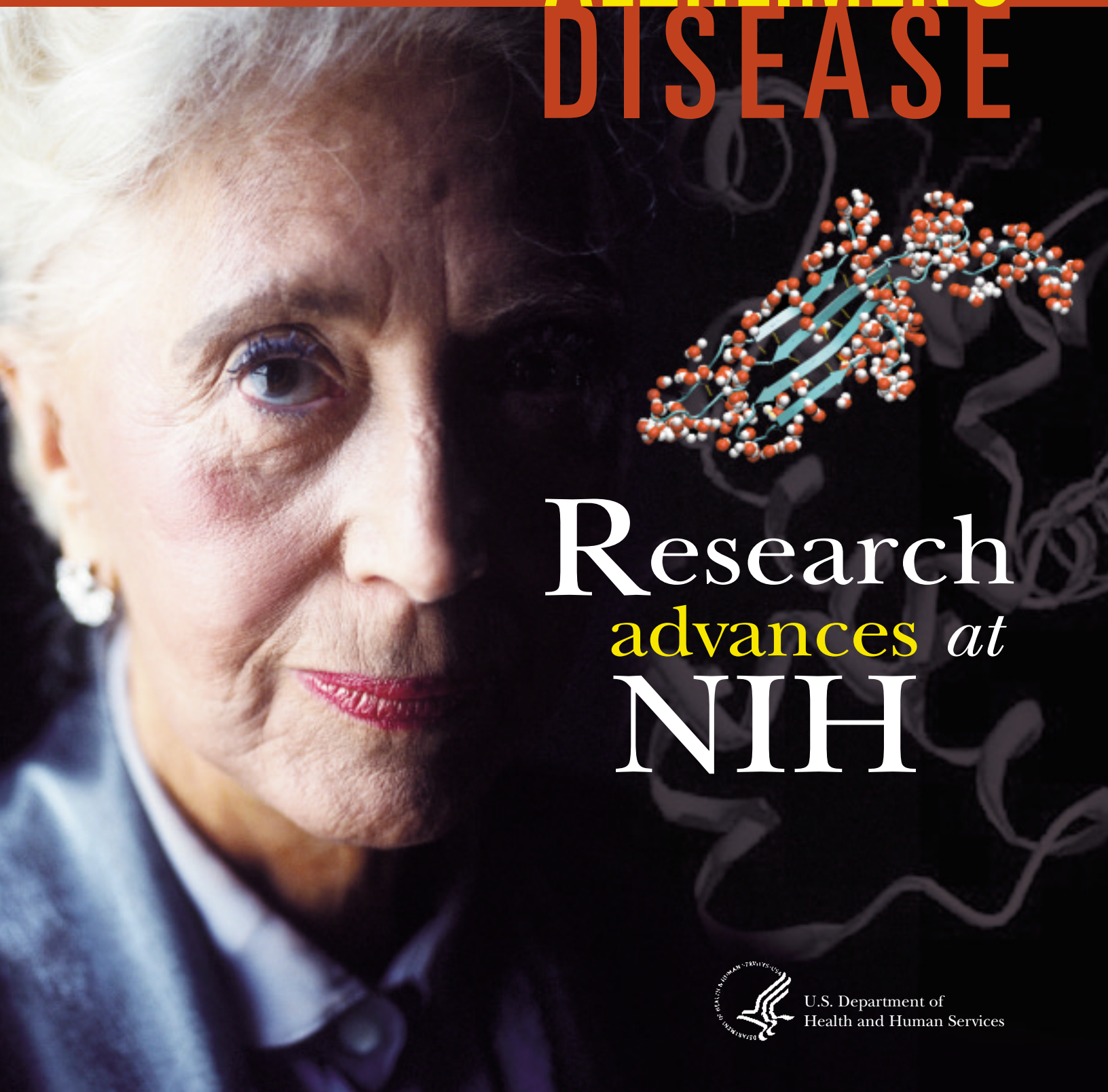
2003 PROGRESS REPORT ON ALZHEIMER'S DISEASE

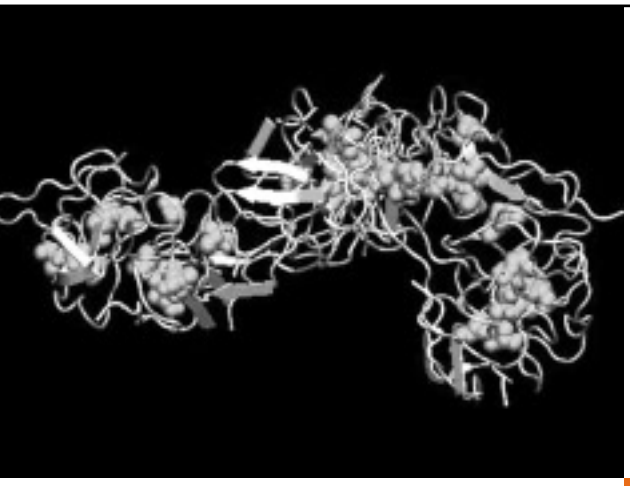


Research advances at NIH

U.S. Department of Health and Human Services

Moving *toward a* brighter future

2003 PROGRESS REPORT ON ALZHEIMER'S DISEASE



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

The National Institute on Aging (NIA), part of the Federal Government's National Institutes of Health (NIH), has primary responsibility for basic research in Alzheimer's disease (AD) as well as research aimed at finding ways to prevent and treat AD. The Institute's AD research program is integral to one of its main goals, which is to enhance the quality of life of older people by expanding knowledge about the aging brain and nervous system. This *2003 Progress Report on Alzheimer's Disease* summarizes recent AD research conducted or supported by NIA and other components of NIH, including:

- National Cancer Institute (pages 12, 50)
- National Center for Complementary and Alternative Medicine (page 51)
- National Center for Research Resources (page 32)
- National Heart, Lung, and Blood Institute (pages 40, 42-43)
- National Human Genome Research Institute (page 32)
- National Institute of Child Health and Human Development (page 25)
- National Institute on Deafness and Other Communication Disorders (pages 12, 42)
- National Institute of Environmental Health Sciences (page 24)
- National Institute of Mental Health (pages 26, 28, 29, 40, 44, 51, 59)
- National Institute of Neurological Disorders and Stroke (pages 11, 20, 28, 41, 42, 59)
- National Institute of Nursing Research (pages 17, 45, 51, 53)

Modest AD research efforts also are supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute on Alcohol Abuse and Alcoholism, National Institute for Biomedical Imaging and Bioengineering, National Center on Minority Health and Health Disparities, and the John E. Fogarty International Center.

CONTENTS


UMass

Introduction

PART 1

Alzheimer's disease is an age-related and irreversible brain disorder that develops gradually and results in memory loss, behavior and personality changes, and a decline in other cognitive abilities, such as thinking, decision-making, and language skills. These losses are related to the breakdown of the connections between certain nerve cells in the brain and the eventual death of many of these cells. AD is one of a group of disorders, termed dementias, that are characterized by cognitive and behavioral problems.

The course of this disease varies from person to person, as does the rate of decline. 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 AD

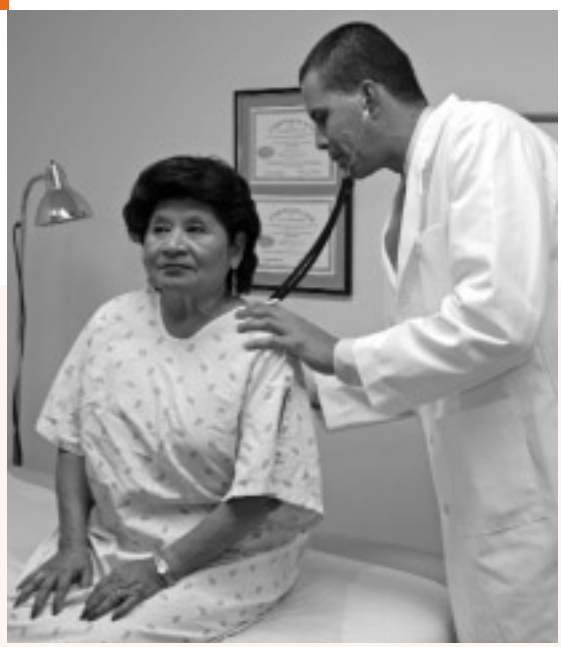
AD is the most common cause of dementia among people age 65 and older. It presents a major health problem for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. Scientists estimate that 4.5 million people currently have the disease,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

These numbers are significant now and will become even more so in the future because of dramatic increases in life expectancy since the early 1900s. Researchers estimate that by 2050, 13.2 million Americans will have AD if current population trends continue and no preventive treatments become available (Hebert et al., 2003). Approximately 4 million Americans are 85 years old or older, and this age group is the fastest growing segment of the population. It also is the group with the highest risk of AD. The U.S. Census Bureau estimates that nearly 19 million Americans will be

aged 85 and older by the year 2050. Some experts who study population trends suggest that the number could be even greater. This trend is not only apparent in the U.S. but also worldwide. As more and more people live longer, the number of people affected by diseases of aging, including AD, will continue to grow. For example, one study shows that nearly half of all people age 85 and older have some form of dementia (Evans et al., 1989).

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

AD's impact is seen not only in the numbers who develop the disease and the cost to society, but also in its effects on people with the disease, their families, friends and caregivers. Slightly more than half of AD patients receive care at home, while the remainder are cared for in a variety of health care institutions. During their years of caregiving, these spouses, relatives, and friends experience emotional, physical, and financial stress. They watch their loved ones become more and more forgetful, frustrated, and confused. Eventually, the person with AD will not even recognize his or her nearest and dearest relatives and friends.



AD Prevalence in Hispanics

Dementia often goes unrecognized or is misdiagnosed during its early stages, and this seems to be especially true for some racial and ethnic groups, where cultural or language barriers may prevent people and their families from seeking a diagnosis. To ensure the development of more effective health care access and diagnostic approaches, it is important to obtain information about the prevalence and types of dementias among diverse populations. This issue is becoming increasingly important because the U.S. Census Bureau projects that between 1999 and 2030, the Hispanic population older than 65 will increase more than 300 percent, compared to increases of 81 percent for older whites and 131 percent for older African Americans.

A recent study conducted by investigators at the University of California at Los Angeles School of Medicine has provided valuable new information on the frequency of different types of dementia in a community outreach sample of Mexican and Central American Hispanics living in California (Fitten et al., 2001). Hispanics from Mexico and Central America constitute about 70 percent of all Hispanics in the United States. California was chosen for this study because about one-third of all Hispanics in the U.S. live in the State, and 80 percent of older California Hispanics are of Mexican origin.

Caregivers—most of whom are women—must juggle child care, jobs, and other responsibilities along with caring for relatives with AD who cannot function on their own. As the disease runs its course and the abilities of people with AD steadily decline, family members face difficult decisions about the long-term care of their loved ones. Frequently, they turn to assisted living facilities, then nursing homes for care and support. The numbers of caregivers—and their needs—can be expected to grow significantly as the population ages and as the number of people with AD increases.

AD: 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 greatly reduce the number of people with the disease. This in turn would reduce the personal and financial costs associated with caring for them.

AD research supported by the Federal Government is divided into three broad,

Annual national costs of caring for people with AD are as high as $100 billion.

Because Hispanics tend not to go to memory clinics, the investigators worked with local churches, social service agencies, and other community groups to devise culturally comfortable strategies to recruit individuals with possible dementia. These strategies included flyers, 24-hour answering services, and articles in Spanish newspapers. A fully bilingual and bicultural staff worked with potential participants, and were especially careful to avoid creating any cultural or social stigma associated with mental health problems. One hundred men and women aged 55 and older and their caregivers participated and were evaluated in Spanish. The presence of dementia was established using neurological evaluation, neuropsychological tests, questionnaires, laboratory tests, and brain imaging. Of the 100 participants, 65 met the research criteria for a diagnosis of dementia. Of these individuals, 25 were diagnosed with probable AD, 25 were diagnosed with vascular dementia (a type of dementia associated with strokes), 3 had mixed AD and vascular dementia, and the remaining participants had other dementia diagnoses.

This study provides information about dementias affecting a community of older California Hispanics. The proportion of study participants with AD was lower and the proportion with vascular dementia was considerably higher than expected based on previous data on whites. The percentage of depressed, non-demented individuals also was high.

This study illustrates the need for accurate and culturally relevant diagnostic evaluations and points to the importance of more effective health care access and diagnostic approaches for this important U.S. population.

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 part of scientific efforts to discover what causes AD. Assessing factors that may increase or decrease the risk of developing AD is a growing component of this research effort.

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

Other researchers are working hard to discover and develop interventions that may help treat symptoms, slow the progress of the disease, delay the onset of, or even prevent AD. Many of these interventions are now being tested in clinical trials (see p.45 for descriptions of AD clinical trials). Finally, scientists and many health care professionals are seeking better ways to help people with AD and caregivers cope with the decline

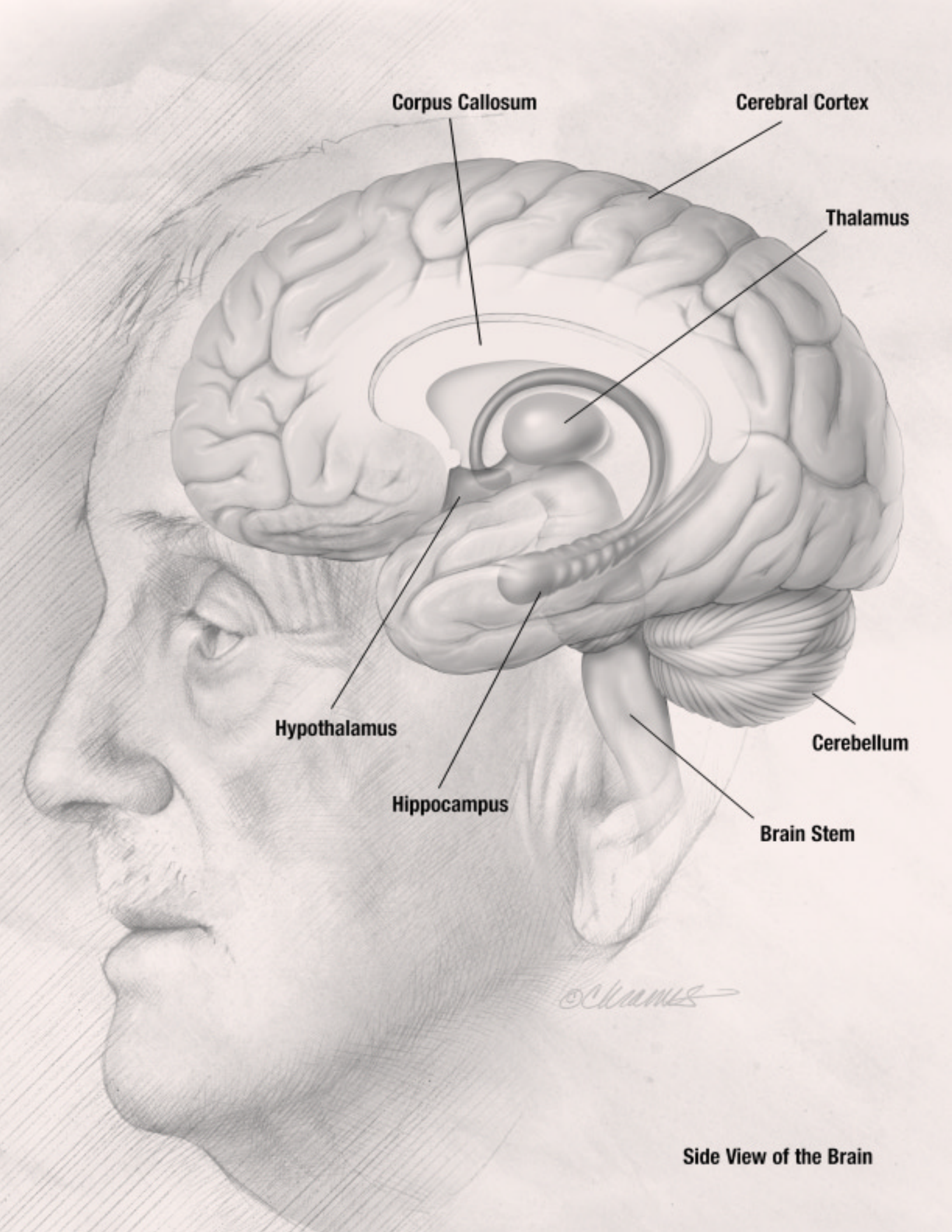
in mental and physical abilities and the difficult behaviors that accompany the disease.

An important complement to the National Institutes of Health's (NIH) research initiatives in AD are its efforts to educate and inform people with AD, their families, the public, providers, and others interested in the disease. The NIA Alzheimer's Disease Education and Referral (ADEAR) Center (www.alzheimers.org) provides a variety of outstanding resources on AD, including information about caregiving, diagnosis and treatment, and results of research findings. For example, NIA's booklet for the general public, *Alzheimer's Disease: Unraveling the Mystery*, uses illustrations and text to explain AD, highlight ongoing research, and describe efforts to support caregivers of people with AD. ADEAR also maintains a database of AD clinical trials, develops reading lists, and provides referrals to local AD resources. In addition, all of the NIA-supported Alzheimer's Disease Centers (ADCs) have Education and Information Transfer Cores that work locally to disseminate information about AD (see p.53 for more about the work of these Centers).

We now know a lot about AD—what it is, who can get it, how it develops, and what course it follows. We also have made significant progress in the critical area of early diagnosis and have some promising leads on possible treatments. All of this research has deepened our understanding of this devastating disease. It also has expanded our knowledge about other late-life neurodegenerative diseases, brain function in healthy older people, and ways to minimize normal age-related cognitive decline.

The **ADEAR** Center provides a **variety** of outstanding **resources** on AD.

The *2003 Progress Report on Alzheimer's Disease* describes this important research effort. It begins with a description of our current knowledge about AD. This provides the backdrop for the next section, which highlights recent research conducted by NIA and other NIH Institutes. The report closes with a section called "Outlook for the Future," which takes a look at some exciting new AD research initiatives. These initiatives are designed to accelerate laboratory and clinical research and collaboration across the Federal Government and in association with the private sector so that research findings can be translated expeditiously into real advances for people with AD, families, and caregivers.



Side View of the Brain

Alzheimer's Disease: Current Knowledge Provides a Firm Foundation for New Research

PART 2

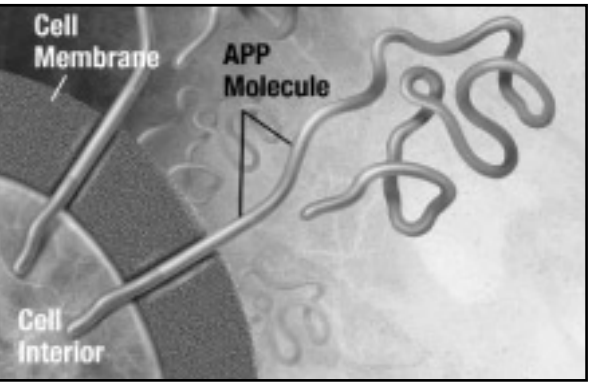
In normal aging, nerve cells (neurons) in the brain are not lost in large numbers. In AD, however, many nerve cells stop functioning, lose connections with other nerve cells, and die. At first, AD destroys neurons in parts of the brain that control memory, including the hippocampus (a structure deep in the brain that helps to encode short-term memories) and related structures. As nerve cells in the hippocampus stop working properly, short-term memory fails, and a person's ability to do easy and familiar tasks often begins to decline. AD later attacks the cerebral cortex (the outer layer of neurons in the brain), particularly the areas responsible for language and reasoning. At this point, AD begins to take away language skills and changes a person's ability to make judgments. Personality changes also may occur. Emotional outbursts and disturbing behaviors, such as wandering, begin to happen and can become more frequent as the disease progresses. Eventually, many other areas of the brain are involved and the person with AD becomes bedridden, helpless, and unresponsive to the outside world.

