Alzheimer's: Unraveling the Mystery
Introduction

“Never have I loved my husband of 41 years more than I do today....Though he may not know I’m his wife, he does know that my presence means his favorite foods and drinks are near at hand....I wonder why I can sit daily by his side as I play tapes, relate bits and pieces of news, hold his hand, tell him I love him. Yet I am content when I am with him, though I grieve for the loss of his smile, the sound of my name on his lips.”

This excerpt from Lessons Learned: Shared Experiences in Coping, by participants of the Duke University Alzheimer Support Groups, gives a glimpse into what a person with Alzheimer’s disease (AD) and a family caregiver might experience as the disease progresses. The gradual slipping away of mind and memory is frightening and frustrating, both for the person with the disease and for family and friends, and can elicit strong feelings of love, grief, anger, and exhaustion.

AD is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks. In most people with AD, symptoms first appear after age 60. AD is caused by a disease that affects the brain. In the absence of disease, the human brain often can function well into the 10th decade of life.

Not so long ago, we were not able to do much for people with AD. Today, that situation is changing. Thousands of scientists, voluntary organizations, and health care professionals are studying AD so that they can find ways to manage, treat, and one day prevent this terrible disease.

AD: A GROWING NATIONAL PROBLEM

For many older adults and their families, AD stands in the way of the “Golden Years.” It also presents a major problem for our health care system and society as a whole. AD is the most common cause of dementia among older people. Recent estimates of how many people in the United States currently have AD differ, with numbers ranging from 2.4 million to 4.5 million, depending on how AD is measured. But scientists agree that unless the disease can be effectively treated or prevented, the numbers will increase significantly if current population trends continue.

Our aging society makes AD an especially critical issue. A 2005 Census Bureau report on aging in the United States notes that the population age 65 and older is expected to double in size to about 72 million people within the next 25 years. Moreover, the 85 and older age group is now the fastest growing segment of the population. This is all the more important for a neurodegenerative
**disease** like AD because the number of people with the disease doubles for every 5-year age interval beyond age 65.

AD not only affects the people with the disease, of course. The number of AD caregivers—and their needs—can be expected to rise rapidly as the population ages and as the number of people with AD grows. During their years of AD caregiving, spouses, relatives, and friends experience great emotional, physical, and financial challenges. As the disease runs its course and the abilities of people with AD steadily decline, family members face difficult, and often costly, decisions about the long-term care of their loved ones.

The growing number of people with AD and the costs associated with the disease also put a heavy economic burden on society. The national direct and indirect costs of caring for people with AD are estimated to be more than $100 billion a year. A 2004 study provided an equally sobering picture of the impact of AD. It is estimated that if current AD trends continue, total Federal Medicare spending to treat beneficiaries with the disease will increase from $62 billion in 2000 to $189 billion in 2015.

For these reasons, AD is an urgent research priority. We need to find ways to manage and treat AD because of its broad-reaching and devastating impact. We now know that the disease process begins many years, perhaps even decades, before symptoms emerge. Discovering ways to identify AD in the earliest stages and halt or slow its progress will benefit individuals, families, and the Nation as a whole.

**ABOUT THIS BOOK**

Thinking about AD leads to questions such as: What causes it? What can be done to cure it or prevent it? Will I get it? Scientists ask the same types of questions, and this book describes their search for answers. It is written for people with AD, their family members and friends, caregivers, and others interested in AD.

This book has four sections:

- **Part 1** gives readers some basics about the healthy brain. Illustrations and text show what a healthy brain looks like and how it works.
- **Part 2** focuses on what happens in the brain during AD.
Part 3 talks about current research and the advances that are bringing us closer to ways of managing and eventually defeating AD.

Part 4 focuses on issues important to AD caregivers and families, including current research that is finding ways to improve caregiver support.

The end of the book includes a list of publications and resources that people with AD, family members, and caregivers may find useful as they live day to day with the disease.

A book like this is possible only because of the major progress that scientists throughout the world have made. Not long ago, we knew very little about AD other than some facts about its major characteristics. Today, we are beginning to understand more about what AD is and who gets it, how and why it develops, and what course it follows. We are learning about the complex interface between AD and normal age-related changes in the brain. We also are getting much

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**Then and Now: The Fast Pace of Developments in AD Research**

As shown in this timeline, we have learned a lot since Dr. Alzheimer presented the case of his patient, Auguste D. The pace of research continues to accelerate as new findings open more and more doors to discovery.

### 1906
- Dr. Alois Alzheimer, a German neurologist and psychiatrist, describes the case of a 51-year-old woman, Auguste D., who had been admitted to a hospital 5 years earlier with a cluster of unusual symptoms, including problems with comprehension and memory, an inability to speak, disorientation, behavioral problems, and hallucinations. After her death, Dr. Alzheimer examined her brain tissue and described two of the hallmarks of AD—numerous globs of sticky proteins in the spaces between neurons (beta-amyloid plaques) and a tangled bundle of fibrils within neurons (neurofibrillary tangles).

### 1910s – 1940s
- Belief persists that “senile dementia” is a normal part of aging.

### 1950s
- Scientists study the biological structure of plaques and tangles.

### 1960s
- Scientists discover a link between dementia and the number of plaques present in the brain. AD is recognized as a distinct disease, not a normal part of aging.

### 1970s
- Scientists find that levels of acetylcholine, a neurotransmitter important in memory formation, falls sharply in people with AD. This discovery is one of the first to link AD with biochemical changes in the brain.
- “Alzheimer’s disease” becomes a common term as recognition of AD as a major public health problem grows.
- NIA is established.

### 1980s
- Diagnostic criteria for AD are established.
- Genetic links to early-onset AD begin to surface.
- Congress mandates NIA as lead Federal agency for AD research.
better at diagnosing it early and accurately. Most important, we now have some promising leads on possible treatments. Studies also are beginning to focus on preventive strategies by examining lifestyle factors that might influence a person’s risk of developing AD.

Since the 1970s, research supported by NIA and other organizations has deepened our understanding of this devastating disease. It also has expanded our knowledge of brain function in healthy older people and identified ways we might lessen normal age-related declines in mental function. Most importantly, this accumulated research has increased our appreciation for just how complex AD is. It is now clear that many scientific and clinical disciplines need to work together to untangle the genetic, biological, and environmental factors that, over many years, set a person on a course that ultimately results in AD.

- Scientists start to unravel the biological pathways that lead to the development of beta-amyloid plaques in the brain.
- Abnormal \textit{tau} protein in tangles is identified.

\textbf{1990s}
- The U.S. Food and Drug Administration (FDA) approves tacrine [Cognex\textsuperscript{®}], the first drug used to treat AD. This drug has since been replaced by other medications.
- Genetic mutations linked to early-onset and late-onset AD are discovered.
- The first \textit{transgenic} mouse model of AD is created.
- Additional diagnostic criteria are developed for AD.
- Characteristics of \textit{mild cognitive impairment} are described and defined.
- NIA launches the Alzheimer’s Disease Education and Referral Center, AD Cooperative Study, and other initiatives to conduct and support AD treatment and prevention \textit{clinical trials}.

\textbf{2000s}
- The FDA approves other AD drugs, including rivastigmine [Exelon\textsuperscript{®}], galantamine [Razadyne\textsuperscript{®}], donepezil [Aricept\textsuperscript{®}], and memantine [Namenda\textsuperscript{®}] to treat symptoms of AD.
- Early work on an AD vaccine begins.
- Many new AD clinical trials, initiatives, and studies are launched, looking at a broad array of translational, treatment, and prevention issues.
- New transgenic mouse models, including one that develops both plaques and tangles, are developed.
- Pittsburgh Compound B (PiB) is developed, allowing researchers to “see” beta-amyloid plaques in the brains of living people.
- The growing sophistication of neuroimaging techniques, genetics, memory and cognitive tests, structured interviews, and other technologies improve our ability to identify people at high risk of AD.

To understand AD, it is important to know a bit about the brain. This part of Unraveling the Mystery gives an inside view of the normal brain, how it works, and what happens during aging.

The brain is a remarkable organ. Seemingly without effort, it allows us to carry out every element of our daily lives. It manages many body functions, such as breathing, blood circulation, and digestion, without our knowledge or direction. It also directs all the functions we carry out consciously. We can speak, hear, see, move, remember, feel emotions, and make decisions because of the complicated mix of chemical and electrical processes that take place in our brains.

The brain is made of nerve cells and several other cell types. Nerve cells also are called neurons. The neurons of all animals function in basically the same way, even though animals can be very different from each other. Neurons survive and function with the help and support of glial cells, the other main type of cell in the brain. Glial cells hold neurons in place, provide them with nutrients, rid the brain of damaged cells and other cellular debris, and provide insulation to neurons in the brain and spinal cord. In fact, the brain has many more glial cells than neurons—some scientists estimate even 10 times as many.

Another essential feature of the brain is its enormous network of blood vessels. Even though the brain is only about 2 percent of the body’s weight, it receives 20 percent of the body’s blood supply. Billions of tiny blood vessels, or capillaries, carry oxygen, glucose (the brain’s principal source of energy), nutrients, and hormones to brain cells so they can do their work. Capillaries also carry away waste products.

### The Brain’s Vital Statistics

| **Adult Weight** | about 3 pounds |
| **Adult Size**   | a medium cauliflower |
| **Number of Neurons** | about 100,000,000,000 (100 billion) |
| **Number of Synapses** (the gaps between neurons) | about 1,000,000,000,000,000 (100 trillion) |
| **Number of Capillaries** (tiny blood vessels) | about 400,000,000,000,000 (400 billion) |
The brain has many parts, each of which is responsible for particular functions. The following section describes a few key structures and what they do.

