to brain tissue. Despite these encouraging findings, safety issues in this therapy still need to be addressed in human studies, as small amounts of these metals are necessary for many chemical reactions in the body.

Other researchers are working to deepen our understanding of the relationship between beta-amyloid plaques and neurofibrillary tangles. Scientists at the Mayo Clinic in Jacksonville, Florida, have made an important contribution to this work by developing an animal model that exhibits both amyloid plaques and neurofibrillary tangles (Lewis et al., 2001). Many of the previous animal models of AD developed plaques only. This research team, supported by NIA, NINDS, and

The Honolulu-Asia Aging Study: A Rich Source of Clues about Vascular and Other Risk Factors for AD

In 1965, NIH's National Heart, Lung, and Blood Institute (NHLBI) began the Honolulu Heart Program, a prospective epidemiological study of environmental and biological causes of cardiovascular disease among Japanese-Americans living in Hawaii. This study gave researchers an opportunity to investigate how heart disease prevalence rates, pathologic findings, and risk factors might be related in this population and to compare this population with other groups, especially Japanese men living in Japan and in other parts of the U.S. Initially, the study team examined 8,006 Japanese-American men living on the island of Oahu, Hawaii, who were born between 1900 and 1919. Over the next 25 years, investigators examined this group four additional times, and their findings have contributed enormously to our knowledge of heart disease and its risk factors.

From 1991 to 1996, NIA intramural investigators worked with approximately 3,700 survivors of this same group of Japanese-Americans to explore possible relationships between vascular factors – such as blood pressure, blood cholesterol, and inflammation – and the later development of dementias such as AD. This study, called the Honolulu-Asia Aging Study, built on newly emerging evidence suggesting that vascular factors might contribute to neurodegeneration, lead to co-existing illnesses that increase the severity of dementia, or somehow influence different stages of the dementia process.

As they did for heart disease, this group of Japanese-American men has made a valuable contribution to our understanding of dementia and AD through their participation in the Honolulu-Asia Aging Study. More recently, extramural grants have been awarded so that data collection and analysis can continue. Highlights of recent findings from these grants have shed light on the complex interrelationships among genetics, lifestyle and environmental factors, vascular diseases, and dementia:

- Investigators examined the association of total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) with brain plaques and tangles in deceased study participants (Launer et al., 2001). Cholesterol levels for all participants were measured during late life; for some participants, levels were measured 20 years earlier, when they were middle aged. The investigators found a strong correlation between increases in late-life and mid-life HDL levels and increases in the number of plaques and tangles.

- An examination of the joint effect of the APOE-ε4 allele and midlife systolic blood pressure on the risk of poor cognitive function in late life showed that midlife high blood pressure had a stronger adverse effect on cognitive function in those who carried the APOE-ε4 allele than in those without it (Peila et al., 2001). However, the investigators speculate that this effect might be modified by antihypertension medication.

- Investigators also explored the relationship between Type 2 diabetes, alone or in combination with the APOE-ε4 allele, and various types of dementia, including AD and vascular dementia (Peila et al., 2002). They found that study participants with both Type 2 diabetes and the APOE-ε4 allele had a higher risk of AD than did individuals with neither risk factor. They also found that

participants with both factors had more plaques and tangles in their brains and had a higher risk of cerebral amyloid angiopathy (CAA), a condition in which amyloid is deposited in the walls of the arteries that supply the brain, resulting in an increased risk of dementia and cerebral hemorrhage.

- In a study of brain tissue after death among 211 participants in the study, investigators evaluated the relationship among CAA, dementia, and cognitive function (Pfeifer et al., 2002). The researchers found that 44 percent of these participants had CAA in at least one brain region. The presence of CAA was associated with higher numbers of plaques and tangles and having the APOE-ε4 allele. Scores on cognitive function tests that the participants took before they died were lower for those individuals who were later found to have AD and CAA than for those with AD and no CAA and those with no AD or CAA. The investigators concluded that by interacting with other neuronal pathologic processes, CAA may lead to more severe cognitive impairment.

- Using specimens collected in 1968 during the second examination of Honolulu Heart Program participants, Honolulu-Asia Aging Study investigators measured blood levels of C-reactive protein, a nonspecific marker of inflammation, in 1,050 men (Schmidt et al., 2002). This sample was divided into four groups based on their levels of high-sensitivity C-reactive protein. Compared with men in the group with the lowest level of the protein, men in the other three groups had a 3-fold increased risk of all dementias, AD, and vascular dementia. This relationship was independent of cardiovascular risk factors or cardiovascular disease. The investigators concluded that inflammatory markers may reflect disease mechanisms related to dementia and that these markers can be measured long before clinical symptoms appear.

others, crossed strains of transgenic mice that harbored either a mutation in the amyloid precursor protein or the *tau* protein. The offspring expressed abnormal forms of both molecules. By comparing the cellular changes in these animals to those observed in the parental strains, the investigators found that the combination of these two mutations led to increases in tangles in several regions of the brain affected in AD. In addition, the animals also exhibited movement abnormalities. These results suggest that the same type of interactions may occur in the human brain as AD develops. Because these animals exhibit both plaques and tangles, they may serve as a superior model for AD. In addition, the movement abnormalities exhibited in these animals will allow for the testing of potential therapeutic agents at the behavioral level.

Can Certain Factors Increase the Risk of or Protect Against AD?

Scientists have known for some time that both genetic and non-genetic factors can increase the risk of developing AD. More recently, evidence from some studies suggests that certain protective factors may reduce the chances of developing AD. Developing a clearer understanding of possible risk and protective factors is important because it may provide clues to therapy and also suggest ways in which people might be able to change their lifestyles or environments to reduce AD risk.

Investigators have examined these issues in several different ways and results in the past year have shed light on differences in the rates of new AD cases (incidence) across populations, genetic links to the development of AD, and the implications of lifestyle issues for the development of AD.

Epidemiology

Comparing AD incidence and prevalence in different populations may provide some clues to genetic, environmental, and lifestyle factors that may predispose or protect individuals. If populations can be identified that have a significantly lower or higher incidence of AD, this will greatly facilitate the search for both genetic and non-genetic risk factors for the disease. For example, over a 5-year period, an Indiana University Medical School research team followed 2,147 African-Americans in Indianapolis and 2,459 Yoruba in Ibadan, Nigeria, to see whether they developed dementia and AD (Hendrie et al., 2001). All the study participants were aged 65 and older. In both communities, two-thirds were female. To screen participants for AD, the study team used the Community Screening Interview for Dementia, a test developed by this group specifically for use in comparative epidemiological studies of dementia in culturally disparate, non-literate and literate populations. All clinically assessed participants at both sites received the same examination, which included a structured interview, neuropsychological testing, and examination by a physician. Some also received laboratory and imaging studies. The investigators took great care to ensure that diagnostic consistency was maintained within and between sites. Results indicated that in the U.S. group, 3.24 percent per year developed dementia, including 2.52 percent per year who developed AD. In the Nigerian group, 1.35 percent per year developed dementia, including 1.15 percent per year who developed AD.

This study provides one of the first reports of

incidence rate differences for dementia and AD in studies of two populations from non-industrialized and industrialized countries using identical methods of evaluation and the same group of investigators in both sites. Further studies of these two populations will focus on identifying genetic factors and potentially modifiable non-genetic factors, such as heart disease, diabetes, high cholesterol, and lifestyle and environmental factors. For example, the Yoruba have a much lower prevalence of vascular risk factors than do African-Americans. These factors include high cholesterol levels and body mass index, hypertension, and diabetes. The lower rates of these risk factors may partially account for the reported difference in AD.

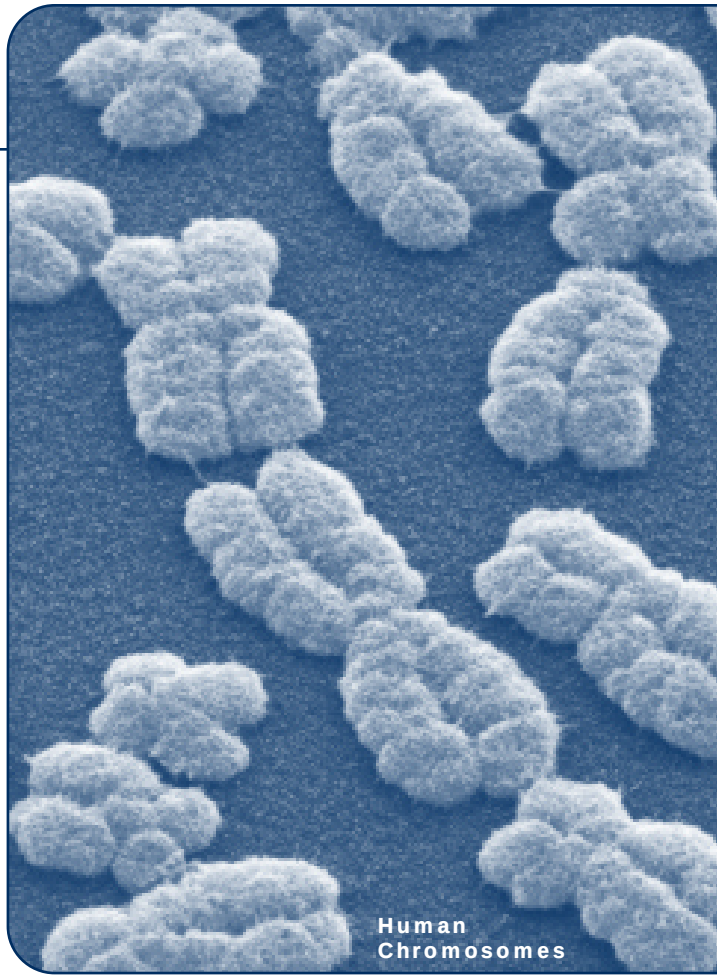
A second large epidemiologic study examined the incidence of dementia in a rural population living in Ballabgarh, India, south of New Delhi, and had analogous results to the Indianapolis-Ibadan study (Chandra et al., 2001). This 2-year prospective study of people aged 55 and older, conducted by researchers from the University of Pittsburgh, used repeated cognitive and functional ability screening measures followed by standardized clinical evaluation of dementia and AD. All the evaluation instruments had been developed and validated in light of the cultural and linguistic characteristics of this population. The investigators took the Indian incidence rates, standardized them against the age distribution of the 1990 U.S. Census, and then compared the rates against those of a population from the Monongahela Valley in Pennsylvania studied by the same researchers. The researchers calculated an overall incidence rate for those more than 65 years old of 4.7 per 1,000 person-years, much lower than the rate of 17.5 per 1,000 person-years in the Monongahela Valley population. The reason(s) for this difference is not known, but may include genetic differences as well as a variety of medical and demographic variables, such as those being analyzed in the Indianapolis-Ibadan study.