What are the Main Brain Characteristics of People with AD?

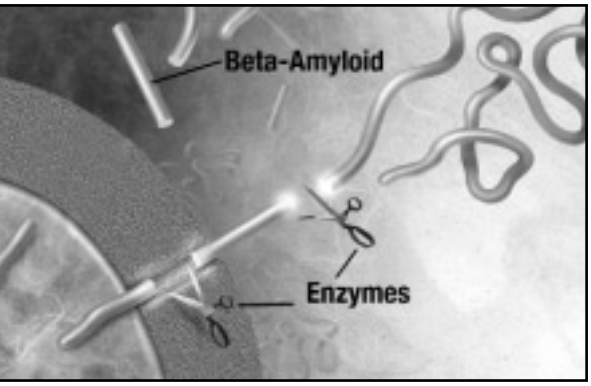
The brain in AD is abnormal in three major ways. Though scientists have known about these abnormal characteristics for many years, more recent research has revealed much about their nature and their possible roles in the development of AD.

Amyloid Plaques

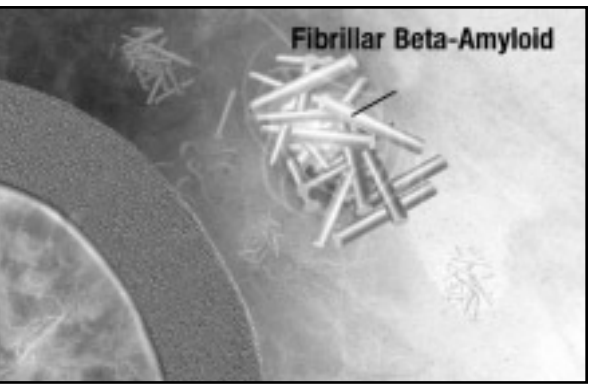
In AD, plaques develop first in areas of the brain used for memory and other cognitive functions. They are found in the spaces between the brain's nerve cells. Plaques consist of thick, sticky deposits of beta-amyloid mixed with other proteins, remnants of neurons, non-nerve cells such as microglia (cells that surround and digest damaged cells or foreign substances that cause inflammation), and other glial cells. Beta-amyloid is a soluble (can be dissolved) protein fragment snipped, or cleaved, from a larger protein called amyloid precursor protein (APP). APP is associated with the cell membrane and in healthy brains, appears to be important in helping neurons grow and survive.



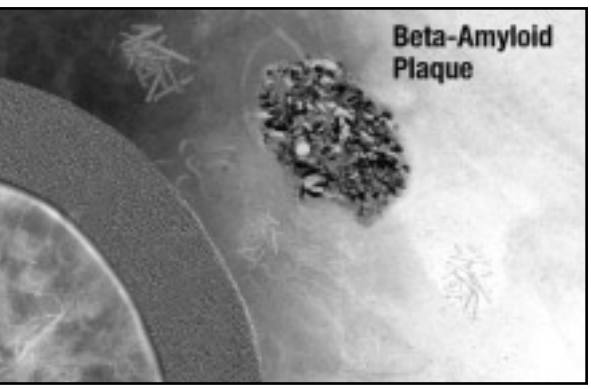
APP is associated with the cell membrane, the thin barrier that encloses the cell. After it is made, APP sticks through the neuron's membrane, partly inside and partly outside the cell.



Enzymes (substances that cause or speed up a chemical reaction) act on the APP and cut it into soluble fragments of protein, one of which is called beta-amyloid.



These soluble beta-amyloid fragments begin clustering together into oligomers and then into increasingly insoluble fibrillar beta-amyloid aggregates.



Eventually, this process leads to the beta-amyloid plaques that are found in abundance outside and around neurons in the brains of people with AD.

Recent studies have helped scientists learn that beta-amyloid fragments go through several stages on their way to becoming plaques: A small number of the fragments cleaved from APP bind with one another to become larger clusters of still soluble amyloid fragments referred to as oligomers. The oligomers then come together into even larger aggregates that contain increasingly insoluble beta-amyloid. These later-stage aggregates contain "fibrillar" insoluble beta-amyloid. Fibrillar amyloid then coalesces into the insoluble plaques that are characteristic of the disease.

Although researchers still do not know whether amyloid plaques themselves cause AD or whether they are a by-product of the AD process, some evidence suggests that amyloid deposition may be a central and defining process of the disease. Many researchers believe that the beta-amyloid found in plaques is no longer the prime suspect, but rather, the earlier-stage soluble beta-amyloid clusters are the major culprit. It is believed that these fibrillar beta-amyloid clusters are toxic to neurons, though the mechanisms for this are still unknown.

Neurofibrillary Tangles

The second hallmark of AD pathology consists of abnormal collections of twisted protein threads found inside nerve cells. The chief component of these neurofibrillary tangles is a protein called *tau*. Healthy neurons are internally supported partly by structures called microtubules. These microtubules act like conduits, guiding nutrients and molecules from the body of the cell down to the ends of the axon and back. *Tau* binds to microtubules and stabilizes them. In AD, *tau* is changed chemically. It does not bind to microtubules but begins to aggregate with other threads of *tau*.

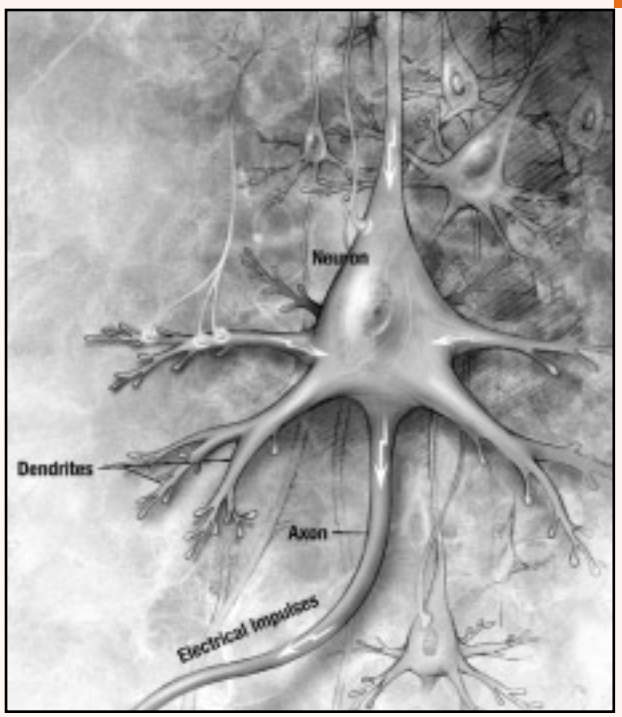
Structure and Function of the Brain

The brain is essential to our survival. With the help of motor and sensory nerves throughout the body, it integrates, regulates, initiates, and controls all the body's functions. The brain governs thinking, personality, moods, the senses, and physical action. We can speak, move, remember, and feel emotions and physical sensations because of the complex interplay of chemical and electrical processes that take place in our brains. The brain also regulates body functions that happen without our knowledge or direction, such as breathing and digesting food.

The healthy human brain is made up of billions of neurons that share information with one another through a diverse array of biological and chemical signals. Each neuron has a cell body, an axon, and many dendrites, all surrounded by a cell membrane. The nucleus, which contains genes composed of deoxyribonucleic acid (DNA), controls the cell's activities. The axon, which extends from the cell body, transmits messages to other neurons, sometimes over very long distances. Dendrites, which also branch out from the cell body, receive messages from axons of other nerve cells or from specialized sense organs. Axons and dendrites collectively are called neurites. Even more numerous are the glial cells, which surround, support, and nourish neurons.

Neurons communicate with each other and with sense organs by producing and releasing special chemicals called neurotransmitters. As a neuron receives messages from surrounding cells, an electrical charge (nerve impulse) builds up within the cell. This charge travels down the axon until it reaches the end. Here, it triggers the release of the neurotransmitters that move from the axon across a gap, called a synapse, between it and the dendrites or cell bodies of other neurons. Scientists estimate that the typical neuron has up to 15,000 synapses. The neurotransmitters bind to specific receptor sites on cell bodies and the receiving end of dendrites of adjacent nerve cells. In this way, signals travel between neurons in a fraction of a second. Millions of signals flash through the brain at any one time.

Groups of neurons in the brain have specific jobs. For example, some neurons are involved in thinking, learning, remembering, and planning.



Others are responsible for vision or hearing, regulating the body's biological clock, or managing the myriad other jobs that keep the human body functioning.

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

The second process is metabolism, the pathways by which cells and molecules break down chemicals and nutrients to generate energy. This chemical energy is then used to replenish the building blocks necessary for optimal cell function. Efficient metabolism requires adequate blood circulation to supply the cells with oxygen and important nutrients, such as glucose (a sugar).

The third process is the repair of injured neurons. Unlike most other body cells, neurons are programmed to live a long time. Brain neurons have the capacity to last more than 100 years. In an adult, when neurons die because of disease or injury, they are usually not replaced (see p.40 to learn more about the advances in knowledge in this area). To prevent their own death, living neurons must constantly maintain and remodel themselves.

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

These *tau* threads become tangled up with one another to form neurofibrillary tangles. When this happens, the microtubules disintegrate, collapsing the neuron's transport system. This may result first in malfunctions in communication between neurons and later in the death of the cells.

Loss of Connections Between Cells and Cell Death

The third major pathological feature of AD is the gradual loss of connections between neurons and eventually, neuron death. As plaques and tangles proliferate, they damage neurons to the point that they cannot function properly or communicate with each other. Eventually, they die. As this process continues and spreads through the brain, affected regions begin to shrink. By the final stage of AD, plaques and tangles are widespread, and brain tissue has shrunk significantly, a process called brain atrophy.

What Causes AD?

Most cases of AD develop in people older than 60. This form of AD is called "late-onset" AD. We don't fully understand the cause of late-onset AD. In contrast, in a very few families who develop early-onset AD, we know exactly what causes the disease. In these families, affected people (about half of the children of an affected parent) get the disease in their 30s, 40s, and 50s. These people have mutations in one of three genes: the APP gene found on chromosome 21, the presenilin 1 gene on chromosome 14, or the presenilin 2 gene on chromosome 1. The APP gene is responsible for making APP. The presenilin genes are responsible for making an enzyme that plays an important part in clipping APP into fragments. Presenilin gene mutations promote the breakdown of APP, leading to beta-amyloid production. So, in those rare cases in which we know the cause of the disease, the genetic findings show that the cause relates to beta-amyloid production.

These findings are supported by knowledge gained from studying Down syndrome. Most of us have two copies of chromosome 21, but people with Down syndrome have three. Therefore, they have an extra copy of the APP gene, which leads to more APP production. By studying the disease process in Down syndrome and in the early-onset AD mutations, we have found that in all cases, too much beta-amyloid is produced. Scientists are divided into different camps on the significance of this finding: Some think that all cases of AD must be caused by beta-amyloid accumulation, either by its overproduction or failure to break it down. Others think it is premature to draw this conclusion from these rare early-onset cases and from people with Down syndrome, and that different mechanisms may operate in the more common late-onset AD.

Perhaps the greatest **mystery** is why **AD** largely strikes the **elderly.**

Because of the belief that beta-amyloid might be the toxic molecule that starts the disease, an enormous amount of work has been aimed at learning more about this protein. We now have a very clear understanding of the enzymes involved in beta-amyloid production, and the process by

which beta-amyloid plaques are formed and deposited in brain tissue. Although there is some way to go, we are now developing a clearer understanding of beta-amyloid breakdown as well. Obviously, many believe that if we could slow beta-amyloid production or speed up its removal, this would have clinical benefit.

However, our knowledge still has some surprising gaps. For example, we don't yet fully understand the normal function of

APP, presenilins, and beta-amyloid. Certainly a better knowledge of normal function would give us clues about the causes of AD. Recent research is helping scientists understand important functions of other parts of the APP molecule and of the presenilins. Beta-amyloid production appears to be increased when nerve cells are damaged. Perhaps this increased production could explain the often reported association between head injury and AD. A recent study funded by NIA and the National Institute of Neurological Disorders and Stroke (NINDS) may shed some light on this hypothesis. In this study, a research team at the University of Pennsylvania used a specially bred, or transgenic, mouse model of AD to test the effects of traumatic brain injury on risk of AD (Uryu et al., 2002). They found that repetitive mild trauma to the brain led to accelerated deposition of beta-amyloid, damage to affected neurons, and impairments in the animals' cognitive function.

Another important gap in our knowledge relates to the fact that we don't understand exactly how beta-amyloid leads to nerve cell damage and death. In test tube studies, scientists have shown that beta-amyloid is toxic to nerve cells, but there can be a big difference between test tubes and animals. Until recently, most of the AD animal models made only beta-amyloid plaques, and the amount of damage caused by beta-amyloid seemed rather limited. However, newer mouse models of AD also have *tau* mutations and make neurofibrillary tangles. Recent data show that most nerve cell death is related to tangles and that beta-amyloid is much more toxic in mice that also make tangles. We still do not understand the relationship between beta-amyloid and plaques on the one hand and *tau* and tangles on the other, but current and future studies in mice that have both pathologies will help scientists solve this puzzle.

Perhaps the greatest mystery is why AD largely strikes the elderly. Why does it take 30 to 50 years for people to develop signs of the disease, even those individuals who are born with disease-causing mutations? It is possible that the processes that cause AD happen slowly and simply take a long time to reach a critical magnitude. It also is possible that the environment of the aging brain is subtly different from that of the young brain.

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

What Do We Know About Diagnosing AD?

AD can be diagnosed conclusively only by examining in an autopsy the brain of a person with dementia to determine whether the plaques and tangles in certain brain regions are characteristic of AD. However, clinicians today can use a range of tools to diagnose "possible AD" (dementia could also be due to another condition) or "probable AD" (no other cause of dementia can be found) in a living person who is having difficulties with memory or other mental functions. These tools include a patient history; physical exam; tests that measure memory, language skills, and other abilities related to changes in brain functioning; and sometimes, brain scans. Much is known about the clinical and behavioral characteristics of the disease, and this also helps in diagnosing AD. The diagnostic process is crucial to identify AD accurately as well as to rule out other conditions that might be causing cognitive problems or dementia, such as stroke, tumors, Parkinson's disease, or side effects of medications. For example, a recent review conducted by a Dartmouth Medical School research team and funded by the National Cancer Institute (NCI), discussed the growing body of evidence showing that cancer chemotherapy can produce long-term cognitive changes (Ahles and Saykin, 2002). Given the growing numbers of older cancer survivors, it is clearly important to understand this effect and to be able to distinguish it from AD dementia or other causes of cognitive changes.

An early, accurate diagnosis is especially important to people with AD and their families because it helps them plan for the future and pursue care options while the patient can still take part in making decisions. Researchers are making progress in

developing accurate diagnostic tests and techniques. In specialized research facilities, trained clinicians can now diagnose AD with up to 90 percent accuracy. Scientists are working in several areas that may improve the ability of clinicians to make accurate diagnoses of AD even sooner and that are providing important insights into the earliest changes that occur in the brain of a person with AD even before a clinical diagnosis is made. For example, neuropsychological diagnostic tests for AD, such as those that measure delayed recall, verbal fluency, and overall cognitive status, continue to improve. In one study, researchers at the University of California, San Diego, found that these tests were highly accurate in distinguishing between cognitively healthy individuals and people with mild AD (Salmon et al., 2002).

Studies also are pointing to other intriguing clues that might help in early diagnosis. For example, a study funded by the National Institute on Deafness and Other Communication Disorders (NIDCD) and conducted by scientists at San Diego State University, followed up on data suggesting that alterations in sensory or motor function accompany the cognitive

symptoms of AD. Changes in the sense of smell have been found in some studies to be a very early sign in many people with AD. This study involved a group of healthy older adults and a group who had probable AD. Investigators measured activity in brain regions that control the sense of smell while the groups took part in odor identification tests (Morgan and Murphy, 2002). Based on the results of the test, the investigators were able to accurately distinguish those with AD from the healthy participants. They also found that decreased activity in these brain regions was related to increased severity of dementia.

Insights from these and many other studies will help scientists understand the natural history of AD and the ways in which changes in memory and other cognitive functions differ in normal aging, AD, and other dementias. This knowledge will help clinicians diagnose AD earlier and more accurately and also will help researchers pinpoint early changes that could be targets for drug therapy.

How Is AD Treated?

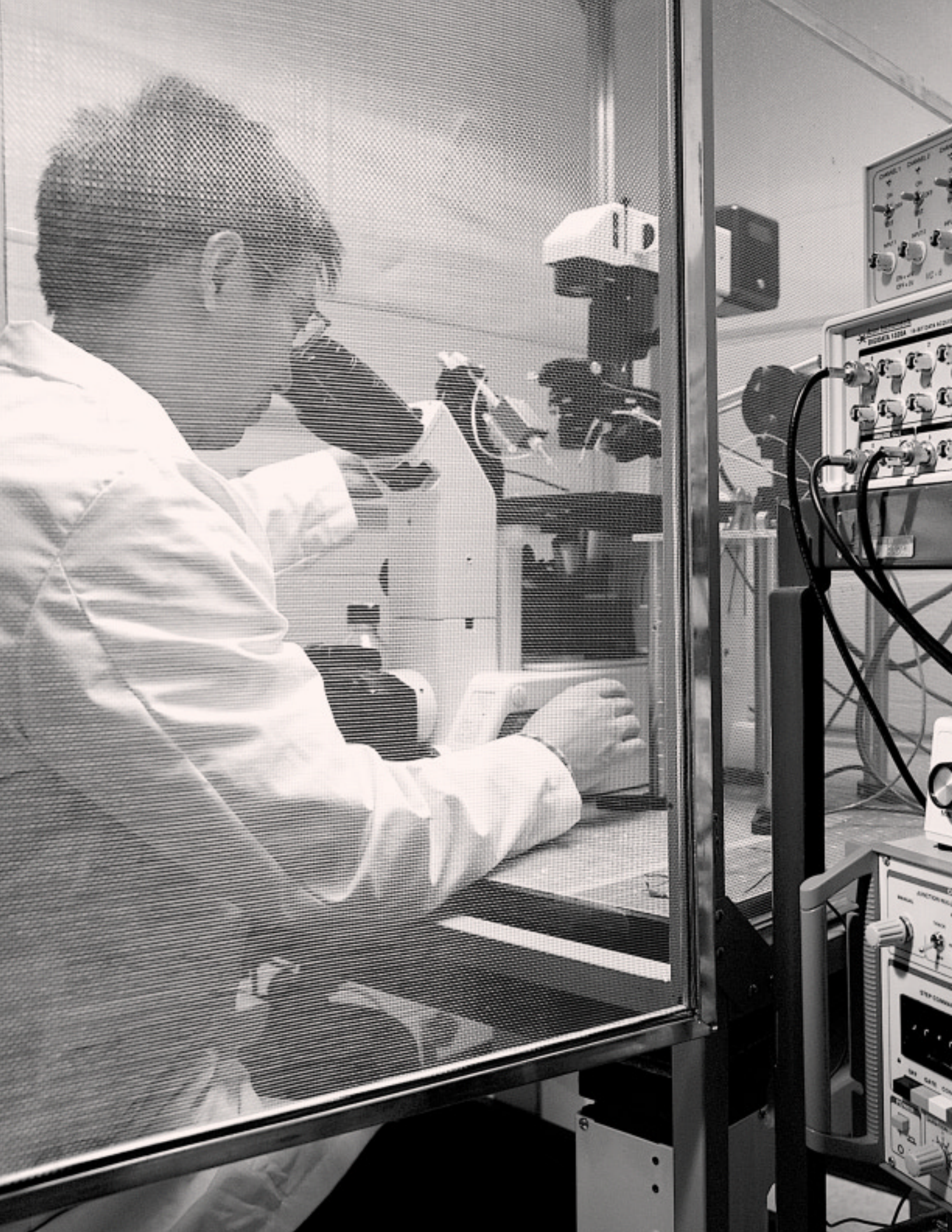
For those who are already suffering from the effects of AD, the most immediate need is for treatments to control cognitive loss as well as problem behaviors, such as verbal and physical aggression, agitation, wandering, depression, sleep disturbances, and delusions. Treatments are needed that work on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

The Food and Drug Administration (FDA) has approved five medications to treat AD symptoms. The first drug approved has been replaced by three others that are commonly used to treat mild to moderate AD symptoms. The fifth and newest drug is used to treat moderate to severe symptoms. However, these medications will not stop or reverse AD (for more on these medications, see p.43).