**THE MAIN PLAYERS**

- Two cerebral hemispheres account for 85 percent of the brain's weight. The billions of neurons in the two hemispheres are connected by thick bundles of nerve cell fibers called the corpus callosum. Scientists now think that the two hemispheres differ not so much in what they do (the “logical versus artistic” notion), but in how they process information. The left hemisphere appears to focus on details (such as recognizing a particular face in a crowd). The right hemisphere focuses on broad background (such as understanding the relative position of objects in a space). The cerebral hemispheres have an outer layer called the cerebral cortex. This is where the brain processes sensory information received from the outside world, controls voluntary movement, and regulates cognitive functions, such as thinking, learning, speaking, remembering, and making decisions. The hemispheres have four lobes, each of which has different roles:
  - The frontal lobe, which is in the front of the brain, controls “executive function” activities like thinking, organizing, planning, and problem solving, as well as memory, attention, and movement.
  - The parietal lobe, which sits behind the frontal lobe, deals with the perception and integration of stimuli from the senses.
  - The occipital lobe, which is at the back of the brain, is concerned with vision.
  - The temporal lobe, which runs along the side of the brain under the frontal and parietal lobes, deals with the senses of smell, taste, and sound, and the formation and storage of memories.

- The cerebellum sits above the brain stem and beneath the occipital lobe. It takes up a little more than 10 percent of the brain. This part of the brain plays roles in balance and coordination. The cerebellum has two hemispheres, which receive information from the eyes, ears, and muscles and...
This illustration shows a three-dimensional side view of one of two cerebral hemispheres of the brain. To help visualize this, imagine looking at the cut side of an avocado sliced long ways in half, with the pit still in the fruit. In this illustration, the “pit” is several key structures that lie deep within the brain (the hypothalamus, amygdala, and hippocampus) and the brain stem.
joints about the body’s movements and position. Once the cerebellum processes that information, it
sends instructions to the body through the rest of the brain and spinal cord. The cerebellum’s work
allows us to move smoothly, maintain our balance, and turn around without even thinking about it. It
also is involved with motor learning and remembering how to do things like drive a car or write
your name.

- The **brain stem** sits at the base of the brain. It connects the spinal cord with the rest of the brain.
  Even though it is the smallest of the three main players, its functions are crucial to survival. The
  brain stem controls the functions that happen automatically to keep us alive—our heart rate,
  blood pressure, and breathing. It also relays information between the brain and the spinal
cord, which then sends out messages to the muscles, skin, and other organs. Sleep and
dreaming are also controlled by the brain stem.

**OTHER CRUCIAL PARTS**

Several other essential parts of the brain lie deep inside the cerebral hemispheres in a network of
structures called the **limbic system**. The limbic system links the brain stem with the higher
reasoning elements of the cerebral cortex. It plays a key role in developing and carrying out instinctive
behaviors and emotions and also is important in perceiving smells and linking them with memory,
emotion, and instinctive behaviors. The limbic system includes:

- The **amygdala**, an almond-shaped structure involved in processing and remembering strong
  emotions such as fear. It is located in the temporal lobe just in front of the hippocampus.

- The **hippocampus**, which is buried in the temporal lobe, is important for learning and
  short-term memory. This part of the brain is thought to be the site where short-term
  memories are converted into long-term memories for storage in other brain areas.

- The **thalamus**, located at the top of the brain stem, receives sensory and limbic information,
  processes it, and then sends it to the cerebral cortex.

- The **hypothalamus**, a structure under the thalamus, monitors activities such as body
  temperature and food intake. It issues instructions to correct any imbalances. The hypothalamus also
  controls the body’s internal clock.

**THE BRAIN IN ACTION**

Sophisticated brain-imaging techniques allow scientists to monitor brain function in living
people and to see how various parts of the brain are used for different kinds of tasks. This is
opening up worlds of knowledge about brain function and how it changes with age or disease.

One of these imaging techniques is called **positron emission tomography**, or PET
scanning. Some PET scans measure blood flow and glucose **metabolism** throughout the
brain. (For more on metabolism, see page 16.) During a PET scan, a small amount of a radioac-
tive substance is attached to a compound, such as glucose, and injected into the bloodstream.
This tracer substance eventually goes to the brain. When nerve cells in a region of the brain become
active, blood flow and glucose metabolism in that region increase. When colored to reflect
metabolic activity, increases usually look red and yellow. Shades of blue and black indicate
decreased or no activity within a brain region.
In essence, a PET scan produces a “map” of the active brain.

Scientists can use PET scans to see what happens in the brain when a person is engaged in a physical or mental activity, at rest, or even while sleeping or dreaming. Certain tracers can track the activity of brain chemicals, for example neurotransmitters such as dopamine and serotonin. (To learn about exciting developments using one new tracer, see PiB and PET on page 28.) Some of these neurotransmitters are changed with age, disease, and drug therapies.
The human brain is made up of billions of neurons. Each has a cell body, an **axon**, and many **dendrites**. The cell body contains a **nucleus**, which controls much of the cell’s activities. The cell body also contains other structures, called organelles, that perform specific tasks.

The axon, which is much narrower than the width of a human hair, extends out from the cell body. Axons transmit messages from neuron to neuron. Sometimes, signal transmissions—like those from head to toe—have to travel over very long distances. Axons are covered with an insulating layer called **myelin** (also called white matter because of its whitish color). Myelin, which is made by a particular kind of glial cell, increases the speed of nerve signal transmissions through the brain.

Dendrites also branch out from the cell body. They receive messages from the axons of other neurons. Each neuron is connected to thousands of other nerve cells through its axon and dendrites.

Groups of neurons in the brain have special jobs. For example, some are involved with thinking, learning, and memory. Others are responsible for receiving information from the sensory organs (such as the eyes and ears) or the skin. Still others communicate with muscles, stimulating them into action.

Several processes all have to work smoothly together for neurons, and the whole organism, to survive and stay healthy. These processes are communication, metabolism, and repair.

**COMMUNICATION**

Imagine the many miles of fiber-optic cables that run under our streets. Day and night, millions of televised and telephonic messages flash at incredible speeds, letting people strike deals, give instructions, share a laugh, or learn some news. Miniaturize it, multiply it many-fold, make it much more complex, and you have the brain. Neurons are the great communicators, always in touch with their neighbors.

Neurons communicate with each other through their axons and dendrites. When a dendrite receives an incoming signal (electrical or chemical), an “action potential,” or nerve impulse, can be generated in the cell body. The action potential travels to the end of the axon and once there, the passage of either electrical current or, more typically, the release of chemical messengers, called **neurotransmitters**, can be triggered. The neurotransmitters are released from the axon terminal and move across a tiny gap, or **synapse**, to specific receptor sites on the receiving, or post-synaptic, end of dendrites of nearby neurons. A typical neuron has thousands of synaptic connections, mostly on its many dendrites, with other neurons. Cell bodies also have receptor sites for neurotransmitters.
Once the post-synaptic receptors are activated, they open channels through the cell membrane into the receiving nerve cell’s interior or start other processes that determine what the receiving nerve cell will do. Some neurotransmitters inhibit nerve cell function (that is, they make it less likely that the nerve cell will send an electrical signal down its axon). Other neurotransmitters stimulate nerve cells, priming the receiving cell to become active or send an electrical signal down the axon to more neurons in the pathway. A neuron receives signals from many other neurons simultaneously, and the sum of a neuron’s neurotransmitter inputs at any one instant will determine whether it sends a signal down its axon to activate or inhibit the action of other neighboring neurons.

During any one moment, millions of these signals are speeding through pathways in the brain, allowing the brain to receive and process information, make adjustments, and send out instructions to various parts of the body.

**METABOLISM**

All cells break down chemicals and nutrients to generate energy and form building blocks that make new cellular molecules such as proteins. This process is called metabolism. To maintain metabolism, the brain needs plenty of blood constantly circulating through its billions of capillaries to supply neurons and other brain cells with oxygen and glucose. Without oxygen and glucose, neurons will quickly die.

**REPAIR**

Nerve cells are formed during fetal life and for a short time after birth. Unlike most cells, which have a fairly short lifespan, neurons in the brain live a long time. These cells can live for up to 100 years or longer. To stay healthy, living neurons must constantly maintain and repair themselves. In an adult, when neurons die because of disease or injury, they are not usually replaced. Research, however, shows that in a few brain regions, new neurons can be generated, even in the old brain.
The Changing Brain in Healthy Aging

In the past several decades, investigators have learned much about what happens in the brain when people have a neurodegenerative disease such as Parkinson’s disease, AD, or other dementias. Their findings also have revealed much about what happens during healthy aging. Researchers are investigating a number of changes related to healthy aging in hopes of learning more about this process so they can fill gaps in our knowledge about the early stages of AD.

As a person gets older, changes occur in all parts of the body, including the brain:

- Certain parts of the brain shrink, especially the prefrontal cortex (an area at the front of the frontal lobe) and the hippocampus. Both areas are important to learning, memory, planning, and other complex mental activities.
- Changes in neurons and neurotransmitters affect communication between neurons. In certain brain regions, communication between neurons can be reduced because white matter (myelin-covered axons) is degraded or lost.
- Changes in the brain’s blood vessels occur. Blood flow can be reduced because arteries narrow and less growth of new capillaries occurs.
- In some people, structures called plaques and tangles develop outside of and inside neurons, respectively, although in much smaller amounts than in AD.
- Damage by free radicals increases (free radicals are a kind of molecule that reacts easily with other molecules).
- Inflammation increases (inflammation is the complex process that occurs when the body responds to an injury, disease, or abnormal situation).