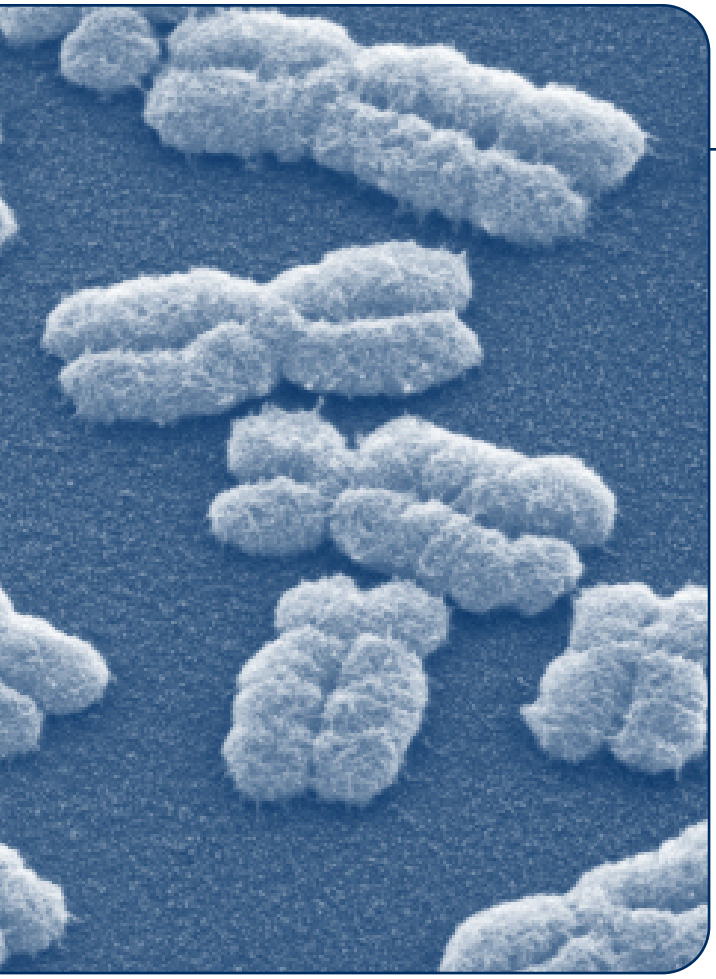
A third epidemiologic study took a slightly different tack by comparing AD incidence rates of different racial and ethnic populations living in one country. This study focused on cognitive abilities and dementia in a population of Caucasians, African-Americans, and Caribbean Hispanics in northern Manhattan (Tang et al., 2001). In this study, investigators from Columbia University studied 1,799 residents of the Washington Heights and Inwood communities of New York City for 7 years, with interviews every 2 years. Results indicated that probable or possible AD occurred more frequently among African-Americans (10.5 percent) and Hispanics (9.8 percent) than among Caucasians (5.4 percent). This differential risk did not seem to depend on diabetes, hypertension, heart disease, or stroke. It also appeared that the differences in incidence could not be attributed to differences in years of education or to frequency of illiteracy. It is important to note, though, that many factors may be responsible for these estimates, because populations vary in many respects. Differences in socioeconomic status, health care, education, events occurring prenatally or right around birth, and life history all may influence a person's eventual risk of AD. Even the ways in which diagnostic tests that measure language, memory, and cognitive function are constructed and applied may play a role in determining whether a person is diagnosed with AD. Clearly, further careful investigation is needed to examine the role that ethnic and racial differences may play in determining risk of AD.

Genetics

Scientists have made enormous strides in the past two decades in unraveling the genetic components of AD and related dementias. For example, we now know that mutations of particular genes on three chromosomes (1, 14, and 21) virtually always lead to early-onset AD. In addition, mutations in the *tau* gene on chromosome 17 cause frontotemporal dementia and related diseases. These discoveries are helping to broaden our understanding of how mutations in particular genes cause changes in cellular pathways that eventually cause different kinds of dementia. For example, in a recent study funded by NICHD, investigators at the University of Connecticut Health Sciences Center examined the ways in which a mutation in the presenilin-1 gene found on chromosomes 14 might affect the cellular structure of neurons during development. They found that mutated presenilin-1 interferes with the ability of brain cells to regulate and stabilize growing neurons by promoting the formation of neurofibrillary tangles, and interfering with brain receptors that help determine the fate of cells during development (Pigino et al., 2001). In other studies, NIA investigators have found that the spectrum of the dementias caused by mutations in the presenilin-1 and APP genes is much wider than had been suspected. These investigators have found that some presenilin-1 mutations can cause a variant of Alzheimer's disease characterized by a spinal disorder resulting in lower body weakness or paralysis (Houlden et al., 2000; Verkkoniemi et al., 2001).

In other genetics and AD research, a team of Columbia University investigators conducted a family-based study series to identify mutations in genes related to familial, early-onset AD among Caribbean Hispanics, a rapidly growing population in the United States (Athan et al., 2001). The study was carried out in an Alzheimer's Disease Research Center in northern Manhattan and in clinics in the Dominican Republic and Puerto Rico. Participants were drawn from 206 Caribbean Hispanic families with two or more living members with AD. Nineteen families and several individuals had developed AD before they were 55 years old. To identify possible genetic mutations, the investigators sequenced the entire coding region of the presenilin-1 gene from these 19 families and their living relatives. Based on these analyses, the study team found a nucleotide change resulting in an amino acid substitution in presenilin-1 that had not been previously described. This same mutation was observed in 23 people from eight of the 19 families. A Caribbean Hispanic with the mutation and early-onset familial AD was also found by sequencing 319 unrelated


Human Chromosomes



individuals in northern Manhattan. This mutation was later found in five people from four Hispanic families with AD who had been referred for genetic testing. Members from another five Hispanic families have also been identified with this mutation. None of the families was related to one another and they came from different places, yet all 18 carriers of the new mutation shared a variant allele indicating a common ancestor. This genetic change probably accounts for a high percentage of early-onset familial AD in the Hispanic population. The researchers also sequenced the parts of the APP gene where mutations are known to cause AD, but found no mutations.

A recent study funded by NINDS, NIA, and other organizations provided further evidence on the genetic basis of AD. This research team identified a new mutation in a Swedish family with a history of the disorder (Nilsberth et al., 2001). Affected individuals have a mutation in a unique location within APP, which leads to early-onset AD. Information collected from the family with this variation as well as from test tube studies suggests that a novel beta-amyloid processing mechanism may be involved, specifically one in which the formation of protofibrils (a very small beta-amyloid toxic precursor to a plaque) is an initial event in the degeneration of neurons. The location of the mutations appears to have a direct effect on the nature of beta-amyloid plaque formation in affected individuals. In turn, this may affect the clinical features of their particular disease. The suggestion that a novel form of beta-amyloid processing may be occurring in individuals with this mutation may help researchers better understand the cellular mechanisms that contribute to the development of AD.

We also know that slightly different forms of the APOE gene on chromosome 19 can influence a person's risk of developing late-onset AD. However, the APOE-ε4 allele of this gene may explain only about 10 to 15 percent of the genetic risk of late-onset AD, and it is likely that other major risk factor genes also are involved. The roles that genetic changes play in increasing or decreasing a person's chances of developing late-onset AD are under intense scrutiny by many scientists.

The NIA's AD Genetics Initiative: Accelerating the Pace of Research

In the 10 years since APOE-ε4 was identified as a risk factor gene, scientists have made great progress in narrowing the search for other risk factor genes that may have links to late-onset AD. They have drawn significantly closer to identifying at least four regions of chromosomes where other risk factor genes might be. As this research has intensified, however, it has become increasingly clear that scientists need many more samples of genetic material if they are to continue making progress.

In the spring of 2002, NIA invited a group of leading scientists to plan a new AD Genetics Initiative that would significantly expand the collection of blood samples from individuals with AD and their family members. These blood samples will allow investigators to create and maintain "immortalized" cell lines – cells that are continuously regenerated in the laboratory. These cell lines are crucial for the exhaustive DNA analysis studies needed to identify risk factor genes.

NIA hopes to gather between 1,000 and 2,000 samples from people with AD and their family members, and has provided supplemental funding to 10 Alzheimer's Disease Centers (ADCs) so that they can recruit new people for genetics research and encourage these people to provide blood samples for the Initiative. (The ADCs conduct research, provide investigator training and patient care, and support the research process by developing centralized databases and research tools.) NIA also is collaborating with the Alzheimer's Association to develop community outreach programs to foster participation in the Initiative, especially among families that have two or more members with late-onset AD.

The National Cell Repository for AD (NCRAD), located at Indiana University, will serve as the centralized repository for the Initiative. NCRAD was established to provide genetic researchers with cell lines and/or DNA samples from people with well-documented family histories of AD. Since 1989, the Repository has been banking DNA and cells and building a database of rare and unique DNA information, family histories, and medical records. Many researchers working to identify genetic defects associated with AD have used genetic material stored in the Repository. To enhance the diversity of analysis and promote innovative research, NIA will provide access to the Repository to AD genetics researchers and encourage them to share data.

Future plans of the Initiative include creating a national case-control sample set, in which the genes of people with AD (cases) will be compared to those who have no symptoms of the disease (controls). Creating such a sample set will give investigators additional opportunities to evaluate potential candidates for risk factor genes for late-onset AD.

Three teams of investigators studying late-onset AD published papers recently reporting results of studies investigating one particularly intriguing chromosome – chromosome 10. In the first study, investigators at the Mayo Clinic in Jacksonville, Florida, confirmed a linkage between high levels of beta-amyloid in blood and a region on the long arm of chromosome 10 (Ertekin-Taner et al., 2001). Because beta-amyloid is intimately associated with the neuropathology of AD, the investigators think that genes that elevate these beta-amyloid levels could be risk factor genes for AD. A second team, located at the Washington University School of Medicine, conducted a study on pairs of siblings who had definite or probable AD. They also found a suggestive linkage to AD in the same region of the long arm of chromosome 10 (Myers et al., 2000). In a third analysis, a Harvard Medical School research team focused upon a specific gene called the insulin degrading enzyme (IDE) gene (Bertram et al., 2000). IDE is found in neurons and another type of brain cell called glia, and it acts to degrade beta-amyloid. These investigators found a linkage between one form of IDE, present in a region on the long arm of chromosome 10, with AD. These studies indicate that there may be more than one late-onset AD gene on the long arm of chromosome 10 that affects the risk of developing AD.

Chromosome 10 is of interest for another reason as well. Little is currently known about genes that might influence the age at which AD begins ("age of onset"). Because AD and Parkinson's disease (PD) share some common characteristics, including dementia, Duke University Medical Center investigators supported by NCRR and NIA performed a genomic screen in the families of 449 AD and

174 PD families to see whether one or more genes controlled age at onset for both diseases. Results showed that this characteristic is highly heritable and that a specific region on chromosome 10 affects age of onset for both diseases (Li et al., 2002b).