An early, accurate **diagnosis** is especially **important** to people with AD and their families.

Helping people with AD live their daily lives and maintain their cognitive abilities is one of the most important goals of AD treatment research. Many investigators are working to develop new and better drugs that can preserve this critical function for as long as possible. Many other investigators are improving the quality of life for patients as well as caregivers through research to develop better behavioral management techniques and caregiver skills.

One of the primary characteristics of the NIH AD research effort over the past 25 years has been support for a wide range of studies conducted by a large and multidisciplinary cadre of researchers. All of these studies have contributed to building the solid base of knowledge that exists today. The continuing expansion of this base is pointing scientists in new and productive research directions. It is also helping investigators ask more incisive questions about the issues that still remain unclear.



2003 AD Research Advances: The Process of Discovery Continues

PART 3

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

- What happens in the brain to cause the transformation from healthy aging to AD?
- Can certain factors 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 focus on the central issues of AD: What happens at the very beginning of the disease process, what might we be able to do to prevent AD, and what can be done once the disease process has started. They can be asked only because of the knowledge that has accumulated through past research. Answers to these questions are slowly emerging, and they hold the key to future prevention, treatment, and caregiving strategies.

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

Many studies are underway to clarify the changes that occur during normal aging and their effects on memory and thinking skills. Learning more about the changes that occur in aging will help scientists decipher the transformation from healthy aging to AD. For example, researchers at the University of Michigan conducted a study that examined vocabulary knowledge and the ability to process, learn, and remember information among a group of people ranging in age from 20 to 90 (Park et al., 2002). They found that subtle declines in the ability to process and remember information started as early as the 20s and that the declines continued throughout adulthood. In contrast, indicators of vocabulary and general knowledge improved across the 20 to 90 age range. These results are surprising because they indicate that cognitive decline starts early in

adulthood and because it seems to happen at the same rate for many different cognitive tasks. The finding of increasing general knowledge in the face of declining memory performance suggests that older adults may process information and react to it more slowly than younger adults. However, this lag may be offset by knowledge accumulated over the years. Because the investigators examined a group of people at different ages between 20 and 90 during one time period rather than following the same people over time from age 20 to 90, they caution that factors other than age may have been responsible for the pattern of steady cognitive decline. These factors, such as illnesses or differences in life experiences, need to be considered to be sure that the changes seen are age-related.

A second study, conducted by researchers at Washington University in St. Louis, followed up on earlier research that has consistently found that different brain regions are activated in older than in younger adults during cognitive tasks, even when they are performing the same task (such as taking a memory test). The reasons for this difference are unknown,

The Matrix of Scientific Inquiry

The progress that has occurred over the past 25 years in AD research would not have been possible without the various threads of scientific inquiry that, together, have provided a firm foundation for today's treatment and prevention clinical trials. These threads include studies of populations, basic research in laboratories, and animal studies.

Epidemiologic studies

Studies of groups of people allow scientists to examine characteristics, lifestyles, and disease rates. This information often provides valuable clues about the disease or the factors that could increase or decrease the risk of developing it. Some epidemiologic studies compare two different groups; such studies help investigators understand factors that influence why some people get a disease and others do not. Other "epi" studies follow one group over time, and the data gathered can reveal important clues about the origin or development of a disease. Epi studies cannot determine exactly what causes a disease, however. Clinical trials are necessary to achieve this objective.

Basic research in laboratories

Scientists in laboratories all over the world are working with the most up-to-date tools in an effort to seek answers to the mysteries of AD at the cellular and molecular level. Many of the studies described in this report are laboratory studies in animal or human tissue.

Studies of animals

Studies of animals, an important component of laboratory research, give investigators another crucial way to examine a scientific problem. As this report describes, animal studies are used to explore the major questions in AD—what causes the transformation from healthy aging to AD, what factors increase or decrease risk of developing AD, and what can be done to treat the disease. Because no one animal represents humans exactly, scientists work with a variety of models. Mice are by far the most common model.

but the increasingly sophisticated use of imaging technology is allowing scientists to observe patterns of brain activation in humans and to learn more about the areas of the brain necessary for performing specific cognitive tasks. This improved knowledge will help scientists understand what areas of the brain may be most vulnerable, and at what times. In this study, the researchers used functional magnetic resonance imaging (fMRI) to image brain activity in the frontal cortex of younger and older adults as they performed memory tasks (Logan et al., 2002). The investigators found that certain regions of the frontal cortex were less activated in the older adults than in the younger adults. However, this "under-recruitment" of specific areas in the frontal cortex in the older adults was reversed when they had more time to study and think about the information before being tested on it. Older adults also showed activation of additional and different regions in the frontal cortex than did the younger adults during their performance of the memory task. This "nonselective recruitment" of other brain regions did not change when the older adults were allowed extra time to prepare before the test. These findings suggest that two distinct forms of age-related change occur in this brain region in older adults. One is when neural resources are available but not spontaneously engaged (under-recruitment) unless training or cueing occurs. The other is when neural resources are no longer available (nonselective recruitment) so the brain must make use of other regions to accomplish the task. The researchers also found that older adults in their late 60s and in their 80s both showed under-recruitment, but that nonselective recruitment was most likely to emerge only in the oldest adults. This under-recruitment finding suggests that cognitive training strategies in late middle age could help to lessen age-related cognitive decline in some adults.

Different **brain** regions are **activated** in older than in younger adults during **cognitive tasks.**

Another study, conducted by investigators at the University of Alabama at Birmingham and other institutions, also demonstrated the potential of cognitive training. In this Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) intervention, which was co-funded by the National Institute of Nursing Research (NINR) and NIA, certified trainers provided 10 sessions of memory training, reasoning training, or speed of processing training to healthy adults 65 years old and older (Ball et al., 2002). The sessions improved participants' cognitive ability in the area in which they were trained. Even better, the improved abilities persisted for 2 years after the training ended, although the interventions did not make any real improvement in the daily functioning of the participants. The study investigators do not know whether these strengthened abilities might help a

person who develops cognitive problems later in life, but the findings do provide encouraging evidence that it is possible to conserve or improve some cognitive abilities in healthy older adults.

By identifying the changes that occur in the brain as it ages normally, investigators hope to be able to understand the additional pathological changes that lead to AD. Complementing this area of research, other scientists are focusing on learning more about the very earliest stages of AD. They hope that findings in this area may eventually open doors to treatments that may delay the onset of the disease or prevent its progression.

Scientists continue to **explore** the **early** stages of **AD.**

In the past year, scientists have continued to explore the early stage of AD from several perspectives. They have examined cognitive and pathological changes that could signal potential AD development. They have refined neuroimaging techniques and neuropsychological tests that can reveal what happens in the brain in the early stages. They have studied biomarkers of oxidative stress, which may provide clues to essential parts of the disease process. And they have worked to answer pressing questions about beta-amyloid and presenilins.

Earliest Cognitive and Pathological Changes that Indicate Potential Development of AD

The transition from normal aging to dementia is characterized by subtle changes that indicate a gradual decline in cognitive function. These early changes are difficult to differentiate from those that occur in healthy aging. Although declining cognitive function is not the same as AD or dementia, learning more about these changes is key to understanding the early stages of AD. Several teams of scientists have conducted community-based studies in which they have followed groups of older individuals for 6 to 10 years to explore patterns of cognitive decline in people with no obvious symptoms of dementia. In one of these studies, a research team from the University of Pittsburgh School of Public Health conducted clinical and neuropsychological evaluations of a group of more than 1,400 older adults every 2 years for 10 years (Chen et al., 2001). The study indicated that those who eventually developed dementia were significantly older and tended to have low educational levels compared to those who remained cognitively healthy. The test scores of those who did not develop dementia improved over time. In contrast, among the older adults who eventually developed dementia, a decline on the same tests during the two evaluation periods before symptoms appeared predicted the development of the symptoms. In a smaller but more in-depth study, researchers studied 108 older adults from the Oregon Alzheimer's Disease Center (see p.53 for more on the work of the Alzheimer's Disease Centers) for at least 6 years (Marquis et al., 2002). They found that poor recall on a memory test, small hippocampal volume, and the time needed to walk 30 feet predicted cognitive decline in this group of adults, some of whom eventually developed AD.

Similar to the other team, these researchers found that performance on the memory test improved over time for those participants who remained cognitively healthy. This suggests that practice over time might partly counteract the effects of age in those who remain cognitively healthy.

Another way that scientists are investigating the early stages of AD is by characterizing the biochemical and pathological changes that occur during this period. Two changes are of particular interest. The first is change in levels of choline acetyltransferase (ChAT), the enzyme that makes acetylcholine, a neurotransmitter important in the formation of memories. In the 1970s, scientists discovered that levels of acetylcholine fall sharply in people with AD. Four of the five current AD medications work to inhibit acetylcholinesterase, an enzyme that breaks down this neurotransmitter. Until recently, we did not know whether cognitive decline in the very early stages of the disease is also associated with falling acetylcholine levels. However, a University of Pittsburgh School of Medicine team of investigators working with Religious Orders Study participants set out to see whether this connection exists (DeKosky et al., 2002). The Religious Orders Study is a long-term study involving more than 30 religious communities in a dozen States. The study is being conducted through the Rush Alzheimer's Disease Center of the Rush-Presbyterian-St. Luke's Medical Center in Chicago, Illinois. Since 1993, scientists have been tracking the mental and physical capacities of the participants through annual physical and mental function tests. This study is providing a rich source of data on the process of normal aging as well as the development of AD. The investigators originally hypothesized that ChAT activity would be decreased in the hippocampus of participants with mild AD or mild cognitive impairment (MCI), a condition in which a person experiences significant memory problems but not the other cognitive problems found in AD (see the box on p.20 for more on MCI). However, they found that hippocampal ChAT activity levels in those with MCI were higher than in cognitively healthy participants and had not decreased even in those with mild AD.

Advances in Basic Research Suggest Avenues for Future AD Therapies

Scientists are rapidly improving their understanding of very early changes in the brain that eventually result in full-blown AD. This knowledge is suggesting a number of avenues that may someday be used to prevent or treat AD. These avenues involve preventing the development of AD's three main features—plaques, tangles, and loss of connections between neurons.

Prevent build up of plaques
- Slow or prevent beta-amyloid production
- Slow aggregation of beta-amyloid into plaques
- Dissolve plaques

Prevent build up of neurofibrillary tangles
- Slow or prevent *tau* aggregation and dysfunction
- Dissolve neurofibrillary tangles

Prevent brain cell dysfunction and death
- Slow or prevent oxidative stress, inflammation, reduced blood flow
- Increase levels of protective molecules in the brain
- Maintain viable connections between cells

The Aging Brain, Mild Cognitive Impairment, and AD

As a person gets older, changes normally occur throughout the body, including the brain:

- Some neurons shrink, especially ones in areas important to learning, memory, planning, and other complex mental activities. In some brain areas, neurons actually die.
- Tangles and plaques develop in neurons and surrounding areas, respectively, though in much smaller amounts than in AD.
- Inflammation in brain tissue increases.
- Damage by free radicals increases (free radicals are highly reactive oxygen molecules that combine easily with other molecules; a build up of too many can damage neurons; see p.23 for more on free radicals).

As a result, healthy older people may notice a modest decline in their ability to learn new things and retrieve information, such as remembering names. Although these declines may be frustrating, they do not interfere with the ability of older adults to engage in what they need to do or enjoy doing.

As some people grow older, however, they 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 difficulties in other cognitive areas, such as making decisions, that are required for a diagnosis of AD. These people have a condition called mild cognitive impairment with memory loss. Many people with MCI do go on to develop AD. However, we do not yet know whether progressing to AD is inevitable. Scientists are intensively studying MCI in hopes that a greater understanding of this condition will shed light on the early stages in the development of AD as well as increase our knowledge of the aging brain in general.

They theorized that an initial compensation had occurred in that part of the brain to make up for developing deficits. These findings clearly show that there is still much to learn about the early stages of AD.

The second set of changes of particular interest to scientists occurs in *tau*, the primary component of neurofibrillary tangles. In one study, a team of researchers gave extensive neuropsychological tests to 31 Religious Orders Study participants. Some of these participants had MCI; others were cognitively healthy. After their deaths, the study team, which was led by researchers from the University of Pennsylvania School of Medicine, examined their brain tissue for signs of *tau* tangles (Mitchell et al., 2002). The study confirmed that those with MCI had a higher average number of tangles than did the cognitively healthy participants. Those with mild AD had even more tangles than those with MCI. These findings support the notion that the destructive changes that occur in the brain develop in parallel with outwardly apparent cognitive changes. They also show that characterizing the biochemical and pathological changes that are responsible for the earliest stages of the AD disease process is important because they point to potential targets for therapies aimed at very early AD.

In a second *tau* study, scientists from the Northwestern University Institute for Neuroscience in Chicago, learned more about the relationship between changes in *tau* and beta-amyloid (Rapoport et al., 2002). This research was supported by NIA, NINDS, and the Alzheimer's Association. Using nerve cell cultures from mice with genetically altered *tau*,

the investigators found that neurons containing either human or mouse *tau* proteins degenerated if exposed to fibrillar beta-amyloid. However, neurons from mice without the altered *tau* did not degenerate when exposed to the beta-amyloid. Although the genetically altered *tau* used in this study is generally responsible for another neurodegenerative disease, frontotemporal dementia with parkinsonism linked to chromosome 17 (FDTP-17), these results suggest that the effects of beta-amyloid on the degeneration of neurons in AD may involve the *tau* proteins to some degree.

Scientists are also learning about the early changes in AD by studying changes in several sensory systems. For example, University of Rochester Medical Center investigators have been exploring the issue of optic flow for some time (O'Brien et al., 2001). When people move through a space, they see the environment around them change. It appears to be flowing past them. This changing "picture" is called optic flow. People can orient themselves in space and know the direction in which they are moving because of the brain's ability to process optic flow information. Optic flow is somewhat impaired in older adults compared with younger adults and is even more damaged in people with AD. In a study from the same University of Rochester group, which was conducted with monkeys, scientists found that neurons in particular regions of both sides of the brain encode directional and location information, and may play a critical role in supporting one's orientation in space (Froehler and Duffy, 2002). The fact that these anatomical pathways are associated with brain regions that connect to the hippocampus suggests that changes could play an important role in the disorientation that develops in AD and other neurodegenerative diseases.

In a major scientific breakthrough, scientists used PET to **view amyloid** deposits in the **brains** of **living** humans.

Neuroimaging

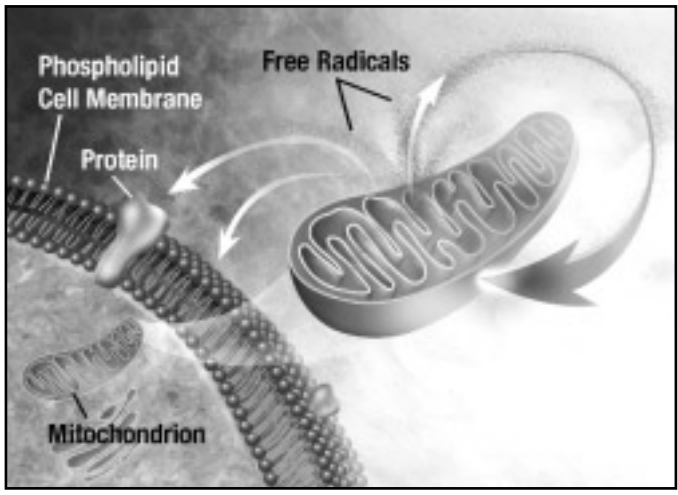
Investigators are continuing to use neuroimaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), to assess whether it is possible to measure aspects of brain structure or function that will identify people who are at risk of AD even before they develop the symptoms of the disease. Over the past year, research has expanded our understanding of the potential usefulness of these techniques for research and diagnostic purposes. The research also has increased our knowledge about early AD changes in specific brain regions.

For example, a University of Pittsburgh team of scientists working with transgenic mice that develop beta-amyloid plaques, has developed a new dye-based compound that has a particular affinity for beta-amyloid present in the

brain (Mathis et al., 2002). The investigators found that this compound was rapidly taken up by brain tissues and bound to plaques. Very recently, in a major scientific breakthrough, the same team of scientists used PET to show that the compound, referred to as Pittsburgh Compound-B, or PIB, can be used to view amyloid deposits in the brains of living humans. In this groundbreaking study, 16 patients diagnosed with mild AD showed markedly more retention of PIB in certain regions of the cortex that are known to contain large amounts of beta-amyloid, than did nine cognitively healthy individuals (Klunk et al., 2004). Future studies with PIB or other similar compounds may contribute to our understanding of the role of beta-amyloid in the natural history of AD, help with early diagnosis, and aid in following disease progression.

The damage to the brain that occurs in AD begins in an area called the entorhinal cortex. It then spreads to the hippocampus, the brain structure that is essential to the formation of short- and long-term memories. Previous neuroimaging studies using MRI have shown that the shrinkage in brain tissue volume and loss of neuronal function that occurs as the disease progresses can be correlated with decreased performance on memory and other AD tests.

Harvard Medical School and Boston University scientists used MRI to see which brain region—the entorhinal cortex or the hippocampus—might better predict which people with MCI would progress to AD (Killiany et al., 2002). Because a high percentage of people with MCI progress to AD



every year, a test that could reliably predict this time course would be extremely valuable. It might even be possible someday to develop a treatment that could delay or prevent AD in these individuals. This research team performed MRI scans on 137 individuals with MCI and measured both the entorhinal cortex and hippocampus. They found that decreased volume in the entorhinal cortex did a better job of predicting which individuals would progress to AD than did decreased hippocampal volume.

A second study clearly shows the progress of damage to brain regions as AD worsens. In this imaging study, which also included pathological data and results from memory and other neuropsychological studies, investigators from the Mayo Clinic in Rochester, Minnesota, used MRI to study individuals whose AD had been diagnosed through memory and neuropsychological tests (Jack et al., 2002). The AD diagnosis was confirmed after death by pathological analysis of brain tissue. The investigators found that the brain tissue of these individuals, who had well-established AD, showed substantial hippocampal

shrinkage. In contrast, individuals whose brains exhibited changes associated with normal aging did not have the same degree of hippocampal shrinkage and no memory decline or clinical diagnosis of AD.