What effects does aging have on mental function in healthy older people? Some people may notice a modest decline in their ability to learn new things and retrieve information, such as remembering names. They may perform worse on complex tasks of attention, learning, and memory than would a younger person. However, if given enough time to perform the task, the scores of healthy people in their 70s and 80s are often similar to those of young adults. In fact, as they age, adults often improve in other cognitive areas, such as vocabulary and other forms of verbal knowledge. It also appears that additional brain regions can be activated in older adults during cognitive tasks,
such as taking a memory test. Researchers do not fully understand why this happens, but one idea is that the brain engages mechanisms to compensate for difficulties that certain regions may be having. For example, the brain may recruit alternate brain networks in order to perform a task. These findings have led many scientists to believe that major declines in mental abilities are not inevitable as people age. Growing evidence of the adaptive (what scientists call “plastic”) capabilities of the older brain provide hope that people may be able to do things to sustain good brain function as they age. A variety of interacting factors, such as lifestyle, overall health, environment, and genetics also may play a role.

Another question that scientists are asking is why some people remain cognitively healthy as they get older while others develop cognitive impairment or dementia. The concept of “cognitive reserve” may provide some insights. Cognitive reserve refers to the brain’s ability to operate effectively even when some function is disrupted. It also refers to the amount of damage that the brain can sustain before changes in cognition are evident. People vary in the cognitive reserve they have, and this variability may be because of differences in genetics, education, occupation, lifestyle, leisure activities, or other life experiences. These factors could provide a certain amount of tolerance and ability to adapt to change and damage that occurs during aging. At some point, depending on a person’s cognitive reserve and unique mix of genetics, environment, and life experiences, the balance may tip in favor of a disease process that will ultimately lead to dementia. For another person, with a different reserve and a different mix of genetics, environment, and life experiences, the balance may result in no apparent decline in cognitive function with age.

Scientists are increasingly interested in the influence of all these factors on brain health, and studies are revealing some clues about actions people can take that may help preserve healthy brain aging. Fortunately, these actions also benefit a person’s overall health. They include:

- Controlling risk factors for chronic disease, such as heart disease and diabetes (for example, keeping blood cholesterol and blood pressure at healthy levels and maintaining a healthy weight)
- Enjoying regular exercise and physical activity
- Eating a healthy diet that includes plenty of vegetables and fruits
- Engaging in intellectually stimulating activities and maintaining close social ties with family, friends, and community
The phrase “use it or lose it” may make you think of your muscles, but scientists who study brain health in older people have found that it may apply to cognitive skills as well. In 2006, scientists funded by NIA and the National Institute of Nursing Research completed a study of cognitive training in older adults. This study, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, was the first randomized controlled trial to demonstrate long-lasting, positive effects of brief cognitive training in older adults.

The ACTIVE study included 2,802 healthy adults age 65 and older who were living independently. Participants were randomly assigned to four groups. Three groups took part in up to 10 computer-based training sessions that targeted a specific cognitive ability—memory, reasoning, and speed of processing (in other words, how fast participants could respond to prompts on a computer screen). The fourth group (the control group) received no cognitive training. Sixty percent of those who completed the initial training also took part in 75-minute “booster” sessions 11 months later. These sessions were designed to maintain improvements gained from the initial training.

The investigators tested the participants at the beginning of the study, after the initial training and booster sessions, and once a year for 5 more years. They found that the improvements from the training roughly counteracted the degree of decline in cognitive performance that would be expected over a 7- to 14-year period among older people without dementia:

- Immediately after the initial training, 87 percent of the processing-speed group, 74 percent of the reasoning group, and 26 percent of the memory group showed improvement in the skills taught.

After 5 years, people in each group performed better on tests in their respective areas of training than did people in the control group. The reasoning and processing-speed groups who received booster training had the greatest benefit.

The researchers also looked at the training’s effects on participants’ everyday lives. After 5 years, all three groups who received training reported less difficulty than the control group in tasks such as preparing meals, managing money, and doing housework. However, these results were statistically significant for only the group that had the reasoning training.

As they get older, many people worry about their mental skills getting “rusty.” The ACTIVE study offers hope that cognitive training may be useful because it showed that relatively brief and targeted cognitive exercises can produce lasting improvements in the skills taught. Next steps for researchers are to determine ways to generalize the training benefits beyond the specific skills taught in ACTIVE and to find out whether cognitive training programs could prevent, delay, or diminish the effects of AD.
Alzheimer’s disease disrupts critical metabolic processes that keep neurons healthy. These disruptions cause nerve cells in the brain to stop working, lose connections with other nerve cells, and finally die. The destruction and death of nerve cells causes the memory failure, personality changes, problems in carrying out daily activities, and other features of the disease.

The brains of people with AD have an abundance of two abnormal structures—amyloid plaques and neurofibrillary tangles—that are made of misfolded proteins (see Protein Misfolding on page 41 for more information). This is especially true in certain regions of the brain that are important in memory.

The third main feature of AD is the loss of connections between cells. This leads to diminished cell function and cell death.

**AMYLOID PLAQUES**

Amyloid plaques are found in the spaces between the brain’s nerve cells. They were first described by Dr. Alois Alzheimer in 1906. Plaques consist of largely insoluble deposits of an apparently toxic protein peptide, or fragment, called beta-amyloid.

We now know that some people develop some plaques in their brain tissue as they age. However, the AD brain has many more plaques in particular brain regions. We still do not know whether amyloid plaques themselves cause AD or whether they are a by-product of the AD process. We do know that genetic mutations can increase production of beta-amyloid and can cause rare, inherited forms of AD (see Genes and Early-Onset Alzheimer’s Disease on page 38 for more on inherited AD).
**From APP to Beta-Amyloid Plaques**

**Amyloid precursor protein** (APP), the starting point for amyloid plaques, is one of many proteins associated with the cell membrane, the barrier that encloses the cell. As it is being made inside the cell, APP becomes embedded in the membrane, like a toothpick stuck through the skin of an orange (Figure 1).

In a number of cell compartments, including the outermost cell membrane, specific enzymes snip, or cleave, APP into discrete fragments. In 1999 and 2000, scientists identified the enzymes responsible for cleaving APP. These enzymes are called alpha-secretase, beta-secretase, and gamma-secretase. In a major breakthrough, scientists then discovered that, depending on which enzyme is involved and the segment of APP where the cleaving occurs, APP processing can follow one of two pathways that have very different consequences for the cell.

In the benign pathway, alpha-secretase cleaves the APP molecule within the portion that has the potential to become beta-amyloid. This eliminates the production of the beta-amyloid peptide and the potential for plaque buildup. The cleavage releases from the neuron a fragment called sAPPα, which has beneficial properties, such as promoting neuronal growth and survival. The remaining APP fragment, still tethered in the neuron’s membrane, is then cleaved by gamma-secretase at the end of the beta-amyloid segment. The smaller of the resulting fragments also is released into the space outside the neuron, while the larger fragment remains within the neuron and interacts with factors in the nucleus (Figure 2).

In the harmful pathway, beta-secretase first cleaves the APP molecule at one end of the beta-amyloid peptide, releasing sAPPβ from the cell (Figure 3). Gamma-secretase then cuts the resulting APP fragment, still tethered in the neuron’s membrane, at the other end of the beta-amyloid peptide. Following the cleavages at each end, the beta-amyloid peptide is released into the space outside the neuron and begins to stick to other beta-amyloid peptides (Figure 4). These small, soluble aggregates of two, three, four, or even up to a dozen beta-amyloid peptides are called oligomers. Specific sizes of oligomers may be responsible for reacting with receptors on neighboring cells and synapses, affecting their ability to function.

It is likely that some oligomers are cleared from the brain. Those that cannot be cleared clump together with more beta-amyloid peptides. As the process continues, oligomers grow larger, becoming entities called protofibrils and fibrils. Eventually, other proteins and cellular material are added, and these increasingly insoluble entities combine to become the well-known plaques that are characteristic of AD.

For many years, scientists thought that plaques might cause all of the damage to neurons that is seen in AD. However, that concept has evolved greatly in the past few years. Many scientists now think that oligomers may be a major culprit. Many scientists also think that plaques actually may be a late-stage attempt by the brain to get this harmful beta-amyloid away from neurons.
NEUROFIBRILLARY TANGLES

The second hallmark of AD, also described by Dr. Alzheimer, is neurofibrillary tangles. Tangles are abnormal collections of twisted protein threads found inside nerve cells. The chief component of tangles is a protein called tau.

Healthy neurons are internally supported in part by structures called microtubules, which help transport nutrients and other cellular components, such as neurotransmitter-containing vesicles, from the cell body down the axon.

Tau, which usually has a certain number of phosphate molecules attached to it, binds to microtubules and appears to stabilize them. In AD, an abnormally large number of additional phosphate molecules attach to tau. As a result of this “hyperphosphorylation,” tau disengages from the microtubules and begins to come together with other tau threads. These tau threads form structures called paired helical filaments, which can become enmeshed with one another, forming tangles within the cell. The microtubules can disintegrate in the process, collapsing the neuron's internal transport network. This collapse damages the ability of neurons to communicate with each other.