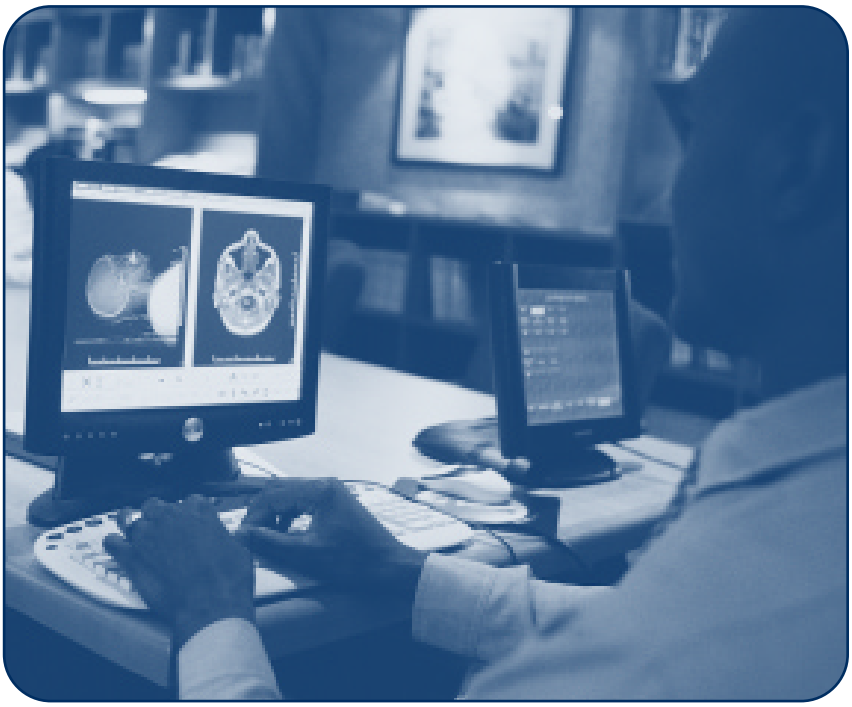
Chromosomes 9 and 12 are also stirring interest as possible sites of genes that might affect AD risk. In collaboration with researchers at Washington University School of Medicine and Cardiff University, scientists at NIA have used genetic analysis strategies to find potentially promising regions on these two chromosomes. They are now conducting sequence analyses to pinpoint the locations more exactly (Myers et al. 2002). These investigators also are sequencing genes that might be involved in oxidative stress and lipid metabolism, two other factors thought to be involved in the development of AD.

Scientist at NIA and investigators from Duke University also have recently completed a study designed to examine whether cognitive decline associated with the APOE-ε4 allele is different in older African-Americans than in Caucasians (Fillenbaum et al., 2001). The study involved more than 4,000 residents of

five adjacent counties in the Piedmont area of North Carolina. Participants were given a brief cognitive function test at the beginning of the study and again 3 years later. The investigators found that participants who had the APOE-ε4 allele scored lower on the first test than did those without APOE-ε4, and that having the allele increased by 59 percent the odds of cognitive decline. However, age and race were not related to performance on the tests.

Other research is demonstrating that finding genes that are involved in protecting cognitive health in the elderly is as important as finding risk factor genes for cognitive decline and AD. University of Pittsburgh scientists supported by NIMH recently began a systematic genome survey to identify the locations of particular genes that might affect the likelihood of reaching age 90 with preserved cognitive abilities (Zubenko et al., 2002). Participants included 100 young adults, aged 18-25 and 100 elders (94 nonagenarians and 6 centenarians). All of the elderly participants were cognitively normal, as reflected by clinical and psychometric assessments and "good" average capacity to carry out their activities of daily living. The majority were living independently despite multiple medical conditions. None had a history of mental disorders in early or middle adulthood, only one was a current smoker, and 80 percent consumed alcohol less than once each month. The genome survey method revealed an elevated frequency of the APOE-ε2 allele (the relatively rare APOE form that is thought to provide some protection against AD), and a reduced frequency in the APOE-ε4 allele among the elders compared to the young adults. These results suggest that several behavioral and genetic factors may contribute to the likelihood of achieving exceptional longevity with preserved cognition.

Increasing knowledge about the genetics of Alzheimer's disease has led to an urgent need for accurate information and materials to educate families, health care providers, and the public about the challenges they may face and to provide models for genetics education in other, equally complex diseases. The National Human Genome Research Institute (NHGRI) has funded a group of researchers at the Massachusetts General Hospital/Harvard Medical School and the University of



THE INTERACTION OF GENETIC AND LIFESTYLE FACTORS MAY BE LINKED TO A REDUCED RISK OF AD.

Alabama to address the ethical, legal, and social implications of the genetics of AD from the critical perspective of a group at high risk of the disease: currently unaffected relatives of people with AD (Tanzi and Blacker, 2001). The researchers have been working together since 1990 as part of the NIMH Genetics Initiative to identify families with Alzheimer's disease for genetic linkage studies. Nearly 350 such families, predominantly affected sibling pairs and over 300 of their unaffected siblings, have been identified. The researchers will use a variety of approaches to study knowledge, attitudes, and behavior related to genetic studies and genetic testing in the unaffected people in these AD families and their primary care physicians, and will develop and pilot educational materials designed to address their needs for genetic information.

A second study, funded by NHGRI and conducted by Boston University School of Medicine investigators, has estimated risk of AD among adult children of persons with AD to determine who chooses to obtain genetic susceptibility testing for AD and to assess the risks and benefits of providing such information (Green et al., 2002). Study investigators hope that their results can inform the development of guidelines for clinicians for genetic testing, risk assessment, and appropriate counseling scenarios.

Lifestyle

Another area that is capturing an increasing amount of attention and interest is the possible influence of education, leisure, physical, and intellectually stimulating activities on the risk of developing AD. The interaction of genetic and lifestyle factors is also of interest. A number of studies over the past few years have provided intriguing hints that these activities may be linked to a reduced risk of AD, and they are consistent with what we know about other health benefits of lifelong physical and intellectual activity.

Several studies in the past year have revealed some clues about the effect of these potentially protective activities. The first study, conducted by a research team at Case Western Reserve University School of Medicine, explored the longstanding notion that high levels of education and occupation are correlated with protection against development of AD (Friedland et al., 2001). Some researchers have speculated that such protective effects occur because these activities may build up brain reserves that delay or buffer against cognitive decline. Others have argued that the protective effect of education is related to its complex associations with economic, medical, and occupational factors. This study attempted to differentiate between these two

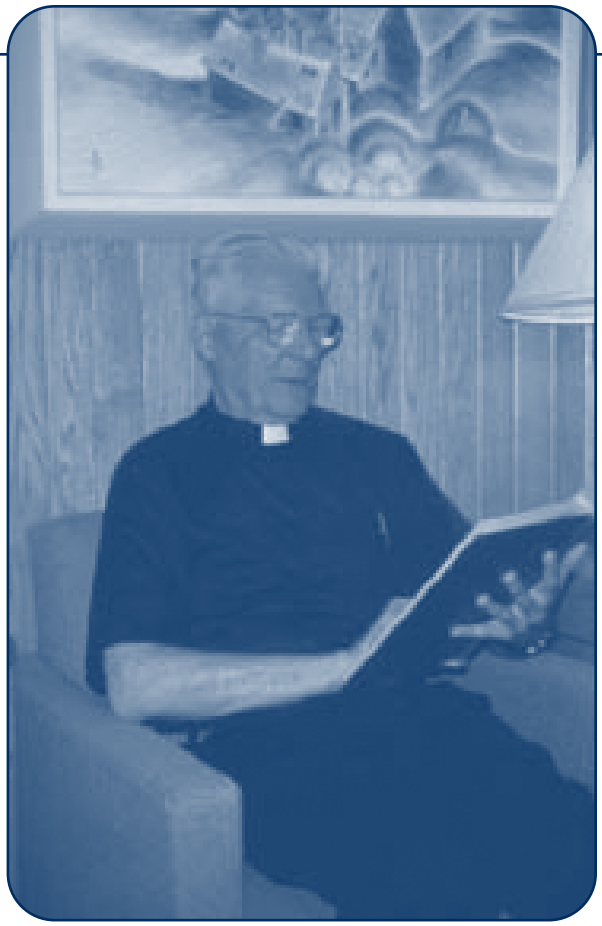
explanations by investigating the potential protective effects of three general categories of recreational activities. These categories included passive (e.g., watching television), intellectual (e.g., playing chess, solving crossword puzzles), and physical (e.g., bowling, skating) activities. Patients with AD were found to have been much less active than healthy control persons of similar background in terms of both diversity and intensity of recreational activities engaged in during early and middle adulthood. These differences were not explained by differing educational or income levels, age, or gender. People who were relatively inactive in midlife had a 250 percent increased risk of developing AD. Differences were greatest for intellectual activities, but were significant for passive and physical activities as well. This study suggests that engaging in physical and intellectual activities may buffer against cognitive decline and that underactivity is related to increased risk of AD. Although these results are provocative, the study authors suggest that they be interpreted with caution because it was not possible to evaluate whether AD could be the cause rather than the consequence of underactivity. The disease may develop several decades before the onset of symptoms and very early deficits might adversely affect participation in recreational activities.

In a similar study, investigators with the Religious Orders Study, an ongoing examination of aging among older Catholic nuns, priests, and brothers across the U.S., tested the hypothesis that frequent participation in intellectually stimulating activities is associated with a reduced risk of AD (Wilson et al., 2002a). About 800 Religious Order Study participants were rated at the beginning of the study for frequency of participation in such cognitive activities as reading a newspaper. A 5-point cognitive activity score was derived from these data, with the highest score given to daily or almost daily participation and the lowest score given to participation less than once a year. Investigators also gathered information on time spent in physical activities. For up to 7 years, participants underwent annual evaluations that included detailed cognitive function testing to determine whether they had developed AD. During an average of 4.5 years of follow-up, 111 people developed AD. In an analytic model that controlled for age, sex, and education, each 1-point increase in the cognitive activity score was associated with a 33 percent reduction in risk of AD. Results were comparable when those with memory impairment were excluded at the beginning of the study and when the presence of the APOE-ε4 allele and medical conditions were

factored in. In other analytic models that controlled for age, sex, education, and beginning level of cognitive function, a 1-point increase in cognitive activity was associated with reduced decline in global cognition (by 47 percent), working memory (by 60 percent), and perceptual speed (by 30 percent). Participation in physical activity was unrelated to risk of disease or rate of cognitive decline. The results suggest that more frequent participation in intellectually stimulating activities is associated with reduced risk of AD.

Another research project with the Religious Orders Study participants examined individual differences in the rates of change in cognitive abilities (Wilson et al., 2002b). Participants, who were aged 65 years and older and free of clinical evidence of AD at the beginning of the study, underwent annual clinical evaluations for up to 6 years. Cognitive function was assessed at each evaluation with a battery of tests, from which summary measures of performance in seven cognitive areas, or domains, were derived. On average, decline occurred in each domain and was more rapid in older persons than in younger persons. However, wide individual differences were evident at all ages. The rate of change in a given domain was not strongly related to the beginning level of function in that domain, but was moderately associated with rates of change in other cognitive domains. The results suggest that change in cognitive function in old age primarily reflects person-specific factors rather than an inevitable developmental process.

A recent study by scientists at the University of Washington in Seattle explored how environmental risk may interact with the APOE genotype to clarify the possible relationships between early life environment and the development of



AD (Moceri et al., 2001). The researchers used information from Census data to index socioeconomic risk through measures of the father's occupation, parental age, household size, number of siblings, and birth order. They found that the risk of AD increased among individuals whose fathers were unskilled manual workers or laborers compared to those whose fathers had nonmanual occupations, but this increased risk was significant only among individuals who carried the APOE-ε4 allele. Therefore, compared to those with neither risk factor, the risk for Alzheimer's disease was greatly elevated when both the genetic and the environmental risk factors were present. These findings highlight some intriguing clues about the possibility that the APOE-ε4 allele may modify any relationship between early-life environmental factors and the development of Alzheimer's disease.