Biological Markers and Oxidative Stress

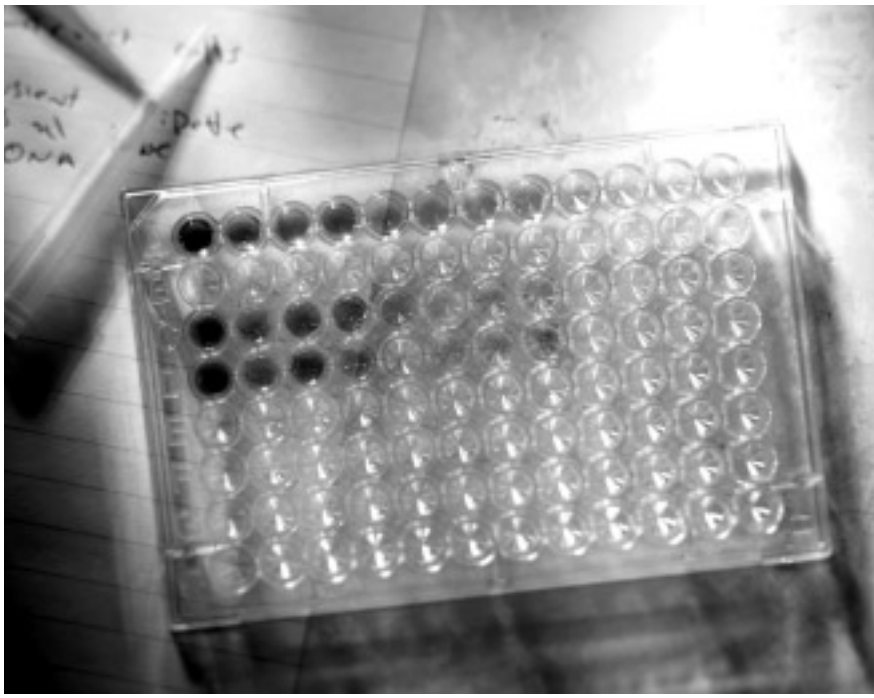
Scientists also are trying to discover whether biological markers exist that could indicate early changes in the brain associated with AD. Understanding these markers—what they are, how they function, and how and when their levels change—will help investigators answer questions about the cause and early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

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 development of several neurodegenerative disorders. In the AD brain, in particular, such damage has been observed, especially in the late stages, when both beta-amyloid plaques and neurofibrillary tangles are present in abundance. However, scientists do not know whether the oxidative stress causes or results from the process of beta-amyloid plaque formation, or is related to other triggers.

Researchers from the University of California at Irvine have studied the impact of oxidative damage on cognitive function in dogs (Cotman et al., 2002; Milgram et al., 2002). As in humans, dogs naturally accumulate beta-amyloid plaques in their brains as they age, and the amount of beta-amyloid plaques in dogs correlates with the severity of cognitive decline. Oxidative changes are also apparent in the brain tissue of old dogs. The scientists speculated that if beta-amyloid is related to the oxidative changes seen in the brain in normal aging and in disease, then a reduction in oxygen free radicals should bring about improvements in cognition. To test their hypothesis, the researchers developed a series of increasingly difficult behavioral and learning tests for 23 old and 16 young dogs. One group of the young and old dogs ate a regular diet; a second group of young and old dogs ate the same diet supplemented with antioxidants. The antioxidant-enriched diet improved the learning and memory in the old dogs but it had little effect on young animals. These results suggest that the impact on behavior of oxidative changes in the brain occurs in later life and that this can be modified in dogs by a diet high in antioxidants.

Oxidative stress may play a role in the development of several neurodegenerative disorders.

Several recent studies, funded by the National Institute of Environmental Health Sciences (NIEHS), explored aspects of the oxidative stress process. One area of study involves lipids, a substance found in all living cells. (Fats are a type of lipid.) Scientists are interested in the extent to which lipids in the central nervous system are affected by oxidative stress. This can be assessed by measuring levels of a newly described class of lipids—the isoprostanes. Isoprostanes are formed by the addition of oxygen to specific lipids, and this process, called lipid peroxidation, is a known feature of AD. A University of Pennsylvania team funded by NIEHS and NIA quantified levels of a specific isoprostane—8,12-iso-iPF (2alpha)-VI—in brain tissues from cognitively healthy people, people with AD, and people with frontotemporal dementia (Yao et al., 2003). They found that this particular isoprostane was a specific and sensitive marker of brain oxidative stress in those with AD but not in those with frontotemporal dementia or those who were cognitively healthy. Understanding and identifying biological markers that can distinguish AD from other neurodegenerative diseases may one day lead to new diagnostic and therapeutic tools.



Another NIEHS-supported study illustrates how basic research into molecular pathways can provide potentially important insights into future treatment strategies. In this study, researchers from the University of Wisconsin at Madison built on knowledge that oxidative stress and its products can induce apoptosis (Lee et al., 2003). Apoptosis, also called programmed cell death, is a normal mechanism that allows a cell to self-destruct under certain situations, such as when it is no longer needed within the body or when it becomes a threat to the health of the organism. Programmed cell death can be prevented in many ways, such as by adding external growth factors, supplementing with antioxidants, and inhibiting cell death pathways. These investigators found an alternative way to protect cells from apoptosis through coordinated upregulation of genes that make different components of a cell defense system (such as antioxidant and detoxification products). The investigators refer to this process as "programmed cell life." The researchers hypothesize that activating more programmed cell

life pathways can balance programmed cell death. In combination with other techniques known to prevent detrimental programmed cell death, this strategy may be a powerful tool to control progressive neurodegenerative diseases like AD.

Beta-amyloid

The study of beta-amyloid, the primary component of AD plaques, continues to be a vital part of the quest to discover what goes wrong in the brain as AD develops. Investigators continue to pursue studies that will clarify the process by which APP is cleaved by enzymes to release beta-amyloid fragments, how these fragments clump together and accumulate in the brain to form plaques, and whether and how plaques might be cleared from the brain. In studies published during the past year, investigators reported on several different issues related to beta-amyloid.

Beta-amyloid is a vital part of the **quest** to discover what goes wrong in the **brain** as AD develops.

A team of scientists from the Mt. Sinai School of Medicine in New York reported on research that examined more closely the toxicity of specific forms of beta-amyloid (Parvathy et al., 2001). Their study examined brain tissue after death from individuals who had earlier been shown through cognitive testing to have had some level of dementia (questionable, mild, moderate, or severe) or no dementia. The scientists discovered a striking pattern in the deposition of three common beta-amyloid fragments, or peptides. They found that some of these peptides had accumulated in brain tissue before AD was diagnosed, and they found that a significant number of plaques contained longer peptides. This suggests the possible involvement of at least these beta-amyloid peptides early in the progression of AD, even though these longer beta-amyloid fragments are generally found in lesser amounts than are other fragments. The researchers hypothesize that the unique properties of each are keys to brain amyloid burden and, possibly, to the toxicity attributed to beta-amyloid.

In a related study using brain tissue from rats, investigators from Northwestern University Medical School in Chicago suggested that clusters of fibrillar beta-amyloid might contribute to AD by impairing the ways in which neurons involved in the formation of memory signal to each other. Conceivably, these clusters also could cause harm at the structural level by interfering with the way in which brain neurons repair damage to their connections with other neurons (Wang et al., 2002).

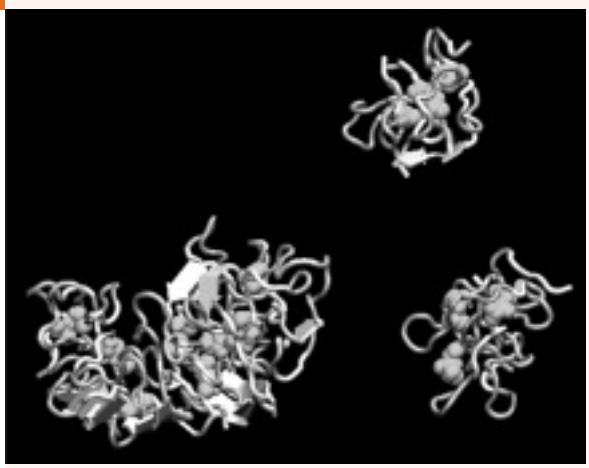
Another study, supported by the National Institute of Child Health and Human Development, also focused on the way in which beta-amyloid may damage neurons (Grace and Busciglio, 2003). In this study, investigators from the University of Connecticut Health Center found that fibrillar beta-amyloid may induce damage to neurons by

adversely affecting the function of key proteins in the cell membrane called focal adhesion proteins. Studies like this, which clarify the cascade of events in beta-amyloid biology, are making a critically important contribution to our understanding of what happens in the brain to cause the transformation from healthy aging to AD.

A multi-site collaborative study headed by a research team at the Haldeman Laboratory of Molecular and Cellular Neurobiology at Sun Health Research Institute in Sun City, Arizona, examined beta secretase, an enzyme that is thought to play a pivotal role in cleaving APP into beta-amyloid fragments (Yang et al., 2003). The scientists showed that both the amounts and activity level of this enzyme were modestly higher in affected brain regions (the temporal cortex and hippocampus) of individuals with AD compared to cognitively healthy individuals. These statistically significant correlations suggested that the higher levels of beta secretase are at least in part responsible for more beta-amyloid being formed.

Stanford University scientists funded by the National Institute of Mental Health (NIMH) and NIA looked at another aspect of beta-amyloid—whether it is possible to remove plaques once they have formed. In this study, the investigators examined whether a substance called macrophage colony stimulating factor receptor (M-CSFR) could induce a particular kind of brain cell called microglia to surround and destroy beta-amyloid plaques (Mitrasinovic and Murphy, 2002). Using mice, the scientists demonstrated that these cells had an increased

Other May Shed



A number of neurodegenerative diseases, including AD, dementia with Lewy bodies (DLB), Parkinson's disease (PD), Huntington disease, amyotrophic lateral sclerosis (ALS), and prion diseases such as Creutzfeldt-Jakob disease (CJD), are characterized by excessive amounts of abnormally folded proteins being deposited in the brain. Each disease has unique clinical symptoms and pathological characteristics, and the way they progress and develop over time are different. However, they also share some characteristics with each other. For example, some people with AD have slowed movements and tremors, the most obvious symptoms of Parkinson's disease. People who have dementia with Lewy bodies (abnormal structures in the brain that contain a protein called synuclein) experience cognitive, behavioral, and psychotic symptoms similar to AD as well as the slowed movements and tremors that are characteristic of PD.

Neurodegenerative Diseases Light on Early Changes in AD

Many scientists are intensively studying these diseases, and their growing knowledge about the characteristics of each is helping to answer questions about the others. Several recent studies highlight the progress being made in this area.

One study conducted by scientists at a number of institutions explored some of the factors that might account for why disease progression and survival vary so much in people with AD (Haan et al., 2002). Previous research had found that people with AD who have parkinsonian symptoms (for example, shuffling gait, slowed movements, rigid muscles, and tremors) and symptoms of delusions and hallucinations experience faster cognitive decline and shorter survival times than do people with AD who do not have those symptoms. The research team examined the relationship between parkinsonian symptoms, delusions and hallucinations, age of death, and the presence of Lewy bodies in a group of 379 individuals with AD who were evaluated during the time they had AD and autopsied after death. Confirming previous work, these findings suggested that parkinsonian symptoms may predict reduced survival in patients with AD. The results also suggested that the presence of Lewy bodies and of parkinsonian symptoms may work together to reduce survival more than either characteristic by itself.

One hypothesis about AD, PD, and other neurodegenerative diseases is that "misfolded" proteins that accumulate in brain tissue cause the disease. When a protein is first created, it exists as a long string of amino acids. Within a fraction of a second, the amino acids fold themselves into a distinctive three-dimensional shape. Each type of protein has a unique shape, which allows it to carry out its particular function. For example, hemoglobin's shape lets it carry oxygen in blood. If a protein is not folded properly, it cannot function normally. A University of California at San Francisco research team explored this issue in a study on the transmission of prion diseases between different species of animals (Peretz et al., 2002). Prions are infectious proteins that change the shapes of normal cellular proteins, transforming them into abnormal proteins. CJD and other fatal neurological diseases are caused by accumulations of prions in the brain, which somehow cause sponge-like holes to develop in brain tissue. This damage to brain tissue results in movement, emotional, sleep, and cognitive disturbances and premature death. By learning more about prion diseases and protein misfolding, researchers hope to understand the pathological mechanisms that underlie the transformation of normal proteins into abnormal ones, thereby shedding light on the disease process in AD and other diseases.

In another study that reinforced the possible commonality of misfolded proteins in neurodegenerative disorders, scientists from the University of Pennsylvania conducted a study on a transgenic fruit fly with human genes inserted (see p.30 for more about the use of transgenic animals in AD research). This fly makes human synuclein protein in particular neurons (Auluck et al., 2002). Mutations in the gene that directs the production of the synuclein protein causes it to misfold, resulting in one form of Parkinson's disease in humans. Expression of both the normal and the mutated human synuclein genes in these fly neurons caused the neurons to die. Scientists then studied transgenic flies that made both the human synuclein protein and one called hsp70 in these same neurons. Hsp70 protein refolds misfolded proteins and its expression in the synuclein-containing neurons prevented their death. This is one approach scientists hope will be applicable to several major neurodegenerative diseases caused by protein misfolding, including AD.

capacity to clear beta-amyloid from brain tissue. Activation of microglia to destroy plaques was the concept behind the recent development of the AD vaccine, and the Stanford study provides an additional and valuable contribution to this body of knowledge. Other studies have important implications for future drug and vaccine development. For example, a Mayo Clinic research team in Minneapolis worked with mice to build on earlier studies that suggested that the presence of antibodies to beta-amyloid could reduce the accumulation of this toxic material in the brain and prevent continued cognitive decline. This team, funded by NIA, NINDS, and NIMH, administered antibodies to mice who had beta-amyloid plaques and impaired memory, but not neuronal loss (Kotilinek et al., 2002). This refinement of earlier vaccine approaches reversed the memory deficits without having a significant impact on the overall amount of beta-amyloid in the brain.

Another avenue of beta-amyloid research has focused on finding or developing compounds that might inhibit APP formation, thereby limiting beta-amyloid formation. Under normal circumstances, the amount of APP that a cell makes appears to be regulated by a particular sequence in its messenger RNA (mRNA). This intermediary carries from the gene a blueprint that is necessary to make a protein. A Massachusetts General Hospital research team funded by NIMH postulated that interfering with this sequence would interfere with APP formation and ultimately with beta-amyloid formation (Rogers et al., 2002). If a compound binding to this sequence could be developed, it would be important to determine whether, in fact, it worked to block APP formation. This research team developed a fluorescent APP mRNA that is easily visualized until it binds with a drug that blocks the sequence that regulates APP formation. In theory, when the fluorescence disappears, APP and beta-amyloid formation are blocked. This simple, rapid screen for drugs that can block APP formation may hasten the development of AD treatments. Some scientists worry, however, that lowering levels of APP might have unwanted side effects if APP itself has an important function in brain cells.

Scientists have made major **progress** in clarifying the biology of **presenilin** proteins.

Presenilins

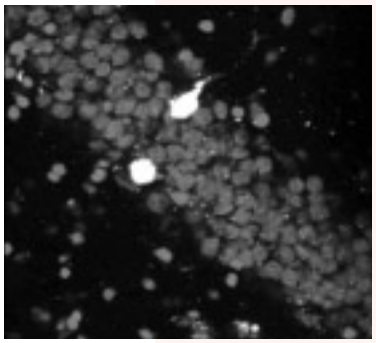
During the past several years, scientists also have made major progress in clarifying the biology of presenilin proteins. Many mutations in the genes coding for the presenilin proteins have been found, and the mutations in the presenilin 1 gene are responsible for the majority of early-onset forms of AD (see p.10 for more on our understanding of what causes AD). Scientists hope that a deeper knowledge of the basic biology of presenilins will help them understand how these proteins are involved in the development of AD.

The presenilin proteins are part of a complex that includes three other

proteins (nicastrin, aph-1, and pen-2) that are involved in causing the cleavage of APP into beta-amyloid fragments. A study in mice conducted by University of Chicago scientists has helped to further elucidate the role of presenilin proteins. Their results suggest that in addition to their role in cleaving the APP protein, presenilins function as "chaperones," which are required to properly fold and move proteins such as nicastrin through intracellular "way stations," where they may be further modified before being distributed to other cellular compartments to do their jobs (Leem, J. Y. et al., 2002).

A second study explored a possible relationship between the presenilin 1 gene and some of the most fundamental concepts involved in memory formation. Short-term memories are formed in the hippocampus and are transferred to the cortex for long-term memory storage. Some scientists believe that the hippocampus has only so much storage capacity for new memories. Therefore, short-term memories that have limited utility must be "cleared" so that storage space remains for critical new information. In this study, a Princeton University team of investigators funded by NIMH and NIA selectively deleted the presenilin 1 gene from a particular kind of neuron in the forebrain of mice (Feng et al., 2002). These "knockout" mice were placed in an enriched environment, meaning that they were in cages that contained toys, running wheels, and small houses. The knockout mice grew normally but they made fewer neurons from stem cells in the

Using catFISH to "See" Neurons at Work



This catFISH image shows IEG-activated neurons (in white) of the hippocampus from an older rat.

To determine what actually happens in the brain during the transformation from healthy aging to AD, scientists need to know more about the ways in which neurons interact. These interactions are directed by genetic instructions about where and when particular cellular proteins are produced.

A case in point is research on a class of genes called immediate-early genes (IEGs). These genes are unique because at certain times their expression is low or undetectable. This means that they are not actively giving instructions for the creation of new proteins. However, within minutes of an extracellular stimulation, such as addition of a growth factor, they begin to direct the production of new proteins.

IEGs are useful markers in studies of behavior and cognition because changes in their expression level can be used to identify those brain areas and neurons that are activated after behavioral or learning tasks.

At the Arizona Research Laboratories in Tucson, a research team has developed a novel imaging method, called cellular Compartment Analysis of Temporal activity by Fluorescent In-Situ Hybridization, or catFISH for short (Guzowski et al., 2001). This imaging technique provides information about what happens when individual IEGs are activated and what happens in the process of protein formation after the IEG is activated.

In studies of rats exposed to two different environments, the researchers used catFISH to image the activation of two IEGs. From this, the scientists were able to infer the activity history of individual hippocampal neurons in the rats. Their results suggest that behavioral experiences are linked to specific neural circuits in the brain.

The development of the catFISH imaging technique now makes it possible to "visualize" single cells where genes are turned on. It will help scientists understand the molecular signaling pathways controlling changes in gene expression. In future, imaging by catFISH may help identify the interactions of nerve cells in the brain that underlie different cognitive and behavioral processes, and their changes during normal aging.

Use of Animal Models to Examine Early AD Changes in Neurons

For many years, scientists have worked with specially bred mice that develop some of the characteristic pathological features of AD. These "transgenic" animals contain normal or mutated forms of human genes implicated in AD, such as the APP gene. As they grow older, APP transgenic mice develop AD-like plaques in the same regions of the brain as do people with AD. However, they do not show other AD changes, such as the formation of neurofibrillary tangles or the death of particular kinds of neurons. Newer animal models have more of these AD-like pathologies.