DYING NEURON

Tangles
**LOSS OF CONNECTION BETWEEN CELLS AND CELL DEATH**

The third major feature of AD is the gradual loss of connections between neurons. Neurons live to communicate with each other, and this vital function takes place at the synapse. Since the 1980s, new knowledge about plaques and tangles has provided important insights into their possible damage to synapses and on the development of AD.

The AD process not only inhibits communication between neurons but can also damage neurons to the point that they cannot function properly and eventually die. As neurons die throughout the brain, affected regions begin to shrink in a process called brain atrophy. By the final stage of AD, damage is widespread, and brain tissue has shrunk significantly.

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**Loss of Connection Between Cells**

This illustration shows the damage caused by AD: plaques, tangles, and the loss of connection between neurons.
The Changing Brain in AD

No one knows exactly what starts the AD process or why some of the normal changes associated with aging become so much more extreme and destructive in people with the disease. We know a lot, however, about what happens in the brain once AD takes hold and about the physical and mental changes that occur over time. The time from diagnosis to death varies—as little as 3 or 4 years if the person is older than 80 when diagnosed to as long as 10 or more years if the person is younger. Several other factors besides age also affect how long a person will live with AD. These factors include the person’s sex, the presence of other health problems, and the severity of cognitive problems at diagnosis. Although the course of the disease is not the same in every person with AD, symptoms seem to develop over the same general stages.

**PRECLINICAL AD**

AD begins deep in the brain, in the entorhinal cortex, a brain region that is near the hippocampus and has direct connections to it. Healthy neurons in this region begin to work less efficiently, lose their ability to communicate, and ultimately die. This process gradually spreads to the hippocampus, the brain region that plays a major role in learning and is involved in converting short-term memories to long-term memories. Affected regions begin to atrophy. Ventricles, the fluid-filled spaces inside the brain, begin to enlarge as the process continues.

Scientists believe that these brain changes begin 10 to 20 years before any clinically detectable signs or symptoms of forgetfulness appear. That’s why they are increasingly interested in the very early stages of the disease process. They hope to learn more about what happens in the brain that sets a person on the path to developing AD. By knowing more about the early stages, they also hope to be able to
Imagining being able to see deep inside the brain tissue of a living person. If you could do that, you could find out whether the AD process was happening many years before symptoms were evident. This knowledge could have a profound impact on improving early diagnosis, monitoring disease progression, and tracking response to treatment.

Scientists have stepped closer to this possibility with the development of a radiolabeled compound called Pittsburgh Compound B (PiB). PiB binds to beta-amyloid plaques in the brain and it can be imaged using PET scans. Initial studies showed that people with AD take up more PiB in their brains than do cognitively healthy older people. Since then, scientists have found high levels of PiB in some cognitively healthy people, suggesting that the damage from beta-amyloid may already be underway. The next step will be to follow these cognitively healthy people who have high PiB levels to see whether they do, in fact, develop AD over time.

In this PET scan, the red and yellow colors indicate that PiB uptake is higher in the brain of the person with AD than in the cognitively healthy person.

develop drugs or other treatments that will slow or stop the disease process before significant impairment occurs (see The Search for New Treatments on page 54 for more information).

**VERY EARLY SIGNS AND SYMPTOMS**

At some point, the damage occurring in the brain begins to show itself in very early clinical signs and symptoms. Much research is being done to identify these early changes, which may be useful in predicting dementia or AD. An important part of this research effort is the development of increasingly sophisticated neuroimaging techniques (see Exciting New Developments in AD Diagnosis on page 50 for more on neuroimaging) and the use of biomarkers. Biomarkers are indicators, such as changes in sensory abilities, or substances that appear in body fluids, such as blood, cerebrospinal fluid, or urine. Biomarkers can indicate exposure to a substance, the presence of a disease, or the progression over time of a disease. For example, high blood cholesterol is a biomarker for risk of heart disease. Such tools are critical to helping scientists detect and understand the very early signs and symptoms of AD.

**Mild Cognitive Impairment**

As some people grow older, they develop memory problems greater than those expected for their age. But they do not experience the personality changes or other problems that are characteristic of AD. These people may have a condition called mild cognitive impairment (MCI). MCI has several subtypes. The type most associated with memory loss is called amnestic MCI. People with MCI are a critically important group for research because
a much higher percentage of them go on to develop AD than do people without these memory problems. About 8 of every 10 people who fit the definition of amnestic MCI go on to develop AD within 7 years. In contrast, 1 to 3 percent of people older than 65 who have normal cognition will develop AD in any one year.

However, researchers are not yet able to say definitively why some people with amnestic MCI do not progress to AD, nor can they say who will or will not go on to develop AD. This raises pressing questions, such as: In cases when MCI progresses to AD, what was happening in the brain that made that transition possible? Can MCI be prevented or its progress to AD delayed?

Scientists also have found that genetic factors may play a role in MCI, as they do in AD (see Genetic Factors at Work in AD on page 36 for more information). And, they have found that different brain regions appear to be activated during certain mental activities in cognitively healthy people and those with MCI. These changes appear to be related to the early stages of cognitive impairment.

Other Signs of Early AD Development
As scientists have sharpened their focus on the early stages of AD, they have begun to see hints of other changes that may signal a developing disease process. For example, in the Religious Orders Study, a large AD research effort that involves older nuns, priests, and religious brothers, investigators have
explored whether changes in older adults’ ability to move about and use their bodies might be a sign of early AD. The researchers found that participants with MCI had more movement difficulties than the cognitively healthy participants but less than those with AD. Moreover, those with MCI who had lots of trouble moving their legs and feet were more than twice as likely to develop AD as those with good lower body function.

It is not yet clear why people with MCI might have these motor function problems, but the scientists who conducted the study speculate that they may be a sign that damage to blood vessels in the brain or damage from AD is accumulating in areas of the brain responsible for motor function. If further research shows that some people with MCI do have motor function problems in addition to memory problems, the degree of difficulty, especially with walking, may help identify those at risk of progressing to AD.

Other scientists have focused on changes in sensory abilities as possible indicators of early cognitive problems. For example, in one study they found associations between a decline in the ability to detect odors and cognitive problems or dementia. These findings are tentative, but they are promising because they suggest that, some day, it may be possible to develop ways to improve early detection of MCI or AD. These tools also will help scientists answer questions about causes and very early development of AD, track changes in brain and cognitive function over time, and ultimately track a person’s response to treatment for AD.

**MILD AD**

As AD spreads through the brain, the number of plaques and tangles grows, shrinkage progresses, and more and more of the cerebral cortex is affected. Memory loss continues and changes in other cognitive abilities begin to emerge. The clinical diagnosis of AD is usually made during this stage. Signs of mild AD can include:

- Memory loss
- Confusion about the location of familiar places (getting lost begins to occur)
- Taking longer than before to accomplish normal daily tasks
- Trouble handling money and paying bills
- Poor judgment leading to bad decisions
- Loss of spontaneity and sense of initiative
- Mood and personality changes, increased anxiety and/or aggression

In mild AD, a person may seem to be healthy but is actually having more and more trouble making sense of the world around him or her. The realization that something is wrong often comes gradually to the person and his or her family.
Accepting these signs as something other than normal and deciding to go for diagnostic tests can be a big hurdle for people and families. Once this hurdle is overcome, many families are relieved to know what is causing the problems. They also can take comfort in the fact that despite a diagnosis of MCI or early AD, a person can still make meaningful contributions to his or her family and to society for a time.

**Moderate AD**

By this stage, AD damage has spread to the areas of the cerebral cortex that control language, reasoning, sensory processing, and conscious thought. Affected regions continue to shrink, ventricles enlarge, and signs and symptoms of the disease become more pronounced and widespread. Behavioral problems, such as wandering and agitation, can occur. More intensive supervision and care become necessary, which can be difficult for many spouses and families. The symptoms of this stage can include:

- Increasing memory loss and confusion
- Shortened attention span
- Inappropriate outbursts of anger
- Problems recognizing friends and family members
- Difficulty with language and problems with reading, writing, and working with numbers
- Difficulty organizing thoughts and thinking logically
- Inability to learn new things or to cope with new or unexpected situations
- Restlessness, agitation, anxiety, tearfulness, wandering—especially in the late afternoon or at night
- Repetitive statements or movement, occasional muscle twitches

- Hallucinations, delusions, suspiciousness or paranoia, irritability
- Loss of impulse control (shown through undressing at inappropriate times or places or vulgar language)
- An inability to carry out activities that involve multiple steps in sequence, such as dressing, making a pot of coffee, or setting the table

Behavior is the result of complex brain processes, all of which take place in a fraction of a second in the healthy brain. In AD, many of those processes are disturbed, and these disrupted communications between neurons are the basis for many distressing or inappropriate behaviors. For example, a person may angrily refuse to take a bath or get dressed because he does not understand what his caregiver has asked him to do. If he does understand, he may not remember how to do it. The anger can be a mask for his confusion and anxiety. Or, a person with AD may constantly follow her husband or caregiver and fret when the person is out of sight. To a person who cannot remember the past or anticipate the future, the world can be strange and frightening. Sticking close to a trusted and familiar caregiver may be the only thing that makes sense and provides security.