Cholesterol and Homocysteine

A third exciting area of research is providing data about factors that may protect against or increase the risk of AD. In recent years, a number of studies have suggested a connection between AD and cholesterol in the blood. For example, the APOE-ε4 allele is a variant of the APOE gene, which codes apolipoprotein E, a protein that helps to carry cholesterol in the blood. Test tube studies also have shown that blood cholesterol increases production of beta-amyloid from its APP precursor, and animal studies show a relationship between blood cholesterol and brain plaque levels in transgenic mice. Epidemiologic studies linking vascular risk factors to dementia have lent further support to this relationship (see the p. 22 sidebar on the Honolulu-Asia Aging Study for more on findings from these studies). Many questions remain about the relationship between blood cholesterol and AD, but these intriguing findings have spurred new research and led scientists to hypothesize that drugs that lower blood cholesterol might also lower risk of developing dementia and AD.

Two recent observational studies examined changes in AD risk with prescription of statins, the most commonly prescribed cholesterol-lowering drugs. Both studies have stirred considerable interest because they showed a significant reduction in dementia risk correlated with individuals who take these drugs. In the first study, a research team at the Boston University School of Medicine, the University of Massachusetts Medical School, and Harvard School of Public Health analyzed data on more than 1,300 people in the United Kingdom (Jick et al., 2000). They found that people with high cholesterol who were prescribed statins had a risk of dementia 70 percent lower than those who did not have high cholesterol (or hyperlipidemia) or who were not on lipid-lowering treatment. The effect was similar regardless of the specific statin prescribed. People with high cholesterol who were prescribed a non-statin drug or those who remained untreated did not have reduced risk for dementia, suggesting that the effect was not due to lowering lipid levels per se.

Investigators at Loyola University Medical School in Maywood, IL, conducted a second study, which involved cases listed in a three-hospital database in the U.S. This study showed a relationship between either lovastatin or pravastatin prescription and a 60 to 73 percent lowered risk of developing AD (Wolozin et al., 2000). This relationship was not found with non-statin medications for hypertension or cardiovascular disease.

Although epidemiologic studies do not prove causality, the implications of this research could be considerable. The authors of these studies speculate that AD risk may be

Improving Clinical Research and Care by Improving Outreach

To thoroughly understand the factors that might increase the risk of AD or protect against it and to develop effective treatment strategies, researchers need to study people who come from a variety of locations, racial and ethnic groups, and demographic backgrounds. For some years, NIH has made a concerted effort to improve the diversity of its research participants and to reach out to groups who traditionally have not participated in clinical studies. Increasing the numbers of non-Caucasians who are over 65 and therefore at higher risk of AD, has been an important priority for Alzheimer's disease researchers.

As part of this effort, in 1990, the NIA began a program of Satellite Diagnostic and Treatment Clinics

through its existing Alzheimer's Disease Centers (ADCs) Program. The satellite clinic program was significantly expanded in following years; currently 25 clinics are operating across 18 ADCs.

Many satellite clinics are located in areas where staff can reach out to minority, rural, or underserved populations. The clinics are primarily focused on providing diagnostic and treatment services to people with AD and their families, but through their connection with the ADCs, they can offer families opportunities to participate in research protocols and clinical drug trials.

Before NIA established the satellite clinic program, minority enrollment in the ADCs was approximately 4 percent. Since 1990, the overall ADC rate of minority enrollment has increased significantly, ranging between 10 and 14 percent for African-Americans and 4 to 7 percent for Hispanics. The satellite clinics have had similar success in enrolling Native Americans. For example, the University of Texas Southwestern ADC in Dallas has developed close ties with the Choctaw Nation, with a subsequent enrollment of 146 subjects, representing 6.6 percent of the Center enrollment. This effort comes almost exclusively from their satellite clinic. American Indian/Alaskan Natives represent 18.7 percent of the registry from the University of Washington ADC. Almost all of these study participants come from their satellite clinic.

ADCs are also using other strategies to promote diversity in clinical trial enrollment, such as active community outreach and education activities. Memory screening at health fairs, mass mailing of brochures, educational presentations, and high visibility research projects have all helped to promote enrollment. For example, the Indiana ADC was highly successful in recruiting African-American participants because of its association with the Indianapolis-Ibadan Dementia Project (see p. 24 for more on this study). The Rush-Presbyterian-St. Luke's ADC in Chicago has established a successful working relationship with the president of the National Black Sisters Conference and the National Black Catholic Clergy Caucus and this has led to increased enrollment of African-American nuns, priests, and brothers in the Religious Orders Study. Efforts to cement the relationship with the African-American Catholic Communities continue with the formation of an Advisory Panel of African-American Catholic religious leaders to gain a better appreciation of potential barriers to participation of individual nuns, priests, and brothers.

reduced because onset of dementia is delayed or because age-related changes that result in cognitive impairment are delayed, and they suggest that the use of statins could substantially reduce the risk for dementia in older people. The only way to determine whether statins delay onset of AD is to perform a clinical trial.

A recent epidemiologic study from investigators at Boston University, based on data from the Framingham Heart Study, also found that elevated levels of an amino acid called homocysteine, a risk factor for heart disease, are associated with an increased risk of developing AD (Seshadri et al., 2002). Investigators at NIA have shown in transgenic mice that high homocysteine levels make neurons vulnerable to dysfunction and death (Kruman et al., 2002). The relationship between AD and homocysteine is particularly interesting because blood levels of homocysteine can be reduced by increasing intake of folic acid and vitamins B_6 and B_{12}. These findings have led the NIA to fund a multicenter, randomized, placebo-controlled clinical trial, currently underway, to determine whether reducing homocysteine levels through high-dose supplements of folate and vitamins B_6 and B_{12} will slow the rate of decline in people with AD.

What Can Be Done to Halt AD, Slow Its Progress, or Lessen its Effects?

As the earlier sections of this report have shown, recent advances in genetics and molecular biology have vastly increased our understanding of the brain – how it works normally and what happens when something goes wrong. Improvements in this understanding have opened the doors to a number of

potential therapeutic targets for AD. NIA, other NIH Institutes, and private industry are conducting studies on an estimated 30 compounds that may be active against AD. These studies focus on four issues:

- helping people with AD maintain cognitive function over the short-term;
- slowing the progress of the disease;
- treating AD-associated behavioral problems; and
- preventing AD.

The remainder of this section provides highlights of several ongoing clinical trials.

- The Memory Impairment Study – Launched in March 1999, this study has completed enrollment with 769 participants in 68 sites in the Alzheimer's Disease Cooperative Study (ADCS) network. The ADCS is a study in which many Alzheimer's Disease Centers and other clinical sites cooperate to investigate promising drugs for AD and develop and improve tests for evaluating AD patients in clinical trials. The purpose of the

Memory Impairment Study is to determine whether daily doses of vitamin E or donepezil (Aricept) given over a 3-year period can delay or prevent the onset of AD in people who have MCI. A major challenge for this trial was screening and recruiting enough people with MCI and retaining them for the long study period. The design of the trial and the success of the recruitment phase represent a major advance in AD clinical trial methodology, and this protocol has been widely copied by the pharmaceutical industry, which has now used this study design to set up several independent trials of various agents using volunteers with MCI. Results of this trial are expected in mid-2004.

- Estrogen and cognitive function – Over the past 25 years, animal studies have suggested that estrogen has some positive effects on the brain and memory function. Some human epidemiological studies have supported this notion. These findings have created scientific interest in the relationship among estrogen, memory, and cognitive function. Although scientists still don't know whether normally aging women who take estrogen alone will be protected from developing AD, women aged 65 and older taking a combination of estrogen/progestin (Prempro) in a recent clinical trial were found to have a significantly increased risk of developing dementia (Shumaker et al., 2003). Another part of this same study, the Women's Health Initiative, previously showed that combined estrogen/progestin therapy also increases risk of heart disease, stroke, blood clots, and breast cancer, while decreasing the risk for hip fracture and colon cancer. The NIA continues to explore potential benefits of estrogen alone in an ongoing clinical trial on cognitively normal older women with a family history of dementia. Safety monitoring boards that include expert physicians and scientists are carefully monitoring the side effects of treatment for women participating in this study. Clearly, more research is needed on this complex issue.

- Simvastatin and AD progression – This study, which is actively recruiting, is testing whether simvastatin (Zocor), a commonly prescribed cholesterol-lowering drug, can slow the rate of disease progression in people with AD. Results of this trial are expected in late 2005.

- NSAIDs and inflammation – One of the hallmarks of AD is inflammation in the brain, but whether it is a cause or an effect of the disease is not yet known. Epidemiologic evidence suggests that anti-inflammatory agents,

such as non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, naproxen, and indomethacin are associated with a decreased risk of AD. One clinical trial designed to determine whether naproxen or rofecoxib (a new selective cyclooxygenase, or COX-2, inhibitor) found that neither NSAID slowed the rate of cognitive deterioration in people with mild to moderate AD. Researchers hope

that prevention trials underway will prove the effectiveness of NSAIDs in preventing AD in people at risk, but not yet showing symptoms, of the disease (Aisen et al., 2003).

- Nicotinic agents and cognitive function – The mainstay of current AD treatment is drugs that help to maintain levels of acetylcholine, a neurotransmitter that is crucial in the formation of memories. These drugs have limited effectiveness, however, so researchers also are exploring other therapeutic strategies.

Ongoing NCRR-supported investigations of the molecular substructure of central nervous system nicotinic receptors, their accompanying pharmacology, and the effects of nicotinic agents on cognitive function have suggested the possibility that nicotinic cholinergic receptor stimulation may have beneficial effects in AD and other neuropsychiatric disorders. Results from recent NCRR-supported pilot clinical trials with nicotine and novel nicotinic agents suggest that acute nicotinic stimulation in AD patients can transiently improve the acquisition and retention of verbal and visual information and decrease errors in cognitive tasks, as well as improve accuracy and response time (Newhouse et al., 2001).

- Drug treatments for psychiatric and behavioral problems in AD – Many people with AD have periods of restless or irritable behavior and become easily agitated. Agitation may be an expression of pain, anger, anxiety, or depression, or it may be a still unexplained part of the disease. Whatever the cause, it is a frequent and often difficult behavioral issue for people with AD and their caregivers. An ADCS research team is now conducting a clinical trial among 120 nursing home residents with severe AD to see whether divalproex sodium (Valproate), an antiseizure medication, can help to ease agitation.

Other psychiatric and behavioral problems, such as delusions, mood changes, and aggression, also are common in patients with Alzheimer's disease and other dementias, and are disturbing to the person and his or her family. A range of medications and non-medication approaches are used to help treat these symptoms, but many questions remain about which treatments to use for which symptoms and how to balance positive treatment effects

against potential side effects. The NIMH and NIA are supporting several clinical trials examining the effectiveness of drugs used to treat aggression, psychosis, depression, and other common behavioral problems in persons with AD (Pollock et al., 2002; Schneider et al., 2001; Sultzer et al., 2001). Findings from this research may lead to improved and more precise therapies for the behavioral and psychotic disturbances associated with AD and other forms of dementia.

In addition to these ongoing or just completed trials, NIA is planning a number of other innovative clinical trials over the next 5 years. These studies, which will be conducted through the ADCS and other clinical sites, include:

- A project to develop sensitive and more effective methods for evaluating change over time in cognitively healthy elderly in a number of areas, such as overall cognitive functioning, memory, ability to carry out activities of daily life, and quality of life. These improved evaluation instruments will then be used in AD prevention clinical trials to measure changes that result from the interventions.