APP transgenic mice can be used to find out the effects of other human genes on beta-amyloid production. Scientists do this by breeding the APP transgenic mice to transgenic mice containing a test human gene. This strategy was used to discover the effect on beta-amyloid metabolism of different forms, or alleles, of the risk factor gene for late-onset AD. This gene is called apolipoprotein E, or APOE (see p.31 for more on APOE and its forms).

Investigators at Washington University School of Medicine in St. Louis, conducted a detailed analysis of the various alleles of the APOE gene in transgenic mice. They found that the APOE-ϵ4 allele influences beta-amyloid metabolism early in the disease process by facilitating the formation of fibrillar beta-amyloid (Fagan et al., 2002). In a second study from the same laboratory, the researchers showed that another apolipoprotein gene, APOJ, also influences the deposition of beta-amyloid and the formation of plaques. In the absence of APOJ, the researchers found that damage to neurons usually seen in the presence of amyloid plaques was markedly reduced. This suggests that apolipoproteins E and J appear to influence beta-amyloid structure and toxicity, and that both are likely to play a role in the damage to neurons caused by beta-amyloid deposits (DeMattos et al., 2002).

Though many studies have demonstrated the huge contribution that transgenic mice make to our growing understanding of AD and of potential preventive and therapeutic strategies, another recent study provides a caveat that is important to remember: Mice and humans are different, and AD pathology as it occurs in these animals is not exactly the same as AD in humans. Using transgenic mice, researchers at the Sun Health Research Institute demonstrated that the beta-amyloid deposits found in these mice were more soluble than the beta-amyloid deposits found in human AD (Kalback et al., 2002). These findings raise the possibility that it may be less easy to prevent or remove beta-amyloid deposits in humans than it is in transgenic mouse models. Therefore, treatments that work to remove these deposits in mice may not do so in humans.

hippocampus than did mice in the same enriched environment but who still had the presenilin 1 gene (see p.40 for new discoveries about stem cells and the formation of new neurons in the brain). The knockout mice also were able to learn normally, even when they were quite old, but they retained old memories better than did the normal mice. These results suggest that loss of the presenilin gene may result in an inability to clear old memories from the hippocampus (in other words, to free up "storage space"). In theory, this might result in an inability to store or "remember" new memories, just as happens with people who have AD.

Can Certain Factors Increase Risk of or Protect Against AD?

We've known for some time that certain genetic, non-genetic, and biologic factors can increase the risk of developing AD. Recent evidence has suggested that other factors may actually help to reduce AD risk. Researchers are investigating these risk and protective factors through a variety of studies, including genetic studies and studies of individual lifestyles and behavioral patterns. Scientists also are using epidemiologic studies to examine how lifestyle patterns may interact with genetic factors to change the likelihood that a person may develop AD. Findings from these studies, particularly the genetics studies, are important because they point to cellular pathways that go wrong in AD. This research eventually will be useful in identifying people at increased risk of developing AD.

Risk factor studies already have pointed the way to potential preventive approaches that are being investigated in controlled clinical trials. If confirmed by the trials, these approaches may suggest ways that people can change their lifestyles or environments to reduce the risk of developing AD.

Genetics

Genetic studies generally have focused on two key issues—whether a gene might influence a person's overall risk of developing a disease, or whether a gene might influence some particular aspect of a person's risk, such as the age at which the disease begins (age at onset). A research team at Duke University Medical Center explored genetic links to AD through one of these latter types of studies. The investigators conducted a kind of genetic analysis called a genomic screen on 449 families affected with AD and 174 families affected with Parkinson's disease (Li et al., 2002). Because AD and PD share some common clinical and pathological characteristics, the investigators hypothesized that a gene or genes common to both diseases might control age at onset. Results showed that age at onset appears to be passed down through generations and that age at onset of both diseases may be controlled by a common gene. The study also confirmed that the analytic method used by these researchers is feasible for this type of genetics study. Clearly, further studies are needed on this complex issue, but identifying the genes that regulate disease onset is important because they will help to uncover the molecular pathways involved in its initial development. This knowledge may eventually lead to effective prevention strategies.

AD genetics researchers also have compared risk in various racial and ethnic groups. Previous studies have shown that ethnic and racial groups appear to differ in their genetic risk of AD, but these findings were difficult to interpret because studies looked at different populations and different age groups, and they differed in design and analytic approach. More recently, investigators have completed studies that have shed light on some aspects of our knowledge of genetic background and AD risk and how it might be more similar among certain populations than previously thought. It is important to clarify similarities and differences in genetic risk because they help us understand more about the disease in general as well as help us as a society respond to the needs of all people with AD and their families.

Identifying **genes** that regulate disease onset will help uncover the **molecular pathways** involved in its initial development.

For example, the APOE-ϵ4 allele, located on chromosome 19, is a risk factor for late-onset AD. Unlike the APP and presenilin genes, whose mutation is

associated with the rare early-onset AD, APOE-ϵ4 increases the risk of developing late-onset AD, rather than being its cause. Investigators from Columbia University who studied a population in northern Manhattan over time found that APOE-ϵ4 appeared to be less of a risk factor among African Americans and Hispanics than in Caucasians (Tang et al., 1996). More recently, the same team evaluated 203 Caribbean Hispanic families in the Dominican Republic and Manhattan to reexamine the association between APOE-ϵ4 and AD. They were searching for genes that might be associated with increased risk in Caribbean Hispanic families who had at least two living relatives with AD (Romas et al., 2002). The investigators found a stronger association between APOE-ϵ4 and AD in elderly Caribbean Hispanics than previous studies had suggested. This may have occurred because the AD patients were younger than those in Manhattan and were in families chosen for their high genetic risk. The authors note that this strong association between APOE-ϵ4 and risk of AD suggests that future genetic analyses need to take this factor into account in Hispanics.

In a related study conducted in the Caribbean Hispanic families, the same team of researchers looking for new risk factor genes for late-onset AD found a modest linkage on chromosome 12 (Mayeux et al., 2002). The association varied, depending on the age at onset in the individuals and whether the individuals did or did not carry the APOE-ϵ4 risk factor gene. Identifying populations that have specific chromosome locations that may harbor risk factor genes for AD greatly enhances the likelihood of success in finding the risk factor genes.

Boston University School of Medicine and Mayo Clinic investigators also evaluated APOE in a large group of African Americans with AD and compared them to their siblings and to unrelated cognitively healthy African Americans (Graff-Radford et al., 2002). The study found that the presence of one or two APOE-ϵ4 genes increased the risk of developing AD but the risk decreased substantially with increasing age. The investigators also found that having the APOE-ϵ2 gene appeared to protect against developing AD. All of these findings are true for Caucasians as well.

APOE-ϵ4 is a risk factor gene for late-onset AD.

In another APOE study, funded by the National Center for Research Resources, scientists from Columbia University determined the APOE alleles in 87 people with AD who had psychiatric symptoms (Scarmeas et al., 2002). The researchers found that the presence of one or more APOE-ϵ4 alleles significantly increased the risk of delusions among these study participants.

Increasing knowledge about the genetics of AD has led to an urgent need for accurate information and materials to educate and counsel families, health care providers, and the public about this topic. University of Iowa scientists supported by the National Human

When Comparing Population Groups, Many Factors Must Be Considered

In studying possible differences in AD risk, incidence, and prevalence among various racial and ethnic groups, researchers must keep in mind that populations vary in many respects besides their race or ethnicity. As a result, many factors may be responsible for differing disease estimates. Differences in socioeconomic status, health care, education, events occurring before birth 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 are important. For example, people may be diagnosed with AD if their level of education or cultural assimilation affects their performance on the test in ways that are different from the performance of people with a higher level of education who are more culturally assimilated and for whom the tests were originally designed. Clearly, further careful investigation is needed to examine the role that all these factors may play in determining the risk of AD.

One recent study, conducted by a Columbia University team of scientists, illustrates the complexity of comparative studies and the need for careful analysis (Manly et al., 2002). The researchers matched 192 African American and 192 Caucasian older adults by their years of education and gender. All were cognitively healthy and none had a history of neurological disease, stroke, mental illness, or head injury. Both groups took a comprehensive battery of neuropsychological tests. Even though the two groups had the same number of years of education, the African American participants scored lower than the Caucasian participants on measures of word learning and memory, figure memory, abstract reasoning, language fluency, and visual-spatial skills.

The investigators then reanalyzed the results using an estimate of the quality of education rather than number of years of education. After adjusting the participants' scores in light of this new parameter, the investigators found that the effect of race was greatly reduced. All but two of the test score differences between the two groups were significantly reduced if not eliminated.

This work suggests that the use of years of education alone to define the level of educational experience is inadequate. The research also weakens the assumption that if groups are matched on socioeconomic variables, such as years of education, then any persistent group differences are necessarily biologically meaningful. This study has made an important contribution to illuminating factors that can account for ethnic group differences on cognitive tests, and these findings may guide the development of new cognitive tests and measures.

Genome Research Institute are conducting research to address the ethical, legal, and social implications of the genetics of AD and genetic testing. They also are developing related educational materials for health care professionals who work with AD families (Williams, 2002).

Lifestyle

One factor that is capturing an increasing amount of attention from AD researchers is the possible impact of lifestyle factors, such as physically and intellectually stimulating activities, on AD risk. A number of studies over the past few years have provided intriguing hints that these challenging activities may be linked to a reduced risk of AD, and they are consistent with what we know about other health benefits associated with being physically and mentally active throughout life.

Exercise may benefit **brain** health.

Physical exercise was the focus of two recent studies conducted on rats by scientists at the University of California at Irvine. These studies followed up on previous animal research that had suggested that exercise or an enriched environment can increase resistance to brain injury, stimulate the formation of new neurons, and enhance cognitive and behavioral performance. In the first study, the investigators found that several days of exercise increased levels of brain-derived neurotrophic factor (BDNF), a growth factor that stimulates survival, growth, and adaptability of some neurons in the hippocampus (Cotman and Berchtold, 2002). The elevated levels of BDNF remained high even after several weeks of exercise. These findings support the idea that exercise may have a pronounced effect on the brain. Exercise appears to recruit brain processes that contribute to cognitive functioning, and to activate cellular mechanisms that protect the brain from damage and promote its repair. Scientific studies such as these are providing a biological basis for the premise that exercise may benefit brain health, both during aging and possibly in decreasing risk of neurodegenerative diseases.

In other studies, the researchers worked with female rats that were deficient in estrogen (Cotman and Berchtold, 2002). They found that voluntary running on an exercise wheel did not increase levels of BDNF protein in the brain. However, when exercise was combined with long-term estrogen replacement, BDNF levels increased. To identify other possible molecular effects of exercise, the researchers used special techniques to examine changes in gene expression profiles of about 5,000 genes in the rat hippocampus. In normal rats, 3 weeks of exercise led to changes in the expression of a number of genes, particularly those involved in neuronal activity and adaptability and those involved in controlling the structure of synapses.

Dietary Factors

Another exciting area of research that is attracting attention involves possible links between dietary patterns and AD risk. Two recent studies, conducted

Food Sources of Vitamin E

- Vegetable oils, such as safflower, corn, and soybean oil
- Wheat germ
- Nuts, such as almonds, peanuts, and pistachio nuts
- Green leafy vegetables, such as spinach, turnip greens, and dandelion greens
- Some other green vegetables, such as broccoli
- Some fruits, such as mango and kiwi
- Breakfast cereals fortified with vitamin E

as part of the Chicago Health and Aging Project (CHAP), a study of a large, racially diverse community of people age 65 and older, examined the potential preventive effects of vitamin E in foods and supplements on development of AD. Scientists are particularly interested in vitamin E because it is an antioxidant that might protect brain cells from oxidative stress caused by too many free radicals (see p.23 for more on free radicals). In the first study, investigators followed 815 cognitively healthy participants for an average of almost 4 years (Morris et al., 2002a). About 18 months into the study, participants completed a detailed questionnaire about the kinds and quantities of foods and supplements they had consumed during the previous year. At the end of the study period, the investigators examined the relationship between intake of vitamin E and C from foods and supplements, intake of beta carotene (a substance from plants that the body converts into vitamin A), multivitamin use, and development of AD. The most significant association with reduced risk of AD was found among people in the top fifth of vitamin E intake from foods. The scientists found no significant change in risk of AD when they looked at vitamin E supplements, vitamin C and beta carotene, or the multivitamin. Data also were analyzed to see whether age, gender, race, education, or possible genetic risk of AD had any effect. Only the presence or lack of APOE-ϵ4 seemed to matter. The association between vitamin E from food and decreased risk of AD was strongest among people who did not have the APOE-ϵ4 allele.

In the second study, the same research team followed 2,889 community residents for about 3 years. As in the other study, they completed a detailed questionnaire about their usual food intake about 18 months into the study (Morris et al., 2002b). Results from this study indicated that the rate of cognitive decline was reduced by 36 percent among those in the highest fifth of total vitamin E intake (foods plus supplements) compared to the lowest fifth. Cognitive decline was also less

among those with higher vitamin E intake from foods alone.

The findings from these two studies suggest that a diet rich in foods containing vitamin E may help protect some people against age-related cognitive decline and AD. The reasons for the inconsistent effect of vitamin E supplements are not clear, but may have to do with the various forms of the vitamin as well as why and when people start to take supplements. Though these findings are intriguing, it is important to note that foods are more complex than just their vitamin content and that many factors may be involved. It is also important to note that those with highest intake of vitamin E may have been different from the other group in some other way that is protective against AD.

These results have increased interest in the outcome of clinical trials now underway or planned that are testing the effectiveness of vitamin E and other antioxidants in foods and/or supplements in preventing or postponing cognitive decline and AD (see p.50 for information about the PREADVISE vitamin E clinical trial).

Scientists are interested in the role that **inflammation** plays in **AD.**

Inflammation

Inflammation is a dynamic and complex biological process that affects cells and tissues in all parts of the body. This process occurs in response to many types of injuries or abnormal situations, ranging from a simple scrape on the skin to a disease like rheumatoid arthritis that affects the whole body. Scientists have become increasingly interested in the role that inflammation plays in the development and progression of AD, but they don't always agree on its significance. Some scientists think that some aspects of the inflammatory process may be valuable to the brain by helping it clear away beta-amyloid deposits. In contrast, other scientists think that when the inflammatory process begins in the brain, it sets off a vicious cycle that is harmful to neurons. Support for this hypothesis comes from studies such as the NIA-funded Honolulu-Asia Aging Study. In this long-term epidemiologic study of stroke, neurodegenerative diseases, and aging in older Japanese American men, researchers have found that those with higher levels of C-reactive protein (an indicator of inflammation) in their blood at mid-life had an increased risk of AD 25 years later (Schmidt et al., 2002). Risk of both AD and vascular dementia increased. Whatever the final answer, it is clear that inflammation is important to the pathology of AD in several ways, and recent studies are helping to explain this complex process.

Epidemiologic studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs), including naproxen, ibuprofen, and indomethacin, are associated with a decreased risk of AD. A study by researchers at Johns Hopkins University found that the longer people took NSAIDs, the more their risk of developing AD in the future was reduced (Zandi et al., 2002a). Risk was reduced

by more than one-half, for example, in people who took NSAIDs for 2 or more years. These results indicate that long-term use of NSAIDs is correlated with reduced dementia risk, provided that NSAID use occurs well before the onset of dementia. To explore further the idea that use must occur long before disease onset, a clinical trial was designed to determine whether naproxen (an NSAID that includes Aleve, Anaprox, and Naprosyn) or rofecoxib (Vioxx, an NSAID that inhibits the production of cyclooxygenase-2, or COX-2, an enzyme involved in the inflammatory process) slowed the rate of cognitive decline in people who already had mild to moderate AD. The trial found that neither NSAID had this effect (Aisen et al., 2003). Researchers hope that prevention trials underway (see p.50 for details about the ADAPT trial) will show that longer-term use of NSAIDs are effective in preventing AD in people who are at risk but who do not yet show symptoms of the disease.

Three recent animal studies by investigators at the University of South Florida, Northwestern University, and the University of California at San Diego focused on NSAIDs as a way to counteract this damaging response in brain tissues. Using different types of transgenic mice and different types of NSAID compounds, all three studies showed benefits from these compounds, either because they reduced production of beta-amyloid fragments or reduced production of stress-related enzymes (Jantzen et al., 2002; Mirzoeva et al., 2002; Weggen et al., 2001).

Cardiovascular Factors

In recent years, a number of studies have suggested a connection between AD and various heart disease and stroke risk factors, including high cholesterol levels and high blood pressure (hypertension). Although the reasons for this association are not fully understood, it is known that even in relatively healthy older adults, risk factors for stroke, such as age, hypertension, diabetes, and cardiovascular disease, can damage brain blood vessels (the cerebrovascular system) and reduce the oxygen supply to the brain. This damage may disrupt neural circuits thought to be important in cognitive functions, such as decision-making, memory, and verbal fluency.

Studies have suggested a connection between **AD** and **heart disease** and **stroke** risk factors.

Scientists have conducted animal and epidemiologic studies to understand the association between cardiovascular risk factors and risk of AD. Results are consistent with many other studies that point to the benefits of maintaining blood cholesterol and blood pressure at healthy levels. Studies have examined several aspects of this complex issue.

For example, scientists at the University of Washington in Seattle, conducted a study in mice to explore the relationship between high cholesterol levels and AD risk (Shie et al., 2002). This study built on earlier epidemiologic studies that showed a correlation between high blood cholesterol and

AD, and on studies in APP transgenic mice in which animals fed a high cholesterol diet developed high levels of cholesterol in the blood and the brain and increased beta-amyloid deposits (Refolo et al., 2001). The University of Washington investigators found that the burden of amyloid plaques was significantly higher in transgenic mice fed a high fat/high cholesterol diet than in those fed standard chow. Interestingly, they also found that amyloid deposits were directly correlated with levels of APOE and inversely correlated with levels of HDL, the "good" cholesterol.

Another research team from the Department of Veterans Affairs Healthcare System in Boston, studied 235 healthy older men enrolled in the Normative Aging Study to explore relationships between stroke risk factors and decline in verbal fluency, memory, and visuospatial performance (Brady et al., 2001). The investigators found that age was associated with decline in all cognitive functions, whereas stroke risk was associated with decline only on verbal fluency. The relationship between stroke risk and fluency decline was almost as great as the relationship between age and fluency decline. These results suggest that stroke risk, independent of age, may be a strong predictor of decline in a particular cognitive function in healthy older men.

New data from the Honolulu-Asia Aging Study also have provided evidence to link damage to the cerebrovascular system and dementia (White et al., 2002). Investigators from the Kuakini Medical Center in Honolulu, Hawaii, analyzed clinical and neuropathological data from autopsies of 285 older men. The investigators assessed the prevalence at death of four types of damage to brain regions, including damage to the tiny blood vessels in the brain, loss of hippocampal tissue, and the presence of AD plaques and Lewy bodies. In 118 of the 285 men, definite or probable dementia had been determined before death. The study found that damage to the tiny blood vessels in the brain was as likely an explanation for their dementia as was the presence of AD plaques. The investigators concluded that a number of factors may be involved in the development of dementia in this population, and that it is important to consider cerebrovascular risk factors in studies focusing on the causes of dementia.

It is important to consider **cerebrovascular risk factors** in studies of dementia.