**Severe AD**

In the last stage of AD, plaques and tangles are widespread throughout the brain, most areas of the brain have shrunk further, and ventricles have enlarged even more. People with AD cannot recognize family and loved ones or communicate in any way. They are completely dependent on others for care. Other symptoms can include:

- Weight loss
- Seizures
- Skin infections
- Difficulty swallowing
- Groaning, moaning, or grunting
- Increased sleeping
- Lack of bladder and bowel control

Near the end, the person may be in bed much or all of the time. The most frequent cause of death for people with AD is aspiration pneumonia. This type of pneumonia develops when a person is not able to swallow properly and takes food or liquids into the lungs instead of air.

**Severe AD**
The Buddy Program at Northwestern University

The medical school curriculum demands that students spend enormous amounts of time in the classroom and clinic learning the information and skills necessary for a career in medicine. However, little or no time is set aside for students to be with patients outside the hospital or clinic setting. As a result, it is hard for medical students to get to know the human side of the diseases they are learning about.

A program at Northwestern University’s Cognitive Neurology and Alzheimer’s Disease Center is adding just that element to its medical education. The Buddy Program, begun in 1998, matches first-year medical students with people diagnosed with AD or another form of dementia. About 10 to 15 medical students participate every year. They first take a 3-hour orientation course on AD, family issues, and communication skills. Then, for the next year, they spend at least 4 hours a month with a person with dementia in addition to monthly meetings with the program coordinators. Together with the person’s caregiver and the program’s professional staff, students and their “buddies” choose activities for their visits together. Activities can include shopping, visiting museums, exercising together, or even just sharing a coffee or a meal. The students also are able to observe their buddies’ clinical evaluations at the Center. Other medical schools have started similar programs.

The people with AD and their families are selected from Northwestern’s Alzheimer’s Disease Center and other related programs at the university. Families are contacted about participating, and the people with AD are selected based on their ability to understand the nature of the program and their willingness to spend time every month with the student buddy.

The program has clear benefits for both the medical student and the person with AD. For the medical student, it provides a hands-on way to learn about AD and related dementias, and it helps him or her understand the daily realities and issues involved in caring for and supporting people with AD and their families. It also introduces them to the career path of research and clinical practice in AD and related dementias. For the person with AD, participation in the program provides an opportunity for friendship and socializing and an outlet for sharing their experiences with a sympathetic listener.

For many of the students, the program is a formative experience. They become very close to their buddies and family caregivers during their year together, and continue the friendship even after the year is over.
Scientists have studied AD from many angles. They have looked at populations to see how many cases of AD occur every year and whether there might be links between the disease and lifestyles or genetic backgrounds. They also have conducted clinical studies with healthy older people and those at various stages of AD. They have done many studies with laboratory animals. They have begun to look at neuronal circuits and networks of cells to learn how AD pathology develops and spreads. They even have examined individual nerve cells to see how beta-amyloid, tau, and other molecules affect the ability of cells to function normally.

These studies have led to a fuller understanding of many aspects of the disease, improved diagnostic tests, new ways to manage behavioral aspects of AD, and a growing number of possible drug treatments. Findings from current research are pointing scientists in promising directions for the future. They are also helping researchers to ask better questions about the issues that are still unclear.

Part 3 of Unraveling the Mystery describes what scientists are learning from their search for:

- The causes of AD
- New techniques to help in diagnosis
- New treatments

Results from this research will bring us closer to the day when we will be able to delay the onset of, prevent, or cure the devastating disease that robs our older relatives and friends of their most precious possession—their minds.
Looking for the Causes of AD

One of the most important parts of unraveling the AD mystery is finding out what causes the disease. What makes the disease process begin in the first place? What makes it worse over time? Why does the number of people with the disease increase with age? Why does one person develop AD while another remains healthy?

Some diseases, such as measles or pneumonia, have clear-cut causes. They can be prevented with vaccines or cured with antibiotics. Others, such as diabetes or arthritis, develop when genetic, lifestyle, and environmental factors work together to start a disease process. The role that any or all of these factors play may be different for each individual.

AD fits into the second group of diseases. We do not yet fully understand what causes AD, but we believe it develops because of a complex series of events that take place in the brain over a long period of time. Many studies are exploring the factors involved in the cause and development of AD.

**GENETIC FACTORS AT WORK IN AD**

Genetic studies of complex neurodegenerative diseases such as AD focus on two main issues—whether a gene might influence a person’s overall risk of developing a disease and whether a gene might influence some particular aspect of a person’s risk, such as the age at which the disease begins. Slow and careful detective work by scientists has paid off in discoveries of genetic links to the two main types of AD.

One type is the rare, **early-onset Alzheimer’s disease**. It usually affects people aged 30 to 60. Some cases of early-onset disease are inherited and are called familial AD (FAD). The other is **late-onset Alzheimer’s disease**. It is by far the more common form and occurs in those 60 and older. Gaining insight into the genetic factors associated with both forms of AD is important because identifying genes that either cause the disease or influence a person’s risk of developing it improves our ability to understand how and why the disease starts and progresses.
The nucleus of almost every human cell contains an encrypted “blueprint,” along with the means to decipher it. This blueprint, accumulated over eons of genetic trial and error, carries all the instructions a cell needs to do its job. The blueprint is made up of DNA, which exists as two long, intertwined, thread-like strands called chromosomes. Each cell has 46 chromosomes in 23 pairs. The DNA in chromosomes is made up of four chemicals, or bases, strung together in various sequence patterns. The DNA in nearly all cells of an individual is identical.

Each chromosome contains many thousands of segments, called genes. People inherit two copies of each gene from their parents, except for genes on the X and Y chromosomes, which are chromosomes that, among other functions, determine a person’s sex. Each person normally has one pair of sex chromosomes (females are XX and males are XY). The sequence of bases in a gene tells the cell how to make specific proteins. Proteins in large part determine the different kinds of cells that make up an organism and direct almost every aspect of the cell’s construction, operation, and repair. Even though all genes are present in most cells, the pattern in which they are activated varies from cell to cell, and gives each cell type its distinctive character. Even slight alterations in a gene can produce an abnormal protein, which, in turn, may lead to cell malfunction and, eventually, to disease.

Any permanent change in the sequence of bases in a gene’s DNA that causes a disease is called a mutation. Mutations also can change the activation of a particular gene. Other more common (or frequent) changes in a gene’s sequence of bases do not automatically cause disease, but they can increase the chances that a person will develop a particular disease. When this happens, the changed gene is called a genetic risk factor.
**Genes and Early-Onset Alzheimer’s Disease**

In the early days of AD genetics research, scientists realized that some cases, particularly of the rare early-onset AD, ran in families. This led them to examine DNA samples from these families to see whether they had some genetic trait in common. Chromosomes 21, 14, and 1 became the focus of attention. The scientists found that some families have a mutation in selected genes on these chromosomes. On chromosome 21, the mutation causes an abnormal amyloid precursor protein to be produced (see page 22 for more on APP). On chromosome 14, the mutation causes an abnormal protein called presenilin 1 to be produced. On chromosome 1, the mutation causes another abnormal protein to be produced. This protein, called presenilin 2, is very similar to presenilin 1. Even if only one of these genes that are inherited from a parent contains a mutation, the person will almost inevitably develop early-onset AD. This means that in these families, children have about a 50-50 chance of developing the disease if one of their parents has it.

Early-onset AD is very rare, and mutations in these three genes do not play a role in the more common late-onset AD. However, these findings were crucial because they showed that genetics was indeed a factor in AD, and they helped to identify some key cell pathways involved in the AD disease process. They showed that mutations in APP can cause AD, highlighting the presumed key role of beta-amyloid in the disease. Mutations in presenilin 1 and 2 also cause an increased amount of the damaging beta-amyloid to be made in the brain.

**A Different Genetic Story in Late-Onset Alzheimer’s Disease**

While some scientists were studying the role of chromosomes 21, 14, and 1 in early-onset AD, others were looking elsewhere to see if they could find genetic clues for the late-onset form. By 1992, investigators had narrowed their search to a region of chromosome 19. They found a gene on chromosome 19 that they were able to link to late-onset AD.

This gene, called APOE, produces a protein called **apolipoprotein E**. APOE comes in several forms, or alleles—ε2, ε3, and ε4:

- The APOE ε2 allele is relatively rare and may provide some protection against the disease. If AD does occur in a person with this allele, it develops later in life than in those with an APOE ε4 allele.
- APOE ε3 is the most common allele. Researchers think it plays a neutral role in AD.
- APOE ε4 occurs in about 40 percent of all people who develop late-onset AD and is present in about 25 to 30 percent of the population. People with AD are more likely to have an APOE ε4 allele than people who do not have AD. However, at least one-third of people with AD do not have an APOE ε4 allele. Dozens of studies have confirmed that the APOE ε4 allele increases the risk of developing AD, but how that happens is not yet understood. These studies also have helped to explain some of the variation in the age at which AD develops, as people who inherit one or two APOE ε4 alleles tend to develop AD at an earlier age than those who do not. However, inheriting an APOE ε4 allele does not mean that a person will definitely develop AD. Some people with one or two APOE ε4 alleles never get the disease, and others who do develop AD do not have any APOE ε4 alleles.
The Hunt for New AD Genes

For some time, scientists have suspected that, in addition to APOE e4, as many as half a dozen other risk-factor genes exist for late-onset AD, but they have been unable to find them. In 2007, scientists unveiled their discovery of one new AD risk-factor gene.