- A study to see whether low-doses of divalproex sodium (Valproate) can delay or prevent agitation and psychosis from developing in people with mild to moderate AD, and also to see whether its possible neuroprotective properties have any effect on slowing the rate of cognitive decline.

- A study to test the safety and tolerability of indole-3-propionic acid (IPA), a highly potent, naturally occurring antioxidant that also inhibits fibril formation by beta-amyloid. Investigators will measure levels of biological markers related to oxidative damage and AD to assess the biological activity of IPA and also determine whether this antioxidant has any beneficial short-term effects on AD.

RESEARCH MAY LEAD TO IMPROVED THERAPIES FOR THE BEHAVIORAL DISTURBANCES ASSOCIATED WITH AD.

Research to Help Families and Caregivers

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

A number of studies are examining the factors that contribute to stress and depression in family caregivers of people with AD. In one study, Case Western Reserve University investigators explored the relationship between depression in the care recipient and in the caregiver (Neundorfer et al., 2001). They found that the well-being of both people is closely related – the more depressed the person with AD was, the more depressed the caregiver also was. Wives of men with AD and caregivers who were themselves in poor health were at particular risk of depression. The researchers concluded that interventions for caregivers are needed early on in the family member's illness and that further research is needed to understand what interventions will sustain the quality of life and physical and mental well-being of the person with AD as well as the caregiver.

A second study examined caregiving stress from a somewhat different angle. We know that the chronic stress resulting from continuously caring for a family member with dementia has been associated with depression, elevated stress hormones, and increased vulnerability to influenza and poor wound healing in older caregivers. However, only recently have the long-term effects of this stressful period for caregivers after the death of the demented spouse been investigated. This study, funded by NIA and NIMH and conducted by a research group at the Houston Veterans Affairs Medical Center, examined the psychological state of spousal caregivers for up to 4 years following the death of the person with dementia (Robinson-Whelen et al., 2001). The former caregivers were compared to a group of caregivers who were still caring for their husbands or wives throughout the study, as well as to a group of non-caregiving age-matched control participants. The investigators found that although former caregivers experienced slight decreases in stress and negative mood after their spouses had died, their emotional state and levels of depression and loneliness had not returned to levels comparable to non-caregivers up to 3 years later. In fact, they remained similar to those of current spousal caregivers, suggesting that the consequences of long-term caregiving may be long-term as well.

INTERVENTIONS FOR CAREGIVERS ARE NEEDED EARLY ON IN THE FAMILY MEMBER'S ILLNESS.

The investigators also found that social support after the death of the spouse helped more to ensure a positive post-caregiving outcome than support received during the caregiving years. Not surprisingly, an inability to suppress thoughts of the caregiving years was negatively associated with psychological well-being. Clearly, the needs of caregiving spouses must receive long-term attention. Programs aimed at providing social support and working through the persistent traumatic and stressful thoughts of the prior years of spousal caregiving have the potential to help former caregivers and boost their psychological and physical well-being.

A third study looked at ways to help family caregivers by building on previous research showing that people who exercise benefit in various ways, including reduced stress-induced high blood pressure and improved quality of sleep. This study, conducted by Stanford University Medical School researchers, is the first to examine the role that a regular moderate-intensity exercise program plays in enhancing health and quality of life for women caring for loved ones with dementia (King et al., 2002). A group of 100 women caregivers, aged 49 to 82 years old, received either home-based, telephone-supervised moderate-intensity exercise training or a nutrition education program. Exercise consisted of brisk walking for four 30- to 40-minute sessions per week. Compared with the nutrition education group, exercise participants showed significant improvements in physical activity levels, stress-induced blood pressure reactions, and sleep quality. The nutrition group also benefited through reducing the percentage of total calories from fats and saturated fats and consuming fewer fats, oils, sweets, and high-fat snacks. Both groups reported significant reductions in psychological distress, including depressive symptoms and self-rated stress. This research demonstrates that properly tailored health promotion programs can improve the health and functioning of older women family caregivers. A critical challenge remains: How best to tailor programs to the needs and preferences of other populations of caregivers.

Part 3
Outlook for the Future

The future builds upon the events and experience of the past and present. That's certainly true for Alzheimer's disease research, for the explosion of knowledge during the past 25 years has set the stage for a hopeful future in which, one day, we may be able to prevent or even cure this terrible disease, which robs our loved ones of their most precious faculty – their minds.

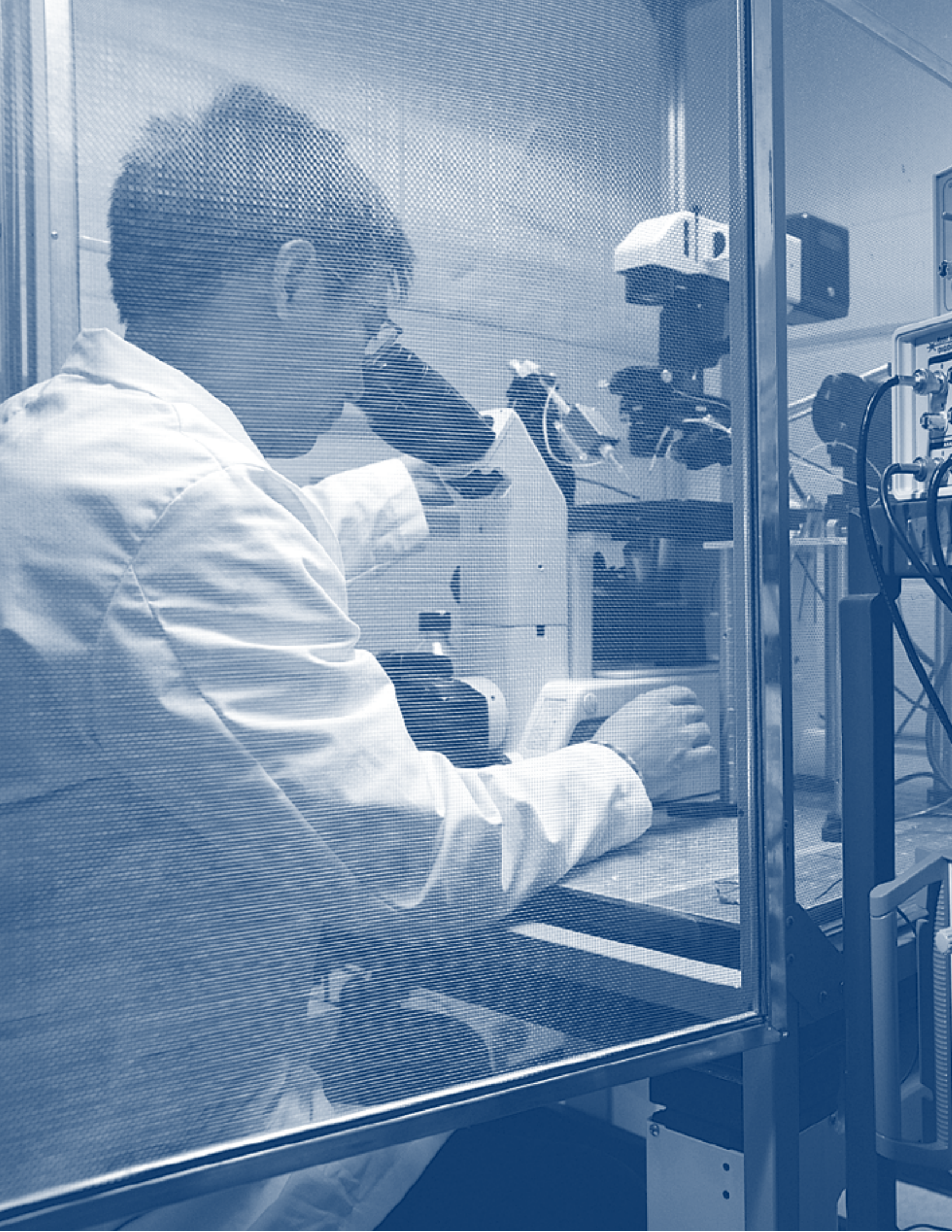
Here are just a few ways in which past and present research findings are providing a foundation for the future:

15 years ago, we did not know any of the genes that could cause AD, and we had only an inkling of the biological pathways that were involved in the development of brain pathology.

Today, we know the 3 major genes for early-onset disease and one of the major risk factor genes for late-onset disease, and we are rapidly expanding the research infrastructure to identify the other major risk factor genes for late-onset AD (see the description of NIA's Genetics Initiative on page 28). The known genes have made major contributions to our extensive knowledge of pathways leading to the development of AD's characteristic amyloid plaques in the brain. Identification of the *tau* gene mutations causing frontotemporal dementia with parkinsonism (FTDP-17), another late-onset dementia, is providing clues to ways in which the formation of the characteristic intracellular tangles in AD may be prevented.

10 years ago, we could not model Alzheimer's disease in animals.

Today, transgenic mice are an invaluable resource for modeling amyloid plaque development in the brain and in testing possible therapies (for more on this work, see the beta-amyloid section on page 16 and the immunization sidebar on page 18). Other animals also are now being effectively used as models for age-related and disease-related changes in brain, as well as models for testing promising interventions.



5 years ago, we had no ways of identifying people at high risk for the disease and did not have any prevention clinical trials funded.

Today, scientists are identifying people at high risk of developing AD by brain imaging, neuropsychological tests, and structured clinician interviews, leading to insights into the preclinical phases of the disease, such as MCI (see page 11 for more about advances in neuroimaging). We have eight ongoing prevention clinical trials, and 11 clinical trials that are aimed at slowing the progression of AD or alleviating distressing symptoms such as agitation (see page 36 for more information on clinical trials).

2 years ago, we did not understand the mechanism by which plaques and tangles relate to each other.

Today, as a result of developing the first double transgenic mouse that produces both plaques and tangles, we know that plaques in the brain can influence the development of tangles in brain regions susceptible in AD (see page 20 for more on the double transgenic mouse). Recent findings also suggest that a number of neurodegenerative disorders have some common mechanisms of disease, and these findings will further inform research in AD.

The challenge for the future is to predict the specific pilot and full-scale clinical trials that are most likely to yield effective strategies for preventing and treating AD in different populations. To facilitate this, we need to develop new strategies for moving compounds that show promise in the laboratory into animal studies to test for safety and efficacy and then into pilot trials in people. The Alzheimer's Disease Prevention Initiative, a major effort by NIH in collaboration with other Federal agencies and the private sector, is providing a focus for AD researchers to meet this challenge through support for current research on genetics, on the basic cellular biology of AD-related pathways, and on the changes taking place in the brains of people with mild cognitive impairment and early AD.

Results from animal model research and tantalizing hints of possible risk and protective factors from epidemiologic studies will contribute further information. Other studies will also provide valuable clues about the possible impact of diseases such as cardiovascular disease and diabetes on AD-related dementia in later life. The ultimate goal of this research is to develop and test a variety of types of interventions, be they behavioral, dietary, or drug, to determine whether they can ameliorate the cognitive and behavioral symptoms of Alzheimer's disease, modify its course, or eventually delay the onset of or prevent the disease entirely.