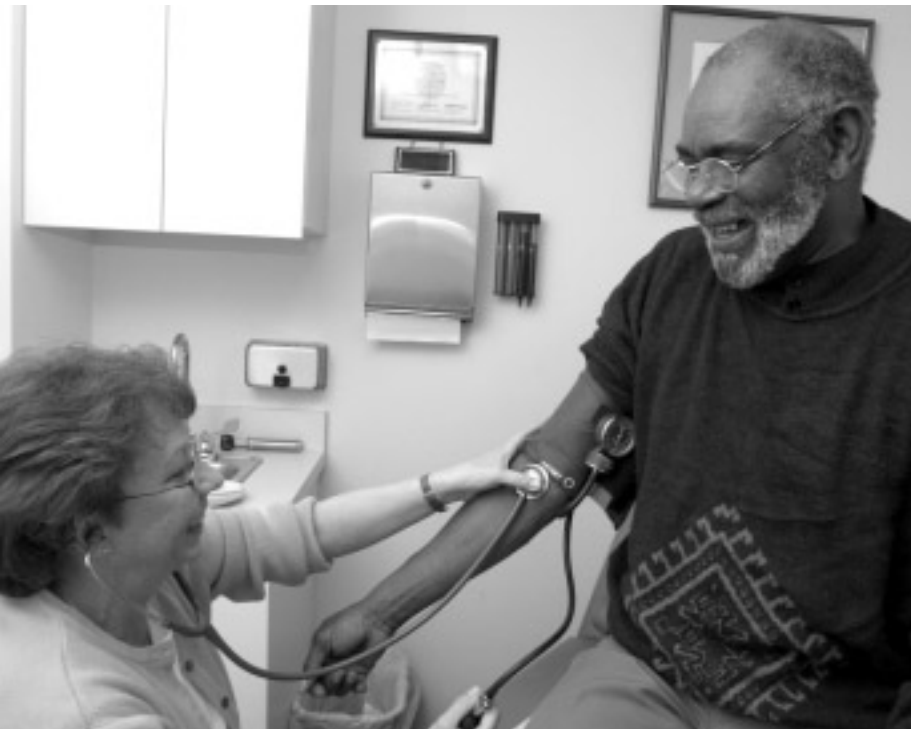
A second study, conducted by investigators at Columbia University, examined data from more than 1,200 Medicare recipients to see what effect hypertension might have on new cases of AD and vascular dementia (Posner et al., 2002). The study concluded that a history of hypertension beginning at age 65, either treated or untreated, does not contribute to the development of AD and does not contribute to a decline in cognitive function as people age. These findings are consistent with other research showing

that AD risk is more associated with hypertension that begins in midlife than to hypertension that begins in later life.

Another hypertension study, conducted in rhesus monkeys, provides some support for the hypothesis that hypertension in earlier life may contribute to later declines in cognitive function. This study involved 13 young adult monkeys, seven of which had surgically-induced high blood pressure. Every 6 months, a Boston University School of Medicine research team tested the monkeys on two cognitive tasks—one that required the animals to switch strategies during the task, and another that required the animals to choose between two options (Moore et al., 2002). After as few as 12 months, the hypertensive monkeys showed a marked decline in their ability to switch strategies, a task that required cognitive flexibility. These findings suggest that chronic, untreated hypertension may have long-term consequences on certain aspects of cognitive function.

Additional data come from the Indianapolis-Ibadan Dementia Project, which studied two populations aged 65 and older—2,147 African Americans in Indianapolis, Indiana, and 2,459 Yoruba in Ibadan, Nigeria. Initially, this epidemiologic study compared the incidence and prevalence of AD in the two groups (the Yoruba had much lower AD incidence and prevalence than did the African Americans). A number of research teams are now using data from the study to examine genetic and non-genetic factors to see how they may have influenced the development of AD. In one of these analyses, researchers from the Indiana University School of Medicine assessed the long-term effect of antihypertension medications on cognitive function in the older African American participants (Murray et al., 2002). They found that taking these medications was correlated with a 38 percent lower risk of developing cognitive impairment.

A study conducted by Columbia University investigators focused on another important risk factor associated with heart disease—dietary intake of fat and calories—and their possible association with AD risk (Luchsinger et al., 2002). This study was part of the Washington Heights-Inwood Columbia Aging Project, an epidemiologic study of aging and dementia that currently includes about 3,000 people. The investigators found that higher intake of fats and calories over time was associated with higher risk of AD in elderly individuals, but only in individuals carrying the APOE-ϵ4 allele.



Finally, three major long-term cardiovascular disease epidemiologic studies funded by the National Heart, Lung, and Blood Institute (NHLBI) have provided a rich harvest of data that have allowed researchers to explore the relationships between cardiovascular risk factors and AD. All three of these studies included cognitive decline and dementia related to vascular disease as key elements of their designs. Another distinguishing element of each of these studies has been "add-on" components funded by other Institutes, including NIA and NIMH. These add-on components have provided a cost-effective opportunity for investigators to examine additional issues using existing study populations. Over the years, participants in these studies have made a valuable contribution to our understanding of cardiovascular disease, AD, and dementia. These NHLBI studies are the Framingham Heart Study, the Cardiovascular Health Study, and the Atherosclerosis Risk in Communities Study:

- The Framingham Heart Study, begun in 1948, is a long-term investigation of physical and environmental factors that influence the development of cardiovascular disease in healthy individuals. The study is still following the remaining members of the original study group (500 of the original 5,209), as well as the remaining members of the 5,000 individuals recruited in 1971 into the Framingham Offspring Study, and approximately 3,500 individuals in a third generation group.
- The Cardiovascular Health Study, begun in 1988, is a long-term study of risk factors for the development and progression of coronary heart disease (CHD)

Neurogenesis, and Brain

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

However, this view has dramatically changed in the last few years based on a number of research studies showing that neurogenesis (the formation of new neurons) does in fact take place in the adult brain, at least in a limited number of brain regions.

Several recent studies have shown that new neurons come from a population of dividing cells called neural stem cells (NSC). For example, after growing NSCs in a laboratory dish and giving them special growth factors, scientists at the Salk Institute for Biological Studies in La Jolla, California, transplanted the NSCs into brain tissue and found that they formed normally functioning neurons and glial cells (Song et al., 2002; van Praag et al., 2002).

The story does not end there, though. In a recent NIA-funded study, scientists at the Salk Institute and Humboldt University in Berlin, Germany, gave one group of mice an enriched environment that included running wheels, plastic tubes, and nesting materials. (Kempermann et al., 2002). Another group of mice did not receive these extras. The scientists found that the mice exposed to the

Physical and Mental Activity, Repair

enriched environment had more new neurons in the hippocampus than did the mice not exposed to that environment. Formation and survival of new neurons in the hippocampus were increased, and this was correlated with improved behavioral performance on learning tasks.

Scientists also have found that other conditions can affect neurogenesis. For example, stressful experiences can decrease the formation of new neurons in the hippocampus. Aging also strongly influences neurogenesis in the hippocampus. The rate of neurogenesis declines with age, but some level of neurogenesis persists in the hippocampus in elderly rodents and humans. Interestingly, increased physical and mental activity, even when started in middle age, can enhance the generation of new neurons in the hippocampus of aged mice, and this neurogenesis is correlated with improved learning and exploratory behavior (Kempermann et al., 2002).

These exciting research findings mean that scientists now face an intriguing and important question: Can NSC techniques be used to repair or replace cells that are lost because of trauma or a neurodegenerative disorder? Although clear answers don't exist yet, emerging data indicate that NSCs may be mobilized to generate new neurons in response to brain injury. When the brain is injured, NSCs normally present are activated and migrate to the site of damage. The same is true for NSCs transplanted into the brain. Scientists are now identifying the signals responsible for the activation and growth of stem cells, the way they home in to damaged areas, and their ability to make specific kinds of neurons.

Proteins called growth factors also are increased in the brain during development and after injury, and these factors support neurogenesis in the adult brain. One strategy being considered for repairing brain damage from injury or disease is to identify the optimal combination of growth factors that can activate an individual's own stem cells to repair damaged neurons. Such strategies could include behavioral modifications, such as exercise and mental stimulation, and/or drugs, such as antidepressants, which increase growth factors and stimulate neurogenesis in the adult brain.

The processes at work in diseases such as AD and Parkinson's disease may overwhelm the brain's ability for self-repair, however. Alternative strategies to promote repair may be needed. One being tried is transplanting neural stem cells to replace dying cells or to deliver critical nutrients. One NINDS-funded study showed that embryonic mouse stem cells that had been coaxed into neurons and then transplanted into a rat model of PD made functional connections with surrounding brain cells and reduced disease symptoms (Kim et al., 2002). Such an approach can be envisioned for other brain disorders as well. Because stem cells might integrate effectively with the host tissue following transplantation, these cells might be genetically engineered to deliver therapeutically important molecules, such as growth factors, to promote brain self-repair processes.

The discovery of neurogenesis and the presence of stem cells in the adult brain have dramatically altered the way scientists think of brain function and its regenerative ability (Peterson, 2002). Neurogenesis may be a continuous process that maintains brain structure and function throughout one's life. Though much basic work still needs to be done, researchers are hopeful that effective repair strategies through neurogenesis or through other stem cell therapies can one day be developed to restore nervous system functions lost through trauma, disease, or normal aging. The potential to rebuild a damaged adult nervous system may be greater than we once thought possible.

and stroke in elderly adults. The current phase of the study is identifying risk associations with disease by determining whether presence or progression of preclinical disease (the time before a disease is clinically recognizable) is a better predictor of disease than are traditional risk factors. The study also is identifying determinants of change in preclinical disease and characteristics of subgroups at low risk for developing cardiovascular disease.

- The Atherosclerosis Risk in Communities Study, begun in 1985, measures associations of coronary heart disease risk factors with atherosclerosis by race, gender, and geographic location. It is focused on early detection of cardiovascular disease before symptoms, heart attacks, or strokes occur. The project consists of two parts—one studying the entire community and one studying four selected groups.

Highlights of recent findings from these studies and their add-on components have shed light on the complex interrelationships among lifestyle, genetic, and environmental factors; vascular diseases; and dementia:

- Framingham Heart Study scientists at the University of Washington found that abnormal hearing test results under stressful conditions may suggest an early manifestation of AD that precedes the diagnosis of dementia by many years (Gates et al., 2002). This add-on study was co-funded by NIA, NINDS, and NIDCD.
- A Framingham Heart Study add-on study co-funded by NHLBI and NIA found that obese men who were hypertensive were more likely to develop declines in cognitive function than were men who were not obese or hypertensive (Elias et al., 2003). Interestingly, this association was not found in women.
- Two studies from the Atherosclerosis Risk in Communities Study found that other types of vascular changes were associated with declining cognitive function in later years. University of North Carolina investigators found that people who had increased hypertension measurements over time were more likely to develop declining cognitive function than were people without such changes (Alves de Moraes et al., 2002). Another University of North Carolina team found

that middle-aged people with retinopathy, which is a disorder of the retina of the eye caused by microvascular disease, were more likely to develop declining cognitive function than were people without this disorder (Wong et al., 2002). As retinal microvascular disease may indicate vascular disease in the brain of that individual, the investigators suggest that these results are further proof of a link between cerebrovascular disease and cognitive decline, AD, and perhaps dementia.

- Cardiovascular Health Study investigators at the University of Washington used MRI scans to measure brain infarcts (a lack of oxygen to the brain that can lead to tissue damage; also called "mini-strokes") in older adults. This study concluded that the older a person becomes, the more likely it is that the brain will have a number of problems, including "silent" infarcts, whose effects, such as declines in cognitive function, may ultimately not be so silent (Longstreth et al., 2002).

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

Research described earlier in this report has vastly increased our understanding of brain function, the transformation from healthy aging to AD, and the factors that influence the development of AD. These findings have opened the doors to a range of potential therapeutic approaches. NIA, other NIH Institutes, other research institutions, and private industry are conducting studies on dozens of compounds and strategies to:

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

By late 2003, the FDA had approved five medications to treat AD symptoms.

By 2003, **five medications** had been approved to **treat AD** symptoms.

Of these, four are known as cholinesterase inhibitors and are prescribed to treat mild to moderate AD symptoms. The first, tacrine (Cognex), has been replaced by three newer drugs—donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). These drugs act by stopping or slowing the action of acetylcholinesterase, an enzyme that breaks down acetylcholine. Acetylcholine, a neurotransmitter that is critically important in the process of forming memories, is used by many neurons in the hippocampus and cerebral cortex—regions devastated by AD. These drugs improve some patients' abilities to carry out activities of daily living; may improve certain thinking, memory, or speaking skills; and can help with certain behavioral symptoms. However, these medications will not stop or reverse AD and appear to help patients only for months to a few years.

The fifth medication is memantine (Namenda), which can be prescribed to treat moderate to severe AD symptoms. This drug appears to work by regulating excess glutamate in the brain. Glutamate is another neurotransmitter involved in memory function, but high levels may damage neurons. Like the cholinesterase inhibitors, memantine will not stop or reverse AD. Studies have shown that memantine may delay loss of daily functions in patients with moderate to severe AD (Reisberg et al., 2003; Tariot et al., 2004).

In addition to these medications, physicians use a number of drug and non-drug approaches to treat the behavioral and psychiatric problems that occur frequently as AD progresses. These problems include agitation, verbal and physical aggression, wandering, depression, sleep disturbances, and delusions. Two recent analyses of data from two separate populations—5,092 older residents of Cache County, Utah, and 3,608 participants in the nationally-representative Cardiovascular Health Study—attest to the prevalence of these problems. The Johns Hopkins University investigators who conducted both analyses found that among those in the Utah population who were diagnosed with AD, 60 percent suffered from neuropsychiatric disturbances (Lyketsos et al., 2001). In the second population, 50 percent of those diagnosed with MCI and 80 percent of those with dementia had exhibited at least one neuropsychiatric symptom since the beginning of their cognitive decline (Lyketsos et al., 2002).

One growing focus of work on therapies for behavioral and psychiatric problems deals with depression among people with AD. NIMH recently gathered a group of investigators with extensive research and clinical experience in late-life depression and AD to propose criteria for identifying and managing this common problem (Olin et al., 2002a; Olin et al., 2002b). The experts identified useful indicators for diagnosing significant depressive symptoms in people with AD. Based on substantial research suggesting that the depression that occurs in AD differs in some respects from other depressive disorders, the experts also defined a unique syndrome called Depression of AD. This syndrome is often less severe than Major Depressive Disorder, but it still can have an important effect on the course of AD. These criteria, which are currently being validated, will pave the way for additional research to understand this syndrome and its clinical implications. Studies are now underway to determine the syndrome's responsiveness to standard antidepressant treatment.

In other NIMH-funded research, a University of Pittsburgh study team compared the short-term (up to 17 days) effectiveness of an antidepressant, an antipsychotic medication, and a placebo in treating psychotic symptoms and behavioral disturbances in people with

Physicians use **drug** and **non-drug treatments** for the behavioral and psychiatric problems of AD.

dementia (Pollock et al., 2002). The researchers found that the antidepressant was possibly equal to or even better than standard antipsychotic drugs at treating psychosis and behavioral disturbances. The antidepressants also had a relatively low risk of side effects.

A recent NINR-funded study of 450 nursing home residents also examined treatment approaches for behavioral problems in people with dementia. University of Pennsylvania investigators found that 61 percent of those in the study showed physical and/or verbal aggression at times (Talerico et al., 2002). An impaired ability to communicate, rather than overall cognitive decline, was associated with all forms of aggression. This finding led the study team to propose that if a person is not able to communicate fully, it is more likely that his or her needs may not be met, and this may be expressed through aggression. The investigators also found that physical aggression was associated with depression, whereas verbal aggression was associated with disorientation. It may be that these two forms of aggression may represent separate entities that may respond to different treatments. The correlation between physical aggression and depression also implied that this form of aggression may be a symptom of inadequately treated depression. An evaluation of the medications received by study participants suggested both that antipsychotic drugs alone were not enough to effectively decrease aggression and that antidepressant drug use was suboptimal. This study's findings support the view that individualized mental health interventions that go beyond administering drugs or using restraints are needed to treat aggression in dementia.

AD Clinical Trials

As this report has shown, AD research has progressed to a point where scientists are increasingly able to think about how they can intervene to treat AD or even perhaps to prevent it. This has led them to consider the

importance of timing—when is it best to intervene and what interventions are most appropriate at what time? For example, a physician would certainly treat a patient who is having a stroke differently from a patient who seems healthy but who has a high risk of having a future stroke. AD develops over the course of years or decades, and a person's brain is affected well before any symptoms are evident. It may be that one kind of intervention with a particular compound or approach may be most effective if it is applied well before any symptoms are evident. Other interventions may be most appropriate for use after AD is established.

With this idea in mind, investigators are working to develop an array of options from which clinicians can choose. For example, developing new and better drugs and broadening the range of non-drug therapeutic approaches are critically important for those who already have AD because of the long-term nature of the disease and the high emotional and physical toll that AD exacts. Slowing the progress of the disease and alleviating psychiatric and behavioral problems could do much to delay or prevent institutionalization, maintain the dignity of people with AD, reduce physical and emotional stress on caregivers, and reduce the financial costs associated with the disease. Finding ways to prevent the disease altogether is an increasingly urgent priority because of the enormous current and future impact of AD on our society.

Scientists use clinical trials to reach this goal. Clinical trials that compare a potential new strategy with a standard strategy or with a placebo are the only way to determine whether a drug, other compound, or non-drug approach is safe and effective. Clinical trials also tell researchers which treatments are more effective than others. Trials take place at specialized AD research centers, medical centers, teaching hospitals, private research facilities, and doctors' offices. These complex and expensive studies involve hundreds or even thousands of people and are often conducted over a long period of time. Because of the cost, time, and effort involved, only the most

Innovative Mechanisms for Conducting Research

NIH has used a number of promising grant mechanisms to foster basic and clinical AD research:

- **Small Business Innovation Research Grants (SBIR)** are designed to establish the value and feasibility of ideas that provide an important link between laboratory and clinical work and possible commercial development. For example, recent projects have explored the feasibility of isolating the active ingredient from cat's claw, a plant whose extract seems to inhibit beta-amyloid formation, examined potential immunotherapeutics, and tested compounds from marine microbes for plaque-inhibiting activity.
- **Pilot trials** give investigators funding to conduct smaller-scale clinical trials to test drug responses and generate the data necessary to apply for funding for a full-scale trial. Examples of some of the pilot trials that NIA is funding include a trial of pioglitazone (Actos), a drug used to treat diabetes, which has anti-inflammatory effects; a trial that includes three anti-inflammatory drugs, including the antibiotic dapsone; and a trial of fish oil and alpha-lipoic acid. Epidemiologic studies have shown that people who eat certain types of fish, such as salmon, weekly, have a lower risk of dementia (Morris et al., 2003).
- **Add-on components** to ongoing clinical trials are an efficient way to conduct research. In this strategy, a funding agency adds a cognitive or dementia component onto an ongoing trial that may be investigating a different topic. The PREADVISE trial described on p.50 and the NHLBI cardiovascular studies described on p.40 and 42-43 are good examples of the use of this funding mechanism for clinical trials and for epidemiology and long-term (longitudinal) studies, respectively.

promising few compounds or treatment strategies are tested in full-scale clinical trials. However, funding agencies have developed several additional mechanisms for funding clinical trials, including pilot trials and add-on components (see the box on p.46 for more on these mechanisms).

Some clinical trials are focused on **treatment** strategies—helping people with AD preserve cognitive function for as long as possible, for example, or helping alleviate behavioral or psychiatric problems associated with AD. Other clinical trials are focused on **prevention** strategies—using specific compounds to help people reduce the risk of developing AD in the future, for example. The sections that follow provide highlights from a number of treatment and prevention clinical trials.