This AD risk-factor gene is called SORL1. It is involved in recycling APP from the surface of cells, and its association with AD was identified and confirmed in three separate studies. Researchers found that when SORL1 is expressed at low levels or in a variant form, harmful beta-amyloid levels increase, perhaps by deflecting APP away from its normal pathways and forcing it into cellular compartments that generate beta-amyloid.

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

In 2003, NIA launched the Alzheimer’s Disease Genetics Study to identify at least 1,000 families with members who have late-onset AD as well as members who do not have the disease. All of these family members provide blood samples and other clinical data for the initiative. The material collected allows investigators to create and maintain “immortalized” cell lines—cells that are continuously regenerated in the laboratory. These cell lines are crucial for the exhaustive DNA analysis studies needed to identify risk-factor genes, each of which may have relatively small effects on AD development. More than 4,000 new cell lines are now available for researchers to study risk-factor genes for late-onset AD.

A new initiative, the Alzheimer’s Disease Genetics Consortium, was launched in 2007 to accelerate the application of genetics technologies to late-onset AD through collaborations among most of the leading researchers in AD genetics. The ultimate goal of this effort is to obtain genetic material from 10,000 people with AD and 10,000 cognitively healthy people to comprehensively scan the whole genome for the remaining AD risk-factor genes, as well as those for age-related cognitive decline. Some of the genetic material will be drawn from existing samples of blood and tissue; other genetic material will be collected from new participants.

New AD genetics discoveries are possible largely because of close collaboration among scientists, participation of volunteer families, new genetics technologies, statistical and analytic advances, and rapid data sharing. For example, the SORL1 studies involved 14 scientific institutions in North America, Europe, and Asia and the participation of more than 6,000 people who donated blood and tissue for genetic typing. An important part of NIA’s efforts to promote and accelerate AD genetics research is to make biological samples and data publicly available to approved researchers.

NIA

[Image]
OTHER FACTORS AT WORK IN AD

Genetics explains some of what might cause AD, but it does not explain everything. So, researchers continue to investigate other possibilities that may explain how the AD process starts and develops.

Beta-Amyloid

We now know a great deal about how beta-amyloid is formed and the steps by which beta-amyloid fragments stick together in small aggregates (oligomers), and then gradually form into plaques (see page 22 in The Hallmarks of AD for more on this process). Armed with this knowledge, investigators are intensely interested in the toxic effects that beta-amyloid, oligomers, and plaques have on neurons. This research is possible in part because scientists have been able to develop transgenic animal models of AD. Transgenics are animals that have been specially bred to develop AD-like features, such as beta-amyloid plaques.

Beta-amyloid studies have moved forward to the point that scientists are now carrying out preliminary tests in humans of potential therapies aimed at removing beta-amyloid, halting its formation, or breaking down early forms before they can become harmful.

For example, one line of research by a pharmaceutical company started with the observation that injecting beta-amyloid into AD transgenic mice caused them to form antibodies to the beta-amyloid and reduced the number of amyloid plaques in the brain. This exciting finding led to other studies and ultimately to clinical trials in which human participants were immunized with beta-amyloid. These studies had to be stopped because some of the participants developed harmful side effects, but the investigators did not give up hope. Rather, they went back to the drawing board to rethink their strategy. More refined antibody approaches are now being tested in clinical trials, and additional research on new ways of harnessing the antibody response continues in the lab.

Another important area of research is how beta-amyloid may disrupt cellular communication well before plaques form. One recent study described how beta-amyloid oligomers target specific synaptic connections between neurons, causing them to deteriorate. Other scientists are studying other potentially toxic effects that plaques have on neurons and in cellular communication. Understanding more about these processes may allow scientists to develop specific therapies to block the toxic effects.

Tau

Tau, the chief component of neurofibrillary tangles (see page 25 in The Hallmarks of AD for more on tau), is generating new excitement as an area of study. The recent focus on tau has been spurred by the finding that a mutant form of the protein is responsible for one form of frontotemporal dementia, the third most common cause of late-life dementia, after AD and vascular dementia. This form is known as frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). Finding this mutant protein was important because it suggested that abnormalities in the tau protein itself can cause dementia.

New transgenic mouse models of AD have helped tau research make rapid progress. For example, a recent model, the “triple transgenic” mouse, forms plaques and tangles over time in brain regions similar to those in human AD. Another recent transgenic mouse model, which contains only human tau, forms clumps of damaging tau filaments also in a region-specific fashion similar to AD in humans.

These studies of tau also have suggested a mechanism for tau damage that is different from that previously suspected. With these new insights,
scientists now speculate that one reason tau may damage and kill neurons is because it upsets the normal activity of the cell, in addition to forming neurofibrillary tangles.

Other studies of mutant tau in mice suggest that the accumulation of tau in tangles may not even be the culprit in memory loss. Rather, as with beta-amyloid, it may be that an earlier and more soluble abnormal form of the protein causes the damage to neurons.

**Protein Misfolding**

Researchers have found that a number of devastating neurodegenerative diseases (for example, AD, Parkinson’s disease, dementia with Lewy bodies, frontotemporal lobar degeneration, Huntington’s disease, and prion diseases) share a key characteristic—protein misfolding.

When a protein is formed, it “folds” into a unique three-dimensional shape that helps it

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**Researchers Explore Neurodegenerative “Cousins”**

Neurodegenerative diseases like AD, Parkinson’s disease, amyotrophic lateral sclerosis (ALS), and dementia with Lewy bodies share more than the basic characteristic of misfolded proteins. They also share clinical characteristics. For example, people with AD have trouble moving, a characteristic of Parkinson’s disease. Sleep-wake disorders, delusions, psychiatric disturbances, and memory loss occur in all of these diseases. These diseases also result from a combination of genetic, lifestyle, and environmental causes and they develop over many years.

This graphic shows one way of thinking about how these diseases may be linked as well as what makes them unique. By investigating the unique characteristics of these diseases as well as the characteristics they share, scientists hope to learn even more than they would if they focused on each disease by itself.

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**Lifetime Influences**

- Genes
- Environment
- Systemic factors

**Damaging Processes Occurring Before Symptoms Appear**

- Amyloid plaques
- Tau tangles
- Other abnormal protein deposits
- Reduced oxygen flow to tissues
- Toxic processes

**Early Symptoms**

- Tremor
- Memory loss
- Executive function problems
- Movement problems
- Gait and balance problems
- Sleep-wake disorders
- Hallucinations
- Delusions
- Rigidity

**Neurodegenerative Diseases**

- AD
- AD/PD
- DLB
- PDD
- VaD
- ALS
- FTLD

*AD = Alzheimer’s disease, AD/PD = AD with parkinsonism, ALS = amyotrophic lateral sclerosis, DLB = dementia with Lewy bodies, FTLD = frontotemporal lobar degeneration, VaD = vascular dementia (includes multi-infarct dementia), PD = Parkinson’s disease, PDD = Parkinson’s disease with dementia

*Adapted from an Emory University illustration*
perform its specific function. This crucial process can go wrong for various reasons, and more commonly does go wrong in aging cells. As a result, the protein folds into an abnormal shape—it is misfolded. In AD, the misfolded proteins are beta-amyloid (the cleaved product of APP; see From APP to Beta-Amyloid Plaques on page 22 for more on the formation of beta-amyloid) and a cleaved product of tau.

Normally, cells repair or degrade misfolded proteins, but if many of them are formed as part of age-related changes, the body’s repair and clearance process can be overwhelmed. Misfolded proteins can begin to stick together with other misfolded proteins to form insoluble aggregates. As a result, these aggregates can build up, leading to disruption of cellular communication, and metabolism, and even to cell death. These effects may predispose a person to AD or other neurodegenerative diseases.

Scientists do not know exactly why or how these processes occur, but research into the unique characteristics and actions of various misfolded proteins is helping investigators learn more about the similarities and differences across age-related neurodegenerative diseases. This knowledge may someday lead to therapies.

The Aging Process

Another set of insights about the cause of AD comes from the most basic of all risk factors—aging itself. Age-related changes, such as inflammation, may make AD damage in the brain worse. Because cells and compounds that are known to be involved in inflammation are found in AD plaques, some researchers think that components of the inflammatory process may play a role in AD.

Other players in the aging process that may be important in AD are free radicals, which are oxygen or nitrogen molecules that combine easily with other molecules (scientists call them “highly reactive”). Free radicals are generated in mitochondria, which are structures found in all cells, including neurons.

Mitochondria are the cell’s power plant, providing the energy a cell needs to maintain its structure, divide, and carry out its functions. Any given cell has hundreds of mitochondria. This illustration shows two—a healthy mitochondrion and an oxidatively stressed and damaged one. The arrows indicate the movement of free radicals, which can spread easily from damaged mitochondria to other parts of the cell.
The brain’s functions. Energy for the cell is produced in an efficient metabolic process. In this process, free radicals are produced. Free radicals can help cells in certain ways, such as fighting infection. However, because they are very active and combine easily with other molecules, free radicals also can damage the neuron’s cell membrane or its DNA. The production of free radicals can set off a chain reaction, releasing even more free radicals that can further damage neurons (see illustration on page 42). This kind of damage is called oxidative damage. The brain’s unique characteristics, including its high rate of metabolism and its long-lived cells, may make it especially vulnerable to oxidative damage over the lifespan. The discovery that beta-amyloid generates free radicals in some AD plaques is a potentially significant finding in the quest for better understanding of AD as well as for other neurodegenerative disorders and unhealthy brain aging.