References

Aisen, P.S.; Schafer, K.A.; Grundman, M.; Pfeiffer E.; Sano, M.; Davis, K.L.; Farlow, M.R.; Jin, S.; Thomas, R.G.; Thal, L.J. (2003) for the Alzheimer's Disease Cooperative Study. Effects of Rofecoxib or Naproxen vs Placebo on Alzheimer's Disease Progression, A Randomized Controlled Trial. *JAMA*, 289(21), 2819-2826.

Albert, M.S.; Moss, M.B.; Tanzi, R.; Jones, K. (2001). Preclinical Prediction of AD Using Neuropsychological Tests. *Journal of the International Neuropsychological Society*, 7(5), 631-639.

Athan, E.; Williamson, J.; Ciappa, A.; Santana, V.; Romas, S.N.; Lee, J.H.; Zadroga, H.R.; Lantiqua, R.; Medrano, M.; Torres, M.; Arawaka, S.; Rogaeva, E.; Song, Y.; Sato, C.; Kawarai, T.; Fafel, K.C.; Boss, M.A.; Seltzer, W.K.; Stern, Y.; St. George-Hyslop, P.; Tycko, B.; Mayeux, R. (2001). A Founder Mutation in Presenilin 1 Causing Early-Onset Alzheimer Disease in Unrelated Caribbean Hispanic Families. *JAMA*, 286(18), 2257-2263.

Bertram, L.; Blacker, D.; Mullin, K.; Keeney, D.; Jones, J.; Basu, S.; Yhu, S.; McInnis, M.G.; Go, R.C.; Vekrellis, K.; Selkoe, D.J.; Saunders, A.J.; Tanzi, R.E. (2000). Evidence for Genetic Linkage of Alzheimer's Disease to Chromosome 10q. *Science*, 290(5500), 2302-2303.

Busciglio, J.; Pelsman, A.; Wong, C.; Pigino, G.; Yuan, M.; Mori, H.; Yankner, B.A. (2002). Altered Metabolism of the Amyloid-Beta Precursor Protein is Associated with Mitochondrial Dysfunction in Down Syndrome. *Neuron*, 33(5), 677-688.

Cai, H.; Wang, Y.; McCarthy, D.; Wen, H.; Borchelt, D.R.; Price, D.L.; Wong, P.C. (2001). BACE1 is the Major Beta-Secretase for Generation of Abeta Peptides by Neurons. *Nature Neuroscience*, 4(3), 233-234.

Chandra, V.; Pandav, R.; Dodge, H.H.; Johnston, J.M.; Belle, S.H.; DeKosky, S.T.; Ganguli, M. Incidence of Alzheimer's Disease in a Rural Community in India: The Indo-US Study. (2001). *Neurology*, 57(6), 985-989.

Cherny, R.A.; Atwood, C.S.; Xilinas, M.E.; Gray, D.N.; Jones, W.D.; McLean, C.A.; Barnham, K.J.; Volitakis, I.; Fraser, F.W.; Kim, Y.; Huang, X.; Goldstein, L.E.; Moir, R.D.; Lim, J.T.; Beyreuther, K.; Zheng, H.; Tanzi, R.E.; Masters, C.L.; Bush, A.I. (2001). Treatment with a Copper-Zinc Chelator Markedly and Rapidly Inhibits Beta-Amyloid Accumulation in Alzheimer's Disease Transgenic Mice. *Neuron*, 30(3), 665-676.

Choe, L.H.; Dutt, M.J.; Relkin, N; Lee, K.H. (2002). Studies of Potential Cerebrospinal Fluid Molecular Markers for Alzheimer's Disease. *Electrophoresis*, 23(14), 2247-2251.

DeLeon, M.J.; Convit, A.; Wolf, O.T.; Tarshish, C.Y.; deSanti, S.; Rusinek, H.; Tsui, W.; Kandil, E.; Scherer, A.J.; Roche, A.; Imossi, A.; Thorn, E.; Bobinski, M.; Caraos, C.; Lesbre, P.; Schlyer, D.; Poirier, J.; Reisberg, B.; Fowler, J. (2001). Prediction of Cognitive Decline in Normal Elderly Subjects with 2-[(18)F]fluoro-2-deoxy-D-glucose/Positron-Emission Tomography (FDG/PET). *Proceedings of the National Academy of Sciences USA*, 98(19), 10966-10971.

DeMattos, R.B.; Bales, K.R.; Cummins, D.J.; Dodart, J.C.; Paul, S.M.; Holtzman, D.M. (2001). Peripheral Anti-A Beta Antibody Alters CNS and Plasma A Beta Clearance and Decreases Brain A Beta Burden in a Mouse Model of Alzheimer's Disease. *Proceedings of the National Academy of Sciences USA*, 98(15), 8850-8855.

DeMattos, R.B.; Bales, K.R.; Cummins, D.J.; Paul, S.M.; Holtzman, D.M. (2002a). Brain to Plasma Amyloid-beta Efflux: A Measure of Brain Amyloid Burden in a Mouse Model of Alzheimer's Disease. *Science*, 295(5563), 2264-2267.

DeMattos, R.B.; Bales, K.R.; Parsadanian, M.; O'Dell, M.A.; Foss, E.M.; Paul, S.M.; Holtzman, D.M. (2002b). Plaque-associated Disruption of CSF and Plasma Amyloid-beta (Abeta) Equilibrium in a Mouse Model of Alzheimer's Disease. *Journal of Neurochemistry*, 81(2), 229-236.

Dickerson, B.C.; Goncharova, I.; Sullivan, M.P.; Forchetti, C.; Wilson, R.S.; Bennett, D.A.; Beckett, L.A.; deToledo-Morrell, L. (2001). MRI-Derived Entorhinal and Hippocampal Atrophy in Incipient and Very Mild Alzheimer's Disease. *Neurobiology of Aging*, 22(5), 747-754.

Dodart, J.C.; Bales, K.R.; Gannon, K.S.; Greene, S.J.; DeMattos, R.B.; Mathis, C.; DeLong, C.A.; Wu, S.; Wu, X.; Holtzman, D.M.; Paul, S.M. (2002). Immunization Reverses Memory Deficits Without Reducing Brain Abeta Burden in Alzheimer's Disease Model. *Nature Neuroscience*, 5(5), 452-457.

Du, A.T.; Schuff, N.; Amend, D.; Laakso, M.P.; Hsu, Y.Y.; Jagust, W.J.; Yaffe, K.; Kramer, J.H.; Reed, B.; Norman, D.; Chui, H.C.; Weiner, M.W. (2001). Magnetic Resonance Imaging of the Entorhinal Cortex and Hippocampus in Mild Cognitive Impairment and Alzheimer's Disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 71(4), 441-447.

Elias, M.F.; Beiser, A.; Wolf, P.A.; Au, R.; White, R.F.; D'Agostino, R.B. (2000). The Preclinical Phase of Alzheimer Disease: A 22-year Prospective Study of the Framingham Cohort. *Archives of Neurology*, 57(6), 808-813.

Ernst, R.L.; Hay, J.W. (1994). The U.S. Economic and Social Costs of Alzheimer's Disease Revisited. *American Journal of Public Health*, 84(8), 1261-1264.

Ernst, R.L.; Hay, J.W.; Fenn, C.; Tinklenberg, J.; Yesavage, J. (1997). Cognitive Function and the Costs of Alzheimer's Disease. An Exploratory Study. *Archives of Neurology*, 54(6), 687-693.

Ertekin-Taner, N.; Graff-Radford, N.; Younkin, L.H.; Eckman, C.; Adamson, J.; Schaid, D.J.; Blangero, J.; Hutton, M.; Younkin, S.G. (2001). Heritability of Plasma Amyloid Beta in Typical Late-onset Alzheimer's Disease Pedigrees. *Genetic Epidemiology*, 21(1), 19-30.

Fillenbaum, G.G.; Landerman, L.R.; Blazer, D.G.; Saunders, A.M.; Harris, T.B.; Launer, L.J. (2001). The Relationship of APOE Genotype to Cognitive Functioning in Older African-American and Causasian Community Residents. *Journal of the American Geriatrics Society*, 49(9), 1148-1155.

Fischl, B.; Salat, D.H.; Busa, E.; Albert, M.; Dieterich, M.; Haselgrove, C.; Van der Kouwe, A.; Killiany, R.; Kennedy, D.; Klaveness, S.; Montillo, A.; Makris, N.; Rosen, B.; Dale, A.M. (2002). Whole Brain Segmentation: Automated Labeling of Neuroanatomical Structures in the Human Brain. *Neuron*, 33(3), 341-355.

Friedland, R.P.; Fritsch, T.; Smyth, K.A.; Koss, E.; Lerner, A.J.; Chen, C.H.; Petot, G.J.; Debanne, S.M. (2001). Patients with Alzheimer's Disease Have Reduced Activities in Midlife Compared with Healthy Control-group Members. *Proceedings of the National Academy of Sciences USA*, 98(6), 3440-3445.

Green, R.C.; Cupples, L.A.; Go, R.; Benke, K.S.; Edeki, T.; Griffith, P.A.; Williams, M.; Hipps, Y.; Graff-Radford, N.; Bachman, D.; Farrer, L.A.; MIRAGE Study Group. (2002). Risk of Dementia Among White and African American Relatives of Patients with Alzheimer Disease. *JAMA*, 287(3), 329-336.

Haughey, N.J.; Liu, D.; Nath, A.; Borchard, A.C.; Mattson, M.P. (2002). Disruption of Neurogenesis in the Subventricular Zone of Adult Mice, and in Human Cortical Neuronal Precursor Cells in Culture, by Amyloid Beta-Peptide: Implications for the Pathogenesis of Alzheimer's Disease. *Neuromolecular Medicine*, 1(2), 125-135.

Hebert, L.E.; Beckett, L.A.; Scherr, P.A.; Evans, D.A. (2001). Annual Incidence of Alzheimer Disease in the United States Projected to the Years 2000 Through 2050. *Alzheimer Disease and Associated Disorders*, 15(4), 169-173.

Hendrie, H.C.; Ogunniyi, A.; Hall, K.S.; Baiyewu, O.; Unverzagt, F.W.; Gureje, O.; Gao, S.; Evans, R.M.; Ogunseyinde, A.O.; Adeyinka, A.O.; Musick, B.; Hui, S.L. (2001). Incidence of Dementia and Alzheimer Disease in 2 Communities: Yoruba Residing in Ibadan, Nigeria, and African Americans Residing in Indianapolis, Indiana. *JAMA*, 285(6), 739-747.

Hess, T.M.; Rosenberg, D.C.; Waters, S.J. (2001). Motivation and Representational Processes in Adulthood: The Effects of Social Accountability and Information Relevance. *Psychology and Aging*, 16(4), 629-642.

Houlden, H.; Baker, M.; McGowan, E.; Lewis, P.; Hutton, M.; Crook, R.; Wood, N.W.; Kumar-Singh, S.; Geddes, J.; Swash, M.; Scaravilli, F.; Holton, J.L.; Lashley, T.; Tomita, T.; Hashimoto, T.; Verkkoniemi, A.; Kalimo, H.; Somer, M.; Paetau, A.; Martin, J.J.; Van Broeckhoven, C.; Golde, T.; Hardy, J.; Haltia, M.; Revesz, T. (2000). Variant Alzheimer's Disease with Spastic Paraparesis and Cotton Wool Plaques is Caused by PS-1 Mutations that Lead to Exceptionally High Amyloid-Beta Concentrations. *Annals of Neurology*, 48(5), 806-808.