For more information about AD clinical trials, **contact** the **ADEAR** Center at www.alzheimers.org/trials or 1-800-438-4380.

Recruitment is ongoing for several of these trials. For more information about the clinical trials described here and other trials, visit NIA's ADEAR website at www.alzheimers.org/trials.

Treatment Trials

NIA is currently supporting 19 clinical trials that are or will be investigating treatments for people who already have AD. Here are highlights of just a few of these trials.

- **Divalproex sodium and agitation.** Two clinical trials of divalproex sodium (Valproate) are examining its effect on agitation and psychosis. The first trial, conducted among 150 nursing home residents, was designed to see whether this medication could ease agitation among individuals with severe AD. This study has ended and results are being analyzed. The second trial has recently begun and is designed to examine whether divalproex sodium can delay or prevent agitation and psychosis from developing in individuals with mild to moderate AD. Researchers are also interested in seeing whether its possible neuroprotective properties have any effect on slowing the rate of cognitive decline.
- **Simvastatin and AD progression.** This 18-month trial, which began in 2003, is testing whether simvastatin (Zocor), a commonly prescribed cholesterol-lowering drug, can safely

Estrogen and Cognitive Function: An Update on the Research

Estrogen is a hormone produced by a woman's ovaries during her childbearing years. Over the past 25 years, laboratory and animal studies, as well as observational studies in women, have suggested that estrogen has some positive effects on brain activity. These findings have created scientific interest in the relationship among estrogen, memory, and cognitive function.

To test this relationship, researchers conducted clinical trials of estrogen in postmenopausal women who already had mild to moderate AD to see whether the hormone helps. These trials did not find estrogen beneficial. However, epidemiological and other studies suggested that even if estrogen did not slow the progression of the disease in women already affected with AD, perhaps menopausal hormone therapy (formerly known as hormone replacement therapy, or HRT) might in some way affect age-related cognitive decline or protect a woman from developing AD.

Two types of such therapies have been investigated—the use of estrogen alone in women who have had a hysterectomy, and the use of estrogen plus progestin in women who still have a uterus.

In 1992, the NIH began the Women's Health Initiative (WHI), a very large study with 27,000 participants that was designed to evaluate whether hormonal therapy protected women from heart disease, as epidemiologic studies had indicated. The WHI included a randomized clinical trial to determine the benefits and risks of using menopausal hormone therapy.

A substudy of the WHI, called the Women's Health Initiative Memory Study (WHIMS) began in 1995. This substudy was designed to assess whether menopausal hormone therapy would keep older women from developing dementia.

In July 2002, the part of the WHI involving estrogen plus progestin treatment was stopped early when scientists found that women taking this combination were at increased risk for certain health problems, including heart attacks, breast cancer, strokes, and blood clots (Rossouw et al., 2002). This combination also was beneficial in some ways—fewer hip fractures and less chance of colorectal cancer. Even so, the scientists believed the risks were greater than the benefits. In 2004, scientists stopped the estrogen-alone portion of the WHI because of an excess risk of stroke and no indications that estrogen would be helpful for heart disease.

Scientists evaluating WHIMS data reported that, in women 65 and older, neither the combination of estrogen and progestin nor estrogen alone prevented dementia or slowed its progression over time (Espeland et al., 2004; Shumaker et al., 2003; Shumaker et al., 2004). The older women taking the estrogen plus progestin were at twice the risk of developing dementia as those taking a placebo. This combination also did not prevent general cognitive decline (Rapp et al., 2003). Results for those taking estrogen alone were similar. The scientists recommended that women not take menopausal hormone therapy to prevent dementia or to preserve their mental abilities.

In view of the risks documented in the WHI and WHIMS, the NIA stopped a prevention clinical trial designed to evaluate whether hormone therapy prevents or delays development of AD in cognitively normal older women who are at increased risk of AD, because of their family history. These women will continue to be followed, as will the women in WHIMS, to evaluate how their years of hormonal treatment affect their risk of cognitive decline.

Though these recent clinical trials have answered some questions about estrogen and cognitive function, others remain. Would giving a different estrogen or progestin agent change the result? Would starting therapy around the age of 50, rather than 65, be more beneficial or more harmful? The timing of hormonal therapy is important, for example, in decreasing osteoporosis risk, with positive effects most marked if treatment begins as menopause begins. Evidence that the timing and duration of hormone treatment may be important for dementia risk comes from an ongoing epidemiologic study being conducted in Cache Country, Utah (Zandi et al., 2002b). Researchers from Johns Hopkins University found that prior use of hormones was associated with a decreased risk of AD, although use had to have been longer than 10 years before the onset of dementia. Use of early hormone treatment for more than 10 years was associated with a 2.5-fold lower incidence of dementia. More research is clearly needed on this complex matter.

and effectively slow the rate of disease progression in people with mild to moderate AD. Data from epidemiologic and animal studies indicate that high cholesterol levels increase the risk of AD, and that statin drugs specifically may help to reduce this risk. The trial, which is being conducted in about 40 sites around the country, will enroll 400 participants. Some participants will receive 20 milligrams of simvastatin for 6 weeks and then 40 milligrams of the statin for the rest of the study period or a placebo for the entire study. Clinical trial staff will track changes in participants' cognitive health by measuring a number of indicators, including mental status, functional ability, behavioral disturbances, and quality of life.

■ **Huperzine A and cognitive function.** This trial is evaluating whether huperzine A, a natural cholinesterase inhibitor derived from the Chinese herb, *Huperzia serrata*, can slow the progression of cognitive decline in people with mild to moderate AD. A number of small, randomized controlled trials in China have indicated that people with AD who were treated with huperzine performed better on memory tests than patients on placebo. Investigators also are interested in huperzine because it has antioxidant and neuroprotective properties that suggest it may be useful in treating AD. The study, which will enroll 150 participants, is taking place in about 20 sites nationwide. Participants will be randomly assigned to three equal groups—two groups will receive varying amounts of huperzine A every day and the third group will receive a placebo. All participants will receive huperzine A during the last 8 weeks of the 24-week trial.

■ **Supplements to reduce homocysteine and slow the rate of cognitive decline.** High homocysteine levels are associated with increased AD risk (Seshadri et al., 2002). Levels of this amino acid can be reduced by high-dose supplements of folate and vitamins B_6 and B_{12}. This clinical trial, which began in 2003, is designed to determine whether reduction of homocysteine levels with high-dose supplements of folate, vitamin B_6, and vitamin B_{12} will slow the rate of cognitive decline in older adults with AD. Participants in this 18-month clinical trial are being divided into two groups: 60 percent of participants will receive daily high-dose supplements (5 mg of folate, 25 mg of vitamin B_6, 1 mg of vitamin B_{12}) and 40 percent will receive a placebo. The research team plans to enroll 400 participants.

■ **The TAP-DAP Study.** Some people with AD also suffer from the symptoms of PD, such as rigid muscles, difficulty walking, and tremors. Some people with PD also suffer from dementia and behavioral problems. This poses a therapeutic dilemma because the most frequently used drugs to treat AD behavioral problems, neuroleptic antipsychotics, can worsen parkinsonian symptoms and, in some types of dementia, have been associated with severe movement difficulties. The Treating Agitation/Psychosis in Dementia/Parkinsonism (TAP-DAP) study is a clinical trial designed to determine the safety and efficacy of quetiapine (Seroquel), an antipsychotic medication, in the treatment of psychosis and/or agitation. Participants include those who have dementia and parkinsonian symptoms and those who have

PD with dementia and episodes of agitation or psychosis. All participants are on a stable dose of a cholinesterase inhibitor and/or memantine. Each will participate in the trial for 10 weeks, and the research team will perform systematic ratings of behavior, motor function, cognition, adverse events, and other outcomes at 6 and 10 weeks of treatment.

Prevention Trials

NIA is currently conducting seven AD prevention clinical trials. Several of these trials are assessing the preventive potential of drugs and other compounds that already have been tested as therapeutic agents in people with established AD. Even when results from these trials have indicated that the compounds may not be the most effective treatment strategy, enough laboratory, animal, and epidemiologic evidence exists to suggest that they may still have a potentially useful preventive function. Here are highlights from a few of these AD prevention studies.

- **The Memory Impairment Study.** This 3-year study was designed to compare the effectiveness of vitamin E, donepezil (Aricept), and placebo in delaying the onset of AD in people with MCI. The 769 participants were assigned to three groups, with each group taking one of the three compounds. This landmark trial, which took place in 69 sites around the country and in Canada, represents a major advance in clinical trial methodology designed to prevent AD because it defined a new population for study in clinical trials. Preliminary data from this just-completed trial showed that participants who took donepezil were at reduced risk of progressing to AD initially, but that the benefit disappeared after 18 months. In those who progressed to AD, the difference in the delay to a diagnosis of AD was about 6 months in the donepezil group as compared to the placebo group. Vitamin E did not appear to slow the progression to AD. The investigators are conducting additional analyses to determine why donepezil's effect dropped off over time and to assess the practical and clinical implications of this complex study.

- **NSAIDS and inflammation.** Although a clinical trial showed that neither rofecoxib (Vioxx) nor naproxen (includes drugs such as Aleve, Anaprox, and Naprosyn) slowed the rate of cognitive decline in people with AD, a large, multi-center trial, called the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), has been launched to determine whether beginning treatment with NSAIDs earlier will prevent or delay the onset of AD in people who are cognitively normal but have a family history of AD. The approximately 2,400 participants in this prevention trial will take either naproxen, celecoxib (Celebrex, a COX-2 inhibitor), or a placebo for several years. Their cognitive function will be assessed regularly.

- **The Prevention of Alzheimer's Disease with Vitamin E and Selenium (PREADVISE) trial.** This trial is NIA's addition to NCI's Selenium and Vitamin E Cancer Prevention Trial (SELECT), which is evaluating whether taking selenium and/or vitamin E supplements can prevent prostate cancer in healthy men older than 60. PREADVISE is evaluating

whether these agents can help to prevent memory loss and dementia, such as that found in AD. Studies show that increased oxidative stress may damage brain cells and is linked with AD. Animal and tissue culture studies of vitamin E and selenium suggest that they can protect brain cells from oxidative damage (see p.23 for more on oxidative stress).

■ ***Ginkgo biloba.*** Extracts of leaves from the ginkgo tree are thought to have beneficial effects on brain function, especially those related to dementia and AD. Evidence to date has pointed to a protective effect on neurons, but the mechanisms of action are still unknown. Recently, in a trio of studies supported by the National Center for Complementary and Alternative Medicine (NCCAM), investigators at the University of Southern Mississippi found that a standardized ginkgo extract protects cells from oxidative stress and programmed cell death (Luo et al., 2002; Smith et al., 2002; Wu et al., 2002). Several small clinical studies also have indicated that ginkgo may be beneficial in preventing the onset of dementia. NIA is co-funding NCCAM's prevention trial comparing ginkgo to placebo in more than 3,000 people older than 70 who are cognitively healthy at the beginning of the trial. The study's results should indicate whether ginkgo is helpful in preventing or delaying the onset of dementia.

Improving Support for Caregivers

Although much of NIH's AD research effort is focused on the causes, characteristics, diagnosis, and treatment of AD, the Institutes never lose sight of the enormous personal and emotional toll exacted by AD on those with the disease as well as their families, friends, and caregivers. An "insider's" view of AD recently published by an NINR-funded study team from the University of Texas Health Science Center highlighted some of these emotions and concerns (Ostwald et al., 2002). In a series of interviews with study team members, individuals with AD talked about the stress associated with losing the ability to think and converse clearly. They also described the aggravation of not being able to remember things and the fear of losing control over their lives. They expressed sadness, frustration, and anger about their condition, worry about their families, and trepidation about their uncertain future. The interviews showed that at least some people with AD are acutely aware of their cognitive losses and experience a significant amount of stress in their relationships with family and friends as a result.

The Institutes never lose sight of the **enormous** personal and emotional **toll** exacted by AD.

Studies funded by several Institutes, including the NIA, NINR, and NIMH, have consistently found that caring for a person with AD is highly stressful and can contribute to negative physical and psychological health outcomes.

Many researchers are exploring these emotional, psychological, and physical costs, and are investigating ways to ease the caregiving burden. One recent focus of this caregiving research has been the varying impact of caregiving on diverse populations. Researchers from the University of North Carolina at Greensboro, for example, have found that African American caregivers use fewer formal in-home services and are more reluctant to place their loved ones with AD into institutional care settings than are Caucasian caregivers (Dilworth-Anderson et al., 2002). This may be due to a reluctance to use such services or to an expansive conceptualization of family and support networks in African American culture, as described by a University of California at San Francisco researcher (Johnson, 1999). Most of the information we have about the varying impact of caregiving on diverse populations comes from work with African Americans. Clearly, more information is needed about the impact of caregiving among various groups of caregivers, such as other ethnic populations and male caregivers.

Findings from a growing body of research on ways to ease the caregiving burden are pointing in some similar directions. For example, investigators are finding that interventions structured for individuals are more effective than are group-based interventions. They've also found that interventions that focus on a range of services and needs have a more significant impact on reducing caregiving stresses, such as a sense of burden, depression, and physical symptoms, than do "single-target" interventions. Not surprisingly, regular, moderate exercise also has been found to be an important stress reliever for caregivers. In several studies, investigators from the University of Miami Medical School and from Stanford Medical School used telephone and

computer prompts to encourage exercise among older caregiving women. They found that this strategy reduced blood pressure increases due to stress, improved sleep quality, and reduced psychological distress and depression (Czaja and Rubert, 2002; King et al., 2000). There is still much to be learned about caregiver stress, however. Future research will focus on developing a better understanding of issues such as the transitions into and out of a caregiving role, the interrelationships of coping strategies and behaviors of caregiver and care recipient, and the physiological and clinical manifestations of caregiver stress. Researchers also are interested in testing whether interventions

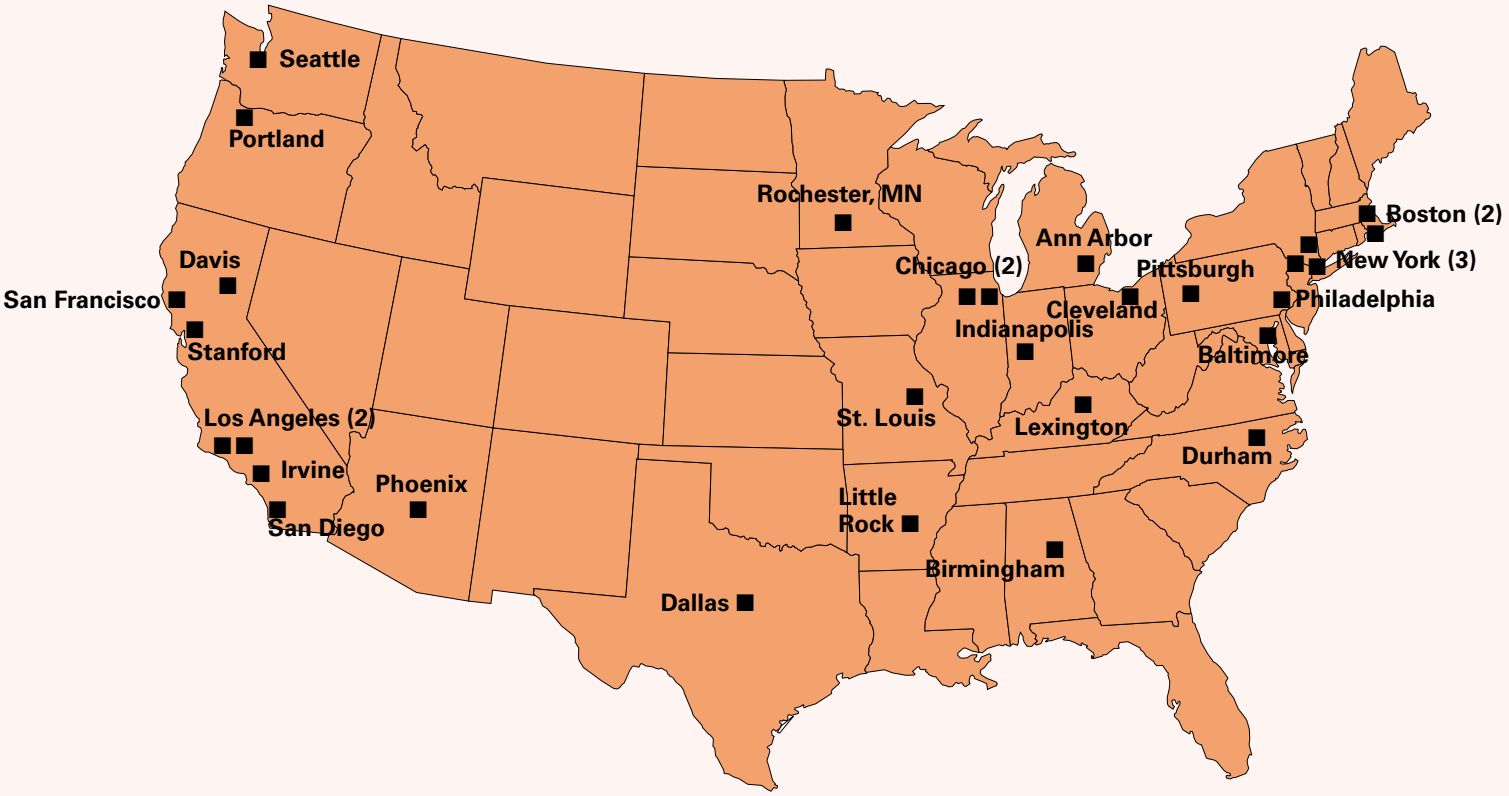
that work in the short term are successful over longer periods as well, and they would like to see whether and how knowledge gained about informal caregiving can be applied to formal caregiving settings, such as nursing homes and assisted living facilities.

A major focus of caregiver research at NIH is Resources for Enhancing Alzheimer's Caregiving Health (REACH), a multi-site effort funded by NIA and NINR. In the first phase, begun in 1995, REACH funded six universities around the country to develop interventions to help family caregivers of people with AD or related disorders. Each intervention tested a different home- or community-based intervention to support family caregiving. These interventions focused on a variety of issues, including the use of advanced communication technology, the design and management of the care recipient's physical environment, and methods for dealing with problem behaviors and other challenges. Detailed analyses of initial findings suggested that certain components of these interventions might be particularly effective in helping caregivers. In 2001, therefore, REACH II was funded to develop and test a single multi-component intervention among family caregivers. The overall objectives of the REACH II intervention are to reduce depression and burden among Caucasian, African American, and Hispanic family caregivers; enhance the quality of care provided; and enhance the well-being of caregivers. Participants in this 6-month trial will be divided into two equal groups, with one group receiving an information-only intervention and the other group the multi-component REACH intervention, which includes 10 home visits by trained staff plus five computer/telephone contacts with the staff. These same two interventions will be carried out in five sites: Birmingham, Alabama; Memphis, Tennessee; Miami, Florida; Palo Alto, California; and Philadelphia, Pennsylvania. Investigators hope that the outcomes from this REACH intervention will be clinically meaningful enough so that they can be used to develop guidance materials for use by a wide range of community service agencies that work with AD caregivers (Schulz et al., 2002). More information about this exciting intervention is available at the REACH website, at www.edc.gsph.pitt.edu/reach.

Regular, moderate **exercise** is an important **stress reliever** for caregivers.

Another important venue for work to improve support for AD caregivers occurs in the 30 NIA-funded Alzheimer's Disease Centers (ADCs) around the country. These state-of-the-art Centers conduct research, provide investigator training and patient care, and support the research process by developing a number of innovative strategies to improve participation of diverse populations in AD clinical trials.