Researchers also are studying age-related changes in the working ability of synapses in certain areas of the brain. These changes may reduce the ability of neurons to communicate with each other, leading to increased neuronal vulnerability in regions of the brain important in AD. Age-related reductions in levels of particular growth factors, such as nerve growth factor and brain-derived neurotrophic factor, also may cause important cell populations to be compromised. Many studies are underway to tease out the possible effects of the aging process on the development of AD.

Vascular Disease
For some time now, hints have been emerging that the body’s vast network of small and large blood vessels—the vascular system—may make an important contribution in the development of dementia and the clinical symptoms of AD. Some scientists are focusing on what happens with the brain’s blood vessels in aging and AD. Others are looking at the relationship between AD and vascular problems in other parts of the body.

AD and Vascular Problems in the Brain
The brain requires a constant and dependable flow of oxygen and glucose to survive and flourish. The brain’s blood vessels provide the highways to deliver these vital elements to neurons and glial cells. Aging brings changes in the brain’s blood vessels—arteries can narrow and growth of new capillaries slows down. In AD, whole areas of nervous tissue, including the capillaries that supply
and drain it, also are lost. Blood flow to and from various parts of the brain can be affected, and the brain may be less able to compensate for damage that accumulates as the disease progresses.

For some time now, study of the brain’s blood vessel system in AD has been a productive line of inquiry. One important finding has been that the brain’s ability to rid itself of toxic beta-amyloid by sending it out into the body’s blood circulation is lessened. Some scientists now think that poor clearance of beta-amyloid from the brain, combined with a diminished ability to develop new capillaries and abnormal aging of the brain’s blood vessel system, can lead to chemical imbalances in the brain and damage neurons’ ability to function and communicate with each other. These findings are exciting because they may help to explain part of what happens in the brain during the development of AD. These findings also suggest several new targets for potential AD therapies.

**AD and Vascular Problems in Other Parts of the Body**

Research also has begun to tease out some relationships between AD and other vascular diseases, such as heart disease, stroke, and type 2 diabetes. It is important to sort out the various effects on the brain of these diseases because they are major causes of illness and death in the United States today.

Much of this evidence comes from epidemiologic studies, which compare the lifestyles, behaviors, and characteristics of groups of people

These studies have found, for example, that heart disease and stroke may contribute to the development of AD, the severity of AD, or the development of other types of dementia. Studies also show that high blood pressure that develops during middle age is correlated with cognitive decline and dementia in later life.

Another focus of AD vascular research is the metabolic syndrome, a constellation of factors that increases the risk of heart disease, stroke, and type 2 diabetes. Metabolic syndrome includes obesity (especially around the waist), high triglyceride levels, low HDL (“good cholesterol”) levels, high blood pressure, and insulin resistance (a condition in which insulin does not regulate blood sugar levels very well). Evidence from epidemiologic studies now suggests that people with the metabolic syndrome have increased risk of cognitive impairment and accelerated cognitive decline.

Nearly one in five Americans older than age 60 has type 2 diabetes, and epidemiologic studies suggest that people with this disease may be at increased risk of cognitive problems, including MCI and AD, as they age. The higher risk associated with diabetes may be the result of high levels of blood sugar, or it may be due to other conditions associated with diabetes (obesity, high blood pressure, abnormal blood cholesterol levels, progressive atherosclerosis, or too much insulin in the blood). These findings about diabetes have spurred research on a number of fronts—epidemiologic studies, test tube and animal studies, and clinical trials. The objective of these studies is to learn more about the relationship between diabetes and cognitive problems and to find out in clinical trials whether treating the disease rigorously can positively affect cognitive health and possibly slow or prevent the development of AD.
Lifestyle Factors
We know that physical activity and a nutritious diet can help people stay healthy as they grow older. A healthy diet and exercise can reduce obesity, lower blood cholesterol and high blood pressure, and improve insulin action. In addition, association studies suggest that pursuing intellectually stimulating activities and maintaining active contacts with friends and family may contribute to healthy aging. A growing body of evidence now suggests that these lifestyle factors may be related to cognitive decline and AD. Researchers who are interested in discovering the causes of AD are intensively studying these issues, too.

Physical Activity and Exercise
Exercise has many benefits. It strengthens muscles, improves heart and lung function, helps prevent osteoporosis, and improves mood and overall well-being. So it is not surprising that AD investigators began to think that if exercise helps every part of the body from the neck down, then it might help the brain as well.

Epidemiologic studies, animal studies, and human clinical trials are assessing the influence of exercise on cognitive function. Here are a few things these studies have found:

- Animal studies have shown that exercise increases the number of capillaries that supply blood to the brain and improves learning and memory in older animals.
- Epidemiologic studies show that higher levels of physical activity or exercise in older people are associated with reduced risk of cognitive decline and reduced risk of dementia. Even moderate exercise, such as brisk walking, is associated with reduced risk.
- Clinical trials show some evidence of short-term positive effects of exercise on cognitive function, especially executive function (cognitive abilities involved in planning, organizing, and decision making). One trial showed that older adults who participated in a 6-month program of brisk walking showed increased activity of neurons in key parts of the brain.

More clinical trials are underway to expand our knowledge about the relationship of exercise to healthy brain aging, reduced risk of cognitive decline, and development of AD. (See Participating in a Clinical Trial on page 59 for more information).

Diet
Researchers have explored whether diet may help preserve cognitive function or reduce AD risk, with some intriguing findings. For example, studies have examined specific foods that are rich in antioxidants and anti-inflammatory properties to find out whether those foods affect age-related
In one of these studies, researchers worked with older adults living in New York who ate the “Mediterranean diet”—a diet with lots of fruits, vegetables, and bread; low to moderate amounts of dairy foods, fish, and poultry; small amounts of red meat; low to moderate amounts of wine; and frequent use of olive oil. The researchers found that sticking to this type of diet was associated with a reduced risk of AD and that the association seemed to be driven by the whole approach, rather than by its individual dietary components. A follow-up study found that this pattern also was associated with longer survival in people with AD.

All of these results are exciting and suggestive, but they are not definitive. To confirm the results, scientists are conducting clinical trials to examine the relationship of various specific dietary components and their effect on cognitive decline and AD.

**Intellectually Stimulating Activities and Social Engagement**

Many older people love to read, do puzzles, play games, and spend time with family and friends. All these activities are fun and help people feel alert and engaged in life. Researchers are beginning to find other possible benefits as well, for some studies have shown that keeping the brain active is associated with reduced AD risk. For example, over a 4-year period, one group of researchers tracked how often a large group of older people did activities that involved significant information processing, such as listening to the radio, reading newspapers, playing puzzle games, and going to museums. The researchers then looked at how many of the participants developed AD. The researchers found that

changes in brain tissue. One laboratory study found that curcumin, the main ingredient of turmeric (a bright yellow spice used in curry), can bind to beta-amyloid and prevent oligomer formation. Another study in mice found that diets high in DHA (docosahexaenoic acid), a type of healthy omega-3 fatty acid found in fish, reduced beta-amyloid and plaques in brain tissue.

Other studies have shown that old dogs perform better on learning tasks when they eat diets rich in antioxidants, such as vitamin E and other healthful compounds, while living in an “enriched” environment (one in which the dogs have many opportunities to play and interact with people and other dogs).

Scientists also have examined the effects of diet on cognitive function in people. A very large epidemiologic study of nurses found an association between participants who ate the most vegetables (especially green leafy and cruciferous vegetables) and a slower rate of cognitive decline compared with nurses who ate the least amount of these foods. An epidemiologic study of older adults living in Chicago found the same association. The researchers do not know the exact reason behind this association, but speculate that the beneficial effects may result from the high antioxidant and folate content of the vegetables.

Dietary studies, such as the curcumin study in mice or the vegetables study in nurses, generally examine individual dietary components so that scientists can pinpoint their specific effects on an issue of interest. This approach has obvious limitations because people do not eat just single foods or nutrients. Several recent epidemiologic studies have taken a different approach and looked at an entire dietary pattern.
the risk of developing AD was 47 percent lower in the people who did them the most frequently compared with the people who did the activities least frequently. Another study supported the value of lifelong learning and mentally stimulating activity by finding that, compared with older study participants who may have had AD or who had AD, healthy older participants had engaged in more mentally stimulating activities and spent more time at them during their early and middle adulthood.

Studies of animals, nursing home residents, and people living in the community also have suggested a link between social engagement and cognitive performance. Older adults who have a full social network and participate in many social activities tend to have less cognitive decline and a decreased risk of dementia than those who are not socially engaged.

The reasons for these findings are not entirely clear, but a number of explanations are possible. Among them:

- Intellectually stimulating activities and social engagement may protect the brain in some way, perhaps by establishing a cognitive reserve.
- These activities may help the brain become more adaptable and flexible in some areas of mental function so that it can compensate for declines in other areas.
- Less engagement with other people or in intellectually stimulating activities could be the result of very early effects of the disease rather than its cause.
- People who engage in stimulating activities may have other lifestyle qualities that may protect them against developing AD.

**Describing Scientific Findings: The Type of Study Makes an Important Difference**

These days, the media are full of stories about scientific studies. It can be hard to know what to conclude about their findings. Knowing how the study was conducted can help put the results into the right perspective.

One main type of research is the epidemiologic study. These studies are observational—they gather information about people who are going about their daily lives. Study participants follow many behaviors and practices. It is difficult, therefore, to determine the exact benefits or risks of one particular behavior from among all the healthy or harmful behaviors followed by the participants. That is why, in epidemiologic studies of AD, scientists only say that a finding is "associated with" AD, or not. The epidemiologic evidence linking a behavior and AD is, at best, suggestive, but we do not know that the behavior by itself actually helps to cause or prevent AD.