Huang, L.F.; Cartwright, W.S.; Hu, T.W. (1988). The Economic Cost of Senile Dementia in the United States, 1985. *Public Health Reports*, 103(1), 3-7.

Hyde, L.A.; Frisone, D.F.; Crnic, L.S. (2001). Ts65Dn Mice, a Model for Down Syndrome, Have Deficits in Context Discrimination Learning Suggesting Impaired Hippocampal Function. *Behavioural Brain Research*, 118(1), 53-60.

Jack, C.R.; Petersen, R.C.; Xu, Y.; O'Brien, P.C.; Smith, G.E.; Ivnik, R.J.; Boeve, B.F.; Tangalos, E.G.; Kokmen. E. (2000). Rates of Hippocampal Atrophy Correlate with Change in Clinical Status and AD. *Neurology*, 55(4), 484-489.

Jick, H.; Zornberg, G.L.; Jick, S.S.; Seshadri, S.; Drachman, D.A. (2000). Statins and the Risk of Dementia. *The Lancet*, 357(9255), 1627-1631.

King, A.C.; Baumann, K.; O'Sullivan, P.; Wilcox, S.; Castro, C. (2002). Effects of Moderate-intensity Exercise on Physiological, Behavioral, and Emotional Responses to Family Caregiving: A Randomized Controlled Trial. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 57(1), M26-M36.

Kordower, J.H.; Chu, Y.; Stebbins, G.T.; DeKosky, S.T.; Cochran, E.J.; Bennett, D.; Mufson, E.J. (2001). Loss and Atrophy of Layer II Entorhinal Cortex Neurons in Elderly People with Mild Cognitive Impairment. *Annals of Neurology*, 49(2), 202-213.

Kruman, I.I.; Kumaravel, T.S.; Lohani, A.; Pedersen, W.A.; Cutler, R.G.; Kruman, Y.; Haughey, N.; Lee, J.; Evans, M.; Mattson, M.P. (2002). Folic Acid Deficiency and Homocysteine Impair DNA Repair in Hippocampal Neurons and Sensitize Them to Amyloid Toxicity in Experimental Models of Alzheimer's Disease. *Journal of Neuroscience*, 22(5), 1752-1762.

Launer, L.J.; White, L.R.; Petrovitch, H.; Ross, G.W.; Curb, J.D. Cholesterol and Neuropathologic Markers of AD – a Population-based Autopsy Study. (2001). *Neurology*, 57(8), 1447-1452.

Lee, J.M.; Moehlenkamp, J.D.; Hanson, J.M.; Johnson, J.A. (2001). Nrf2-dependent Activation of the Antioxidant Responsive Element by Tert-butylhydroquinone is Independent of Oxidative Stress in IMR-32 Human Neuroblastoma Cells. *Biochemical and Biophysical Research Communications*, 280(1), 286-292.

Lewis, J.; Dickson, D.W.; Lin, W.L.; Chisholm, L.; Corral, A.; Jones, G.; Yen, S.H.; Sahara, N.; Skipper, L.; Yager, D.; Eckman, C.; Hardy, J.; Hutton, M.; McGowan, E. (2001). Enhanced Neurofibrillary Degeneration in Transgenic Mice Expressing Mutant Tau and APP. *Science*, 293(5534), 1487-1491.

Li, J; Lee, J.M.; Johnson, J.A. (2002a). Microarray Analysis Reveals an Antioxidant Responsive Element-driven Gene Set Involved in Conferring Protection from an Oxidative Stress-induced Apoptosis in IMR-32 Cells. *Journal of Biological Chemistry*, 277(1), 388-394.

Li, Y.J.; Scott, W.K.; Hedges, D.J.; Zhang, F.; Gaskell, P.C.; Nance, M.A.; Watts, R.L.; Hubble, J.P.; Koller, W.C.; Pahwa, R.; Stern, M.B.; Hiner, B.C.; Jankovic, J.; Allen, F.A., Jr.; Goetz, C.G.; Mastaglia, F.; Stajich, J.M.; Gibson, R.A.; Middleton, L.T.; Saunders, A.M.; Scott, B.L.; Small, G.W.; Nicodemus, K.K.; Reed, A.D.; Schmechel, D.E.; Welsh-Bohmer, K.A.; Conneally, P.M.; Roses, A.D.; Gilbert, J.R.; Vance, J.M.; Haines, J.L.; Pericak-Vance, M.A. (2002b). Age at Onset in Two Common Neurodegenerative Diseases is Genetically Controlled. *American Journal of Human Genetics*, 70(4), 985-993.

Lovell, M.A.; Markesbery, W.R. (2001). Ratio of 8-hydroxyguanine in Intact DNA to Free 8-hydroxyguanine is Increased in Alzheimer Disease Ventricular Cerebrospinal Fluid. *Archives of Neurology*, 58(3), 392-396.

Lyketsos, C.G.; Lopez, O.; Jones, B.; Fitzpatrick, A.L.; Breitner, J.; DeKosky, S. (2002). Prevalence of Neuropsychiatric Symptoms in Dementia and Mild Cognitive Impairment: Results From the Cardiovascular Health Study. *JAMA*, 288(12), 1475-1483.

Moceri, V.M.; Kukull, W.A.; Emanual, I.; van Belle, G.; Starr, J.R.; Schellenberg, G.D.; McCormick, W.C.; Bowen, J.D.; Teri, L.; Larson, E.B. (2001). Using Census Data and Birth Certificates to Reconstruct the Early-Life Socioeconomic Environment and the Relation to the Development of Alzheimer's Disease. *Epidemiology*, 12(4), 383-389.

Morris, J.C.; Storandt, M.; Miller, J.P.; McKeel, D.W.; Price, J.L.; Rubin, E.H.; Berg, L. (2001). Mild Cognitive Impairment Represents Early-stage Alzheimer Disease. *Archives of Neurology*, 58(3), 397-405.

Myers, A.; Holmans, P.; Marshall, H.; Kwon, J.; Meyer, D.; Ramic, D.; Shears, S.; Booth, J.; DeVrieze, F.W.; Crook, R.; Hamshere, M.; Abraham, R.; Tunstall, N.; Rice, F.; Carty, S.; Lillystone, S.; Kehoe, P.; Rudrasingham, V.; Jones, L.; Lovestone, S.; Perez-Tur, J.; Williams, J.; Owen, M.J.; Hardy, J.; Goate, A.M. (2000). Susceptibility Locus for Alzheimer's Disease on Chromosome 10. *Science*, 290(5500), 2304-2305.

Myers, A.; Wavrant De-Vrieze, F.; Holmans, P.; Hamshere, M.; Crook, R.; Compton, D.; Marshall, H.; Meyer, D.; Shears, S.; Booth, J.; Ramic, D.; Knowles, H.; Morris, J.C.; Williams, N.; Norton, N.; Abraham, R.; Kehoe, P.; Williams, H.; Rudrasingham, V.; Rice, F.; Giles, P.; Tunstall, N.; Jones, L.; Lovestone, S.; Williams, J.; Owen, M.J.; Hardy, J.; Goate, A. (2002). Full Genome Screen for Alzheimer Disease Stage II Analysis. *American Journal of Medical Genetics*, 114(2), 235-244.

Neundorfer, M.M.; McClendon, M.J.; Smyth, K.A.; Stuckey, J.C.; Strauss, M.E.; Patterson, M.B. (2001). A Longitudinal Study of the Relationship Between Levels of Depression Among Persons with Alzheimer's Disease and Levels of Depression Among Their Family Caregivers. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, 56(5), P301-P313.

Newhouse, P.A.; Potter, A.; Kelton, M.; Corwin, J. (2001). Nicotinic Treatment of Alzheimer's Disease. *Biological Psychiatry*, 49(3), 268-278.

Nilsberth, C.; Westlind-Danielsson, A.; Eckman, C.B.; Condron, M.M.; Axelman, K.; Forsell, C.; Stenh, C.; Luthman, J.; Teplow, D.B.; Younkin, S.G.; Näslund, J.; Lannfelt, L. (2001). The "Arctic" APP Mutation (E693G) Causes Alzheimer's Disease by Enhanced Abeta Protofibril Formation. *Nature Neuroscience*, 4(9), 887-893.

Peila, R.; Rodriguez, B.L.; Launer, L.J. (2002). Type 2 Diabetes, APOE Gene, and the Risk for Dementia and Related Pathologies: The Honolulu-Asia Aging Study. *Diabetes*, 51(4), 1256-1262.

Peila, R.; White, L.R.; Petrovich, H.; Masaki, K.; Ross, G.W.; Havlik, R.J.; Launer, L.J. (2001). Joint Effect of the APOE Gene and Midlife Systolic Blood Pressure on Late-life Cognitive Impairment: The Honolulu-Asia Aging Study. *Stroke*, 32(12), 2882-2887.

Petersen, R.C.; Stevens, J.C.; Ganguli, M.; Tangalos, E.G.; Cummings, J.L.; DeKosky, S.T. (2001). Practice Parameter: Early Detection of Dementia: Mild Cognitive Impairment (An Evidence-based Review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 56(9), 1133-1142.

Pettit, D.L.; Shao, Z.; Yakel, J.L. (2001). Beta-Amyloid (1-42) Peptide Directly Modulates Nicotinic Receptors in the Rat Hippocampal Slice. *Journal of Neuroscience*, 21(1), RC120.

Pfeifer, L.A.; White, L.R.; Ross, G.W.; Petrovitch, H.; Launer, L.J. (2002). Cerebral Amyloid Angiopathy and Cognitive Function: The HAAS Autopsy Study. *Neurology*, 58(11), 1629-1634.

Pigino, G.; Pelsman, A.; Mori, H.; Busciglio, J. (2001). Presenilin-1 Mutations Reduce Cytoskeletal Association, Deregulate Neurite Growth, and Potentiate Neuronal Dystrophy and Tau Phosphorylation. *Journal of Neuroscience*, 21(3), 834-842.

Pollock, B.G.; Mulsant, B.H.; Rosen, J.; Sweet, R.A.; Mazumdar, S.; Bharucha, A.; Marin, R.; Jacob, N.J.; Huber, K.A.; Kastango, K.B.; Chew, M.L. (2002). Comparison of Citalopram, Perphenazine, and Placebo for the Acute Treatment of Psychosis and Behavioral Disturbances in Hospitalized, Demented Patients. *American Journal of Psychiatry*, 159(3), 460-465.

Praticò, D.; Uryu, K.; Leight, S.; Trojanowski, J.Q.; Lee,V.M. (2001). Increased Lipid Peroxidation Precedes Amyloid Plaque Formation in an Animal Model of Alzheimer Amyloidosis. *Journal of Neuroscience*, 21(12), 4183-4187.

Price, J.L.; Ko, A.I.; Wade, M.J.; Tsou, S.K.; McKeel, D.W.; Morris, J.C. (2001). Neuron Number in Entorhinal Cortex and CA1 in Preclinical Alzheimer's Disease. *Archives of Neurology*, 58(9), 1395-1402.

Rahhal, T.A.; Hasher, L.; Colcombe, S.J. (2001). Instructional Manipulations and Age Differences in Memory: Now You See Them, Now You Don't. *Psychology and Aging*, 16(4), 697-706.