NIA-Supported Alzheimer's Disease Centers



In addition to two Centers that directly support caregiving-related research, all ADCs are engaged in various aspects of caregiving support through their education and information transfer activities. Increasing public knowledge of behavioral and psychological symptoms associated with dementia, ways to deal with difficult situations, and manage caregiver burden is a key part of this effort. Several Centers have teamed up with local officials and Alzheimer Association chapters to widen access to diagnostic services as well as to provide support groups geared to the needs of people with AD and their caregivers. A particular emphasis is reaching out to groups who are less likely to receive information because of language barriers, cultural beliefs, or difficulties accessing information or understanding written materials. Here are just a few examples of the innovative ways in which ADCs are supporting people with AD and their caregivers.

■ **Using Creative Ways to Disseminate Information.**

■ The Arizona ADC recently produced a picture story book (fotonovela) aimed at helping the children and

grandchildren of Hispanic immigrants recognize early signs of AD.

- The Cleveland ADC pioneered the use of theater as an information medium by producing a one-act drama called *The Eighth Day of the Week*, which addresses health care and social issues surrounding dementia in the African American community. The play has been performed free in shopping malls and other public places, and has been adopted by other ADCs.
- The Duke University ADC has produced and distributed a brochure entitled *Wait a Minute*, which provides tips for handling situations in which anger may occur and escalate rapidly. This easy-to-read brochure fills a gap for dementia caregivers who may find lengthy written materials hard to use.
- Many ADCs have expanded their Internet-based community outreach to make it even easier for caregivers to get information, learn about resources, and obtain support.
- The Oregon ADC is working with the Oregon Health Sciences University's Biomedical Engineering Department on a project funded by Intel to investigate the use of unobtrusive technology in the home, such as motion sensing devices, to keep people with AD safe in their homes, prevent wandering, and alert caregivers to the whereabouts of their loved ones.

Providing Support Groups for People with AD and Their Caregivers.

- In collaboration with the New York City Chapter of the Alzheimer's Association, the Mount Sinai ADC operates five support groups—two groups for people with mild AD (one in English, one in Spanish), one group for adult children of people with dementia, one for people with moderate to severe AD, and one for Spanish-speaking caregivers.
- The New York University ADC provides a comprehensive program of support, education, and information for family caregivers of people with AD, from their first contact with the ADC through all stages of the person's illness, whether the person lives at home or in a nursing home.
- The University of Pennsylvania ADC collaborates with the Delaware Valley Alzheimer's Association chapter to offer an educational and support group that is designed to provide practical information and sharing for people in the early stages of AD. The group also offers a concurrent support group for family members.

Conducting Research in Caregiver Issues.

- The New York University ADC is conducting several research projects aimed at lessening caregiver burden. One of these studies is investigating ways to reduce the incidence and magnitude of stress, anxiety, and depression that adult child caregivers frequently experience. Participants are educated about AD and the typical needs, skills, and limitations of people with moderate AD. Participants are then divided into two groups, each of which receives a different package of services geared to helping them relate to their parents so as to enhance the satisfaction of both parties and improve or maintain the functioning of the person with AD. The two packages of services will be compared. A second project is examining the role of sociocultural

Ethics and AD Research: Protecting the Rights and Interests of Study Participants

The success of research efforts to develop treatments for AD rests on the effective enrollment of individuals with AD as research participants. However, this presents an ethical challenge to researchers because the participants' cognitive impairments may make them unable to provide informed consent to enroll. Studies show that people with mild to moderate AD have substantial variations in their ability to provide informed consent, and a number of research teams are investigating this important topic.

A team of scientists at the University of Pennsylvania has an active research program on ethical issues pertaining to participation in research of people with AD and their caregivers. Two recent studies have given them an opportunity to examine various aspects of "capacity" and "competency" in people with AD. "Capacity" refers to a person's performance in various aspects of decision-making, such as understanding information provided, appreciating that the information applies to him or her, being able to compare and describe personal consequences of options, and choosing among options. "Competency" refers to a judgment that a person's capacity is adequate to make a decision. These studies also have raised important questions about the relationship between people with AD and their caregivers and the evolving roles of caregivers as the disease progresses.

In the first study, the researchers evaluated the capacity, competency, and reasons for enrolling in an early phase AD clinical trial of people with AD and their caregivers (Karlawish et al., 2002b). Interviews were conducted with 15 older adults with AD, 15 non-demented older adults who were matched by age and level of education, and 15 caregivers. Capacity was measured using the Mini-Mental State Examination (MMSE), a widely-used method to assess cognitive status in adults. The MMSE helped the researchers assess the participants' decision-making capacities. Results indicated that the capacity to understand is a key factor for study staff to use in determining competency. The researchers also concluded that some people with mild and moderate AD are competent to consent. Thus, the diagnosis in and of itself does not mean that a person with AD is unable to make such a decision. This study also points out the need for further work to examine whether the ability of a person to participate in a conversational exchange can be used to determine competency. These results have implications for the design and conduct of clinical trials, as they suggest that a necessary enrollment criterion be that potential participants score at a certain level on the MMSE, and that this test be supplemented by an interview that can evaluate comprehension.

In the second study, the University of Pennsylvania team evaluated the relationship between AD severity and participation in decisions about medical care (Karlawish, et al., 2002a). Caregivers of 74 older adults with AD were asked to rate the degree of their relative's participation in making decisions about his or her medical care. Results indicated that, in general, caregivers have a key role in making these decisions. Not surprisingly, greater caregiver involvement in decision making was associated with increasing severity of disease and increasing caregiving burden. Only in very mild stages of AD does the person with AD have a greater than 50 percent chance of having either a collaborative or a final role in decision making, though there is considerable variability in decision-making roles even at this stage of the disease. In all other stages, the caregiver makes the final decision. These findings clearly point out the evolving nature of the caregiving role and the importance of recognizing the caregiver's influence on choices about treatment and tests. They also suggest the need to investigate more closely how caregivers practice collaborative decision making with their loved ones who are able to participate.

factors, such as ethnicity, acculturation, education, and income, in a spouse caregiver's perception of the initial symptoms of AD. This project aims to clarify how perceptions of symptoms guide the ways in which Hispanic and non-Hispanic spouse caregivers seek help for their loved one with AD.

- The University of Washington ADC received a Pioneer Award from the Alzheimer's Association for a dementia-specific training program it developed for staff of assisted living residences. This STAR (Staff Training in Assisted-living Residences) program has now been carried out in 12 residences around the Seattle area and has been described at more than a dozen national meetings.

Training and Reaching Out to Physicians.

- The Oregon ADC provides dementia education for primary care providers, including physicians. This project aims to increase awareness of the need for this type of education for providers and to offer education on the best ways to perform assessments and provide AD care in a primary care practice setting.

- Through its Clinical Partners Program and Clinical Dementia Rating On-line Training System, the Washington University ADC has reached a growing number of rural health care professionals and provided education and information on how to assess and counsel families about dementia.

Reaching Out to Diverse Populations.

- The Stanford University ADC provides outreach to various ethnically diverse groups, including Japanese, Hispanic, and Chinese communities. A key component of this effort is working closely with community-based agencies and health care providers who specialize in working with families from these groups.

- Providing information and education to ethnically diverse populations—in their own languages—also is a priority for the University of California at Irvine ADC. Working with local government agencies and Alzheimer's Association chapters, the ADC is able to successfully support people with AD, family members, and caregivers in a number of communities, including Koreans, Hispanics, and Chinese.

Outlook for the Future

PART 4

As this report demonstrates, research in AD continues to move forward rapidly, bringing us ever closer to a full understanding of the causes of this devastating disease and to truly effective prevention and treatment strategies. In the past several years, the NIA, in partnership with other NIH Institutes, the Alzheimer's Association, the Institute for the Study of Aging, and other organizations, has launched several major initiatives to move this process along. Updates on five of these initiatives are provided here, and they are bringing to life a number of key themes described in this *Progress Report*:

- The importance of learning more about normal aging and the healthy brain, in order to understand more fully what triggers and facilitates the transformation from healthy aging to AD.
- The need to continue developing sophisticated and sensitive imaging, biological, and cognitive assessment techniques that can help researchers understand the very early stages and progression of AD, and that may someday help clinicians track the initiation of the disease and more accurately and rapidly assess response to treatments.
- The importance of supporting research to expand our knowledge about genetic links to AD.
- The long-term benefits of building research infrastructures to promote sharing and pooling of data, which can leverage knowledge from a variety of individual sources into a whole that is greater than the sum of its parts.

Cognitive and Emotional Health Project

There are now about 45 million Americans over age 60 and 117 million over age 40. Current evidence indicates that a large number of these Americans are at substantial risk of cognitive impairments from many causes as they age. Much is known and publicized about maintaining a "healthy heart" but relatively little consensus exists about the much more complex "healthy brain."

To jump-start the process of building such a consensus, the NIA, the NIMH, and the NINDS partnered to launch the Cognitive and Emotional Health Project (the "Healthy Brain" Initiative) in 2001. The goals of this program are to assess the current state of knowledge about

predictors of cognitive and emotional health with age and to accelerate the pace of scientific advances in these fields. The Project has completed a number of activities that have laid the groundwork for these efforts. Currently, investigators are conducting an evaluation of existing longitudinal and epidemiologic studies that have assessed cognitive and emotional function. The evaluation will be used to detail the findings and critically assess the value of existing data. This exercise will help Project staff decide whether a new, comprehensive study of factors that can preserve or augment cognitive and emotional health in adults needs to be launched, or whether current data have yielded enough substantive findings to warrant a smaller-scale effort consist-ing of add-on studies to existing projects or secondary analyses of existing data. For detailed information about past and current Cognitive and Emotional Health Project activities, visit http://trans.nih.gov/CEHP/.

Neuroimaging Initiative

NIA also has launched a multi-year neuroimaging and biomarker initiative using serial MRI and PET scans to examine how brains change as MCI and AD progress. The project will follow approximately 200 cognitively normal individuals for 3 years, 400 people with MCI for 3 years, and 200 people with early AD for 2 years. Using MRI and PET scans

at regularly scheduled intervals, investigators hope to learn when and where in the brain degeneration occurs as memory problems develop.

Scientists will correlate this imaging information with clinical, neuropsychological, and biological markers from blood, cerebrospinal fluid, and urine samples. Potential markers include levels of beta-amyloid and *tau*, indicators of inflammation, and measures of oxidative stress. NIA hopes this initiative will help create rigorous imaging and biomarker standards that will aid in early diagnosis and provide the yardstick by which the success of future drug treatments can be measured. This would substantially increase the pace and decrease the cost of developing medications.

This initiative is a partnership among the NIA, the National Institute of Biomedical Imaging and Bioengineering, university investigators, the pharmaceutical and imaging equipment industries, the FDA, and the Foundation for NIH, with participation from the Alzheimer's Association and the Institute for the Study of Aging. An important aspect of this initiative is that the clinical, imaging, and biological data collected will be made available to all qualified scientific investigators for further analysis.

The scans and other data and biological samples for the Neuroimaging Initiative will be collected at approximately 50 clinical sites based in universities throughout the country. Funding began in September 2004, with participant recruitment scheduled for April 2005. The sharing of knowledge and resources among academic, industry, and government institutions, as exemplified by this initiative, can serve as a model for future scientific partnerships in facilitating biomarker and drug development. This initiative is the most comprehensive effort to date to find neuroimaging and other biomarkers for the cognitive changes associated with MCI and AD.

NIA has launched a multi-year **neuroimaging** and **biomarker** initiative.

Genetics Initiative

In the more than 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 and identify the missing risk factor genes.

In early 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

Steps in the National Institute on Aging Genetics Initiative

Identify families
▼
Obtain family member informed consent
▼
Conduct interviews and draw blood samples
▼
Send coded data and samples to NCRAD
▼
Distribute coded samples and data to geneticists
▼
Conduct research to find genes
▼
Share research data with other scientists

Who Can Participate?

Researchers are looking for families with at least three members who can donate blood, including:

- Two siblings (brothers or sisters) who developed AD after age 60, and
- Another family member over 50 who may have memory loss or a family member over 60 who does not have any memory loss.

Participants can live anywhere in the U.S. and can be of any racial or ethnic background.

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 18 ADCs so they can recruit new individuals for genetics research and encourage these individuals to provide blood samples for the Initiative. With the resources of the ADEAR Center, NIA is collaborating with the Alzheimer's Association to develop media and community outreach programs to foster participation in the Initiative among families who have two or more living members with late-onset AD.

The National Cell Repository for AD (NCRAD), located at Indiana University, serves 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. For more information about NCRAD, visit http://ncrad.iu.edu.

Future plans of the Initiative include creating a national case-control sample set, in which the genes of individuals 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. Finding the missing risk factor genes for late-onset AD will give us important additional clues about pathways leading to AD. It also will help identify more accurately persons at high risk of developing AD and aid in individual counseling and in initiating prevention strategies, when they are known. In addition, knowing the risk factor genes will help in recruiting susceptible individuals into clinical trials, which would reduce the number of participants necessary and the cost and complexity of the trials.

Prevention Instrument Project

Through the Alzheimer's Disease Cooperative Study clinical trials consortium, another NIA initiative is focused on a critical "nuts and bolts" aspect of prevention clinical trials—developing sensitive and more effective methods for evaluating change over time in cognitively healthy elderly. Investigators involved in this project are focused on designing, developing, and testing questionnaires and other instruments that can be used to test individuals in a number of areas, such as overall cognitive functioning, memory, ability to carry out activities of daily life, and quality of life. This study will compare the results of evaluation instruments filled out by participants at home versus those done in the clinic to determine whether the home evaluations are equivalent to the clinic evaluations. If they are, then this approach could potentially reduce the cost of prevention trials and also the burden on participants.

National Alzheimer's Coordinating Center

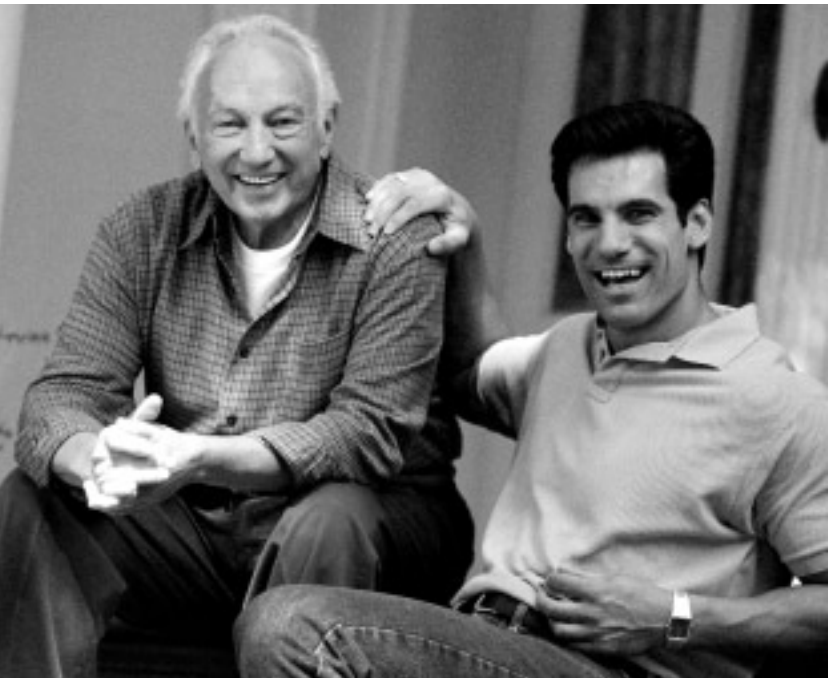
As research on AD and other neurodegenerative diseases has evolved, it has become increasingly clear that AD is genetically heterogeneous. At the same time, researchers have gradually come to appreciate that the dementias of aging are a family of diseases with a variety of overlapping clinical and pathological characteristics. For example, vascular dementia, Lewy body disease, hippocampal sclerosis, Parkinson's dementia, frontotemporal dementia, and other less common neurodegenerative diseases can, to a greater or lesser degree, mimic the symptoms and pathology of AD.

The **dementias** of aging are a **family** of **diseases** with a variety of overlapping clinical and pathological characteristics.

During the late 1990s, the NIA and ADC directors decided to develop a mechanism whereby data on patients from all of the ADCs could be pooled and shared. In 1999, following 2 years of funding for an interim data coordinating center, NIA awarded a grant to the

University of Washington in Seattle to establish the National Alzheimer's Coordinating Center (NACC). Since then, the NACC has made major progress in setting up operating systems and data collection and sharing policies, funding a number of cooperative studies, and making data available to researchers through the NACC website. Having this pooled data resource also has catalyzed efforts to standardize data collection procedures across the ADCs to facilitate complex analyses of data from multiple sites. For more information about the NACC, visit www.alz.washington.edu.

Benefits of the NACC are already evident. For example, access to larger datasets is beginning to allow investigators to characterize rarer neurodegenerative diseases and identify genetic and ethnic differences. This would not be possible with the smaller numbers of study participants available from individual centers. Studies also are in progress on normal aging using cognitively healthy volunteers followed by each ADC and also on the transition from normal aging to MCI to AD. During 2002, NACC funded three new collaborative projects. The first project, led by a research team at the University of Texas Southwestern



simultaneous quantitative analyses using a variety of probes and immunoreagents. The investigators hope that this method will help them define brain abnormalities that may contribute to cognitive impairment. In the third project, researchers from the University of Pittsburgh ADC and from four other ADCs will conduct genome scans of a group of individuals with late-onset AD who also suffer from psychotic symptoms. About half of those with AD suffer from these symptoms, and this combination is associated with more

The explosion of **knowledge** that has occurred during the past 25 years—and that continues today—has **set** the **stage** for a hopeful **future.**

and conducted at seven ADCs, will collaborate with an ongoing NIA-funded statin clinical trial. In this study, older adults with AD will take simvastatin (a cholesterol-lowering statin drug) or a placebo for 18 months. The investigators will compare changes in levels of APP in blood and cognitive changes in the two groups to determine potential beneficial effects from the statin. In the second project, investigators from the University of California at Los Angeles ADC will collaborate with investigators from two other ADCs to systematically examine after-death tissue samples from multiple brain regions and perform rapid cognitive and functional deterioration. The investigators hope that these genome scans will reveal chromosomal regions that might contain genes that are linked to this form of AD.

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

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PART 5

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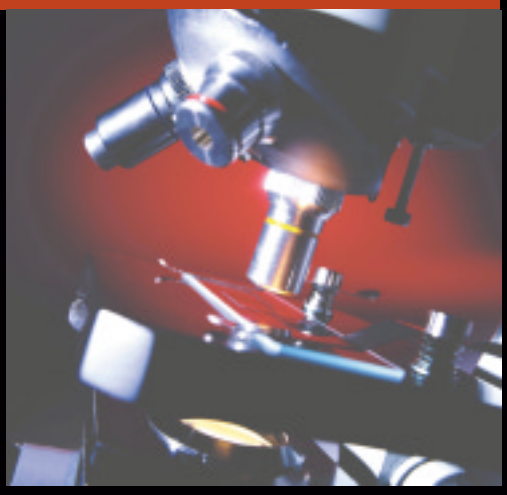

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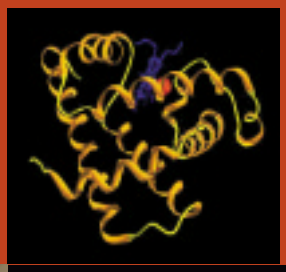

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