Reiman, E.M.; Caselli, R.J.; Chen, K.; Alexander, G.E.; Bandy, D.; Frost, J. (2001). Declining Brain Activity in Cognitively Normal Apolipoprotein E-ε4 Heterozygotes: A Foundation for Using Positron Emission Tomography to Efficiently Test Treatments to Prevent Alzheimer's Disease. *Proceedings of the National Academy of Sciences USA*, 98(6), 3334-3339.

Robinson-Whelen, S.; Tada, Y.; MacCullum, R.C.; McGuire, L.; Kiecolt-Glaser, J.K. (2001). Long-term Caregiving: What Happens When It Ends? *Journal of Abnormal Psychology*, 110(4), 573-584.

Schmidt, R.; Schmidt, H.; Curb, J.D.; Masaki, K.; White, L.R.; Launer, L.J. (2002). Early Inflammation and Dementia: A 25-year Follow-up of the Honolulu-Asia Aging Study. *Annals of Neurology*, 52(2), 168-174.

Schenk, D.; Barbour, R.; Dunn, W.; Gordon, G.; Grajeda, H.; Guido, T.; Hu, K,. Huang, J.; Johnson-Wood, K.; Khan, K.; Kholodenko, D.; Lee, M.; Liao, Z.; Lieberburg, I.; Motter, R.; Mutter, L.; Soriano, F.; Shopp, G.; Vasquez, N.; Vandevert, C.; Walker, S.; Wogulis, M.; Yednock, T.; Games, D.; Seubert, P. (1999). Immunization with Amyloid-Beta Attenuates Alzheimer's Disease-Like Pathology in the PDAPP Mouse. *Nature*, 400(6740), 173-177.

Schneider, L.S.; Tariot, P.N.; Lyketsos, C.G.; Dagerman, K.S.; Davis, K.L.; Davis, S.; Hsiao, J.K.; Jeste, D.V.; Katz, I.R.; Olin, J.T.; Pollock, B.G.; Rabins, P.V.; Rosenheck, R.A.; Small, G.W.; Lebowitz, B.; Lieberman, J.A. (2001). National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer Disease Trial Methodology. *American Journal of Geriatric Psychiatry*, 9(4), 346-360.

Seshadri, S.; Beiser, A.; Selhub, J.; Jacques, P.F.; Rosenberg, I.H.; D'Agostino, R.B.; Wilson, P.W.; Wolf, P.A. (2002). Plasma Homocysteine as a Risk Factor for Dementia and Alzheimer's Disease. *New England Journal of Medicine*, 346(7), 476-483.

Shumaker, S.A.; Legault, C.; Thal, L.; Wallace, R.B.; Ockene, J.K.; Hendrix, S.L.; Jones, B.N.; Assaf, A.R.; Jackson, R.D.; Kotchen, J.M.; Wassertheil-Smoller, S.; Wactawski-Wende, J.; for the WHIMS Investigators. (2003). Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial. *JAMA*, 289(20), 2651-2662.

Small, S.A.; Wu, E.X.; Bartsch, D.; Perera, G.M.; Lacefield, C.O.; DeLaPaz, R.; Mayeux, R.; Stern, Y.; Kandel, E.R. (2000). Imaging Physiologic Dysfunction of Individual Hippocampal Subregions in Humans and Genetically Modified Mice. *Neuron*, 28(3), 653-664.

Sultzer, D.L.; Gray, K.F.; Gunay, I.; Wheatley, M.V.; Mahler, M.E. (2001). Does Behavioral Improvement with Haloperidol or Trazodone Treatment Depend on Psychosis or Mood Symptoms in Patients with Alzheimer's Disease? *Journal of the American Geriatrics Society*, 49(10), 1294-1300.

Tang, M.X.; Cross, P.; Andrews, H.; Jacobs, D.M.; Small, S.; Bell, K.; Merchant, C.; Lantigua, R.; Costa, R.; Stern, Y.; Mayeux, R. (2001). Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in Northern Manhattan. *Neurology*, 56(1), 49-56.

Tanzi, R.E.; Blacker, D. (2001). Genetic Screening in Alzheimer's Disease: Usefulness, Limits, and Future Prospects. *Generations*, 24(1):58.

Vehmas, A.K.; Borchelt, D.R.; Price, D.L.; McCarthy, D.; Wills-Karp, M.; Peper, M.J.; Rudow, G.; Luyinbazi, J.; Siew, L.T.; Troncoso, J.C. (2001). Beta-Amyloid Peptide Vaccination Results in Marked Changes in Serum and Brain A-beta Levels in APPswe/PS1DeltaE9 Mice, as Detected by SELDI-TOF-based ProteinChip Technology. *DNA Cell Biology*, 20(11), 713-721.

Verkkoniemi, A.; Kalimo, H.; Paetau, A.; Somer, M.; Iwatsubo, T.; Hardy, J.; Haltia, M. (2001). Variant Alzheimer Disease with Spastic Paraparesis Neuropathological Phenotype. Journal of Neuropathology and Experimental *Neurology*, 60(5), 483-492.

West, R.; Murphy, K.J.; Armilio, M.L.; Craik, F.I.; Stuss, D.T. (2002). Effects of Time of Day on Age Differences in Working Memory. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, 57(1), P3-P10.

Wilson, R.S.; Beckett, L.A.; Barnes, L.L.; Schneider, J.A.; Bach, J.; Evans, D.A.; Bennett, D.A. (2002b). Individual Differences in Rates of Change in Cognitive Abilities of Older Persons. *Psychology and Aging*, 17(2), 179-193.

Wilson, R.S.; Mendes deLeon, C.F.; Barnes, L.L.; Schneider, J.A.; Bienias, J.L.; Evans, D.A.; Bennett, D.A. (2002a). Participation in Cognitively Stimulating Activities and Risk of Incident Alzheimer's Disease. *JAMA*, 287(6), 742-748.

Wolozin, B.; Kellman, W.; Ruosseau, P.; Celesia, G.G.; Siegel, G. (2000). Decreased Prevalence of Alzheimer Disease Associated with 3-hydroxy-3-methyglutaryl Coenzyme A Reductase Inhibitors. *Archives of Neurology*, 57(10), 1439-1443.

Wyss-Coray, T.; Lin, C.; Yan, F.; Yu, G.Q.; Rohde, M.; McConlogue, L.; Masliah, E.; Mucke, L. (2001). TGF-beta 1 Promotes Microglial Amyloid-beta Clearance and Reduces Plaque Burden in Transgenic Mice. *Nature Medicine*, 7(5), 612-618.

Zubenko, G.S.; Stiffler, J.S.; Hughes, H.B.; Fatigati, M.J.; Zubenko, W.N. (2002). Genome Survey for Loci That Influence Successful Aging: Sample Characterization, Method Validation, and Initial Results for the Y Chromosome. *American Journal of Geriatric Psychiatry*, 10(5), 619-630.

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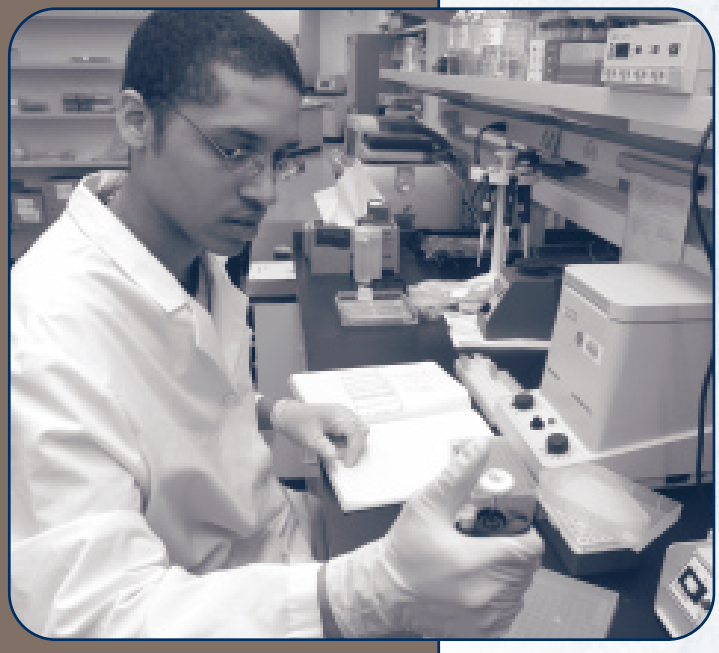

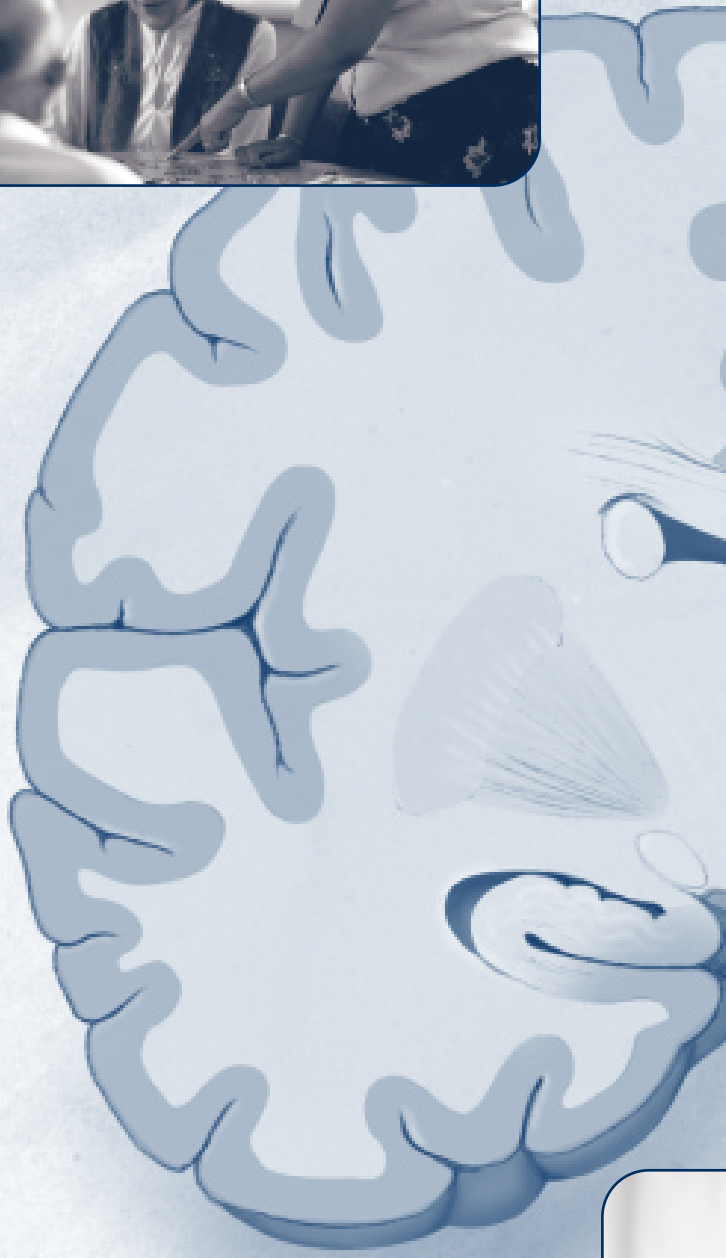

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