Other types of research—test tube studies and studies in animals—add to the findings from epidemiologic studies. Scientists use them to examine the same issue but in ways in which the various factors that might influence a result are controlled to a greater degree. This element of control allows scientists to be more certain about why they get the results they do. It also allows them to be more definitive in the words they use to describe their results. Of course, showing a cause-and-effect relationship in tissue samples or even in animal studies still does not mean that the relationship will be the same in humans. Clinical trials in humans are the gold standard for deciding whether a behavior or a specific therapeutic agent actually prevents or delays AD
New Techniques Help in Diagnosing AD

A man in his mid-60s begins to notice that his memory isn’t as good as it used to be. More and more often, a word will be on the tip of his tongue but he just can’t remember it. He forgets appointments, makes mistakes when paying his bills, and finds that he’s often confused or anxious about the normal hustle and bustle of life around him. One evening, he suddenly finds himself walking in a neighborhood he doesn’t recognize. He has no idea how he got there or how to get home.

Not so long ago, this man’s condition would have been swept into a broad catch-all category called “senile dementia” or “senility.” Although we now know that AD and other causes of dementia are distinct diseases, in the early stages it is difficult to differentiate between the onset of AD and other types of age-related cognitive decline. We have improved our ability to diagnose AD correctly, and doctors experienced in AD can diagnose the disease with up to 90 percent accuracy. A definitive diagnosis of AD, however, is still only possible after death, during an autopsy, and we are still far from the ultimate goal—a reliable, valid, inexpensive, and early diagnostic marker that can be used in any doctor’s office.

Early diagnosis has several advantages. For example, many conditions cause symptoms that mimic those of AD. Finding out early that the observed changes in cognitive abilities are not AD but something else is almost always a relief and may be just the prod needed to seek appropriate medical treatment (see Causes of Dementia on page 50 for more information). For the small percentage of dementias that are treatable or even reversible, early diagnosis increases the chances of successful treatment. Increasing early diagnosis and improving treatment are among NIA’s most important goals.

Even when the cause of a loved one’s dementia turns out to be AD, it is best to find out sooner rather than later. One benefit of knowing is medical. The drugs now available to treat AD can help some people maintain their mental abilities for months to years, although they do not change

Other benefits are practical. The sooner the person with AD and the family have a firm diagnosis, the more time they have to make future living arrangements, handle financial matters, establish a durable power of attorney and advance directives, deal with other legal issues, create a support
Current Tools for Diagnosing AD

With the tools now available, experienced physicians can be reasonably confident about making an accurate diagnosis of AD in a living person. Here is how they do it.

They take a detailed patient history, including:
- A description of how and when symptoms developed.
- A description of the person’s and his or her family’s overall medical condition and history.
- An assessment of the person’s emotional state and living environment.

They get information from family members or close friends:
- People close to the person can provide valuable insights into how behavior and personality have changed; many times, family and friends know something is wrong even before changes are evident on tests.

They conduct physical and neurological examinations and laboratory tests:
- Blood and other medical tests help determine neurological functioning and identify possible non-AD causes of dementia.

They conduct neuropsychological testing:
- Question-and-answer tests or other tasks that measure memory, language skills, ability to do arithmetic, and other abilities related to brain functioning help show what kind of cognitive changes are occurring.

They may do a computed tomography (CT) scan or a magnetic resonance imaging (MRI) test:
- CT and MRI scans can detect strokes or tumors or can reveal changes in the brain’s structure that indicate early AD.

Exams and tests may be repeated every so often to give physicians information about how the person’s memory and other symptoms are changing over time.

Based on findings from these exams and tests, experienced physicians can diagnose or rule out other causes of dementia, or determine whether the person has MCI, “possible AD” (the symptoms may be due to another cause), or “probable AD” (no other cause for the symptoms can be found).

network, and even consider joining a clinical trial or other research study. Being able to participate for as long as possible in making personal decisions is important to many people with AD.

Early diagnosis also gives families time to recognize that life does not stop with a diagnosis of AD. The person is still able to participate in many of the daily activities he or she has always enjoyed, and families can encourage the person to continue with them for as long as possible. Finally, early diagnosis gives family caregivers the opportunity to learn how to recognize and cope with changes over time in their loved one as well as to develop strategies that support their own physical, emotional, and financial health.
Dementia is the loss of cognitive functioning—thinking, remembering, and reasoning—to such an extent that it interferes with a person’s daily life and activities. It is not a disease itself, but a group of symptoms that often accompanies a disease or condition. Some dementias are caused by neurodegenerative diseases. Dementia also has other causes, some of which are treatable.

### Neurodegenerative Diseases that Cause Dementia
- Alzheimer’s disease
- Vascular dementia
- Parkinson’s disease with dementia
- Frontotemporal lobar degeneration, including:
  - frontotemporal dementia
  - frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)
- Pick’s disease
- supranuclear palsy
- corticobasal degeneration

### Other Causes of Dementia
- Medication side effects
- Depression
- Vitamin B₁₂ deficiency
- Chronic alcoholism
- Certain tumors or infections of the brain
- Blood clots pressing on the brain
- Metabolic imbalances, including thyroid, kidney, or liver disorders

Scientists also see advantages to early diagnosis. Developing tests that can reveal what is happening in the brain in the early stages of AD will help them understand more about the cause and development of the disease. It also will help scientists learn when and how to prescribe the use of drugs and other treatments so they can be most effective.

### Exciting New Developments in AD Diagnosis
Scientists are now exploring ways to help physicians diagnose AD earlier and more accurately. For example, some studies are focusing on changes in mental functioning. These changes can be measured through memory and recall tests. Tests that measure a person’s abilities in areas such as abstract thinking, planning, and language can help pinpoint changes in these areas of cognitive function. Researchers are working to improve standardized tests that might be used to point to early AD or predict which individuals are at higher risk of developing AD in the future.

Other studies are examining the relationship between early damage to brain tissue and outward clinical signs. Still others are looking for changes in biomarkers in the blood or cerebrospinal fluid that may indicate the progression of AD.

One of the most exciting areas of ongoing research in this area is neuroimaging. Over the past decade, scientists have developed several
highly sophisticated imaging systems that have been used in many areas of medicine, including AD. PET scans, **single photon emission computed tomography** (SPECT), and MRI are all examples. These “windows” on the living brain may help scientists measure the earliest changes in brain function or structure in order to identify people who are at the very first stages of the disease—well before they develop clinically apparent signs and symptoms.

To help advance this area of research, NIA launched the multi-year AD Neuroimaging Initiative (ADNI) in 2004. This project is following about 200 cognitively healthy individuals and 400 people with MCI for 3 years and 200 people with early AD for 2 years. Over the course of this study, participants undergo multiple MRI and PET scans so that study staff can assess how the brain changes in the course of normal aging and MCI, and with the progression of AD. By using MRI and PET scans at regularly scheduled intervals, study investigators hope to learn when and where in the brain degeneration occurs as memory problems develop.

Another innovative aspect of ADNI is that scientists are correlating the participants’ imaging information with information from clinical, memory, and other cognitive function tests, and with information from blood, cerebrospinal fluid, and urine samples. Results from these samples may provide valuable biomarkers of disease progress, such as changing levels of beta-amyloid and tau, indicators of inflammation, measures of oxidative stress, and changing cognitive abilities.

An important ADNI achievement is the creation of a publicly accessible database of images, biomarker data, and clinical information available to qualified researchers worldwide.

Biological samples also are available for approved biomarker projects. NIA hopes that this initiative will help create rigorous imaging and biomarker standards that will provide measures for the success of potential treatments. This would substantially increase the pace and decrease the cost of developing new treatments. The ADNI study is being replicated in similar studies by researchers in Europe, Japan, and Australia.

These types of neuroimaging scans are still primarily research tools, but one day they may be used more commonly to help physicians diagnose AD at very early stages. It is conceivable that these tools also may someday be used to monitor the progress of the disease and to assess responses to drug treatment.
Traditionally, AD scientists have collected data by asking people to come to a clinic once or twice a year over a period of years. They give the participants a physical exam and ask them to take a series of memory, language, and other cognitive function tests. These studies collect much useful information, but they have their limitations. For one thing, participants are seen only once or twice during the year, so the data collected represent only a “snapshot” in time. The studies cannot effectively capture day-to-day fluctuations in behaviors and cognitive abilities. Another limitation is that participants are seen in a research setting, not in their natural community environment. For many, coming to the clinic can be inconvenient, difficult, or both.

Advances in technology, as shown in the two research projects described here, offer some hope for dealing with these challenges by bringing research to people right in their own homes.

**MOTION DETECTORS TELL AN INTERESTING STORY**

Scientists who are trying to develop methods for diagnosing AD as early as possible continually grapple with two challenges in conducting their research. First, they need to find easy and accurate ways to collect data from older people, who often have physical, emotional, or cognitive problems. Second, they need to find ways to assess accurately the very early changes in physical or cognitive abilities that could indicate that AD is progressing.

Under an NIA grant, the Oregon Center for Aging and Technology (ORCATECH) at Oregon Health & Science University is exploring the use of unobtrusive, simple technology and intelligent systems to detect and monitor subtle changes in movement that may indicate age-related cognitive changes. This project is building on research that has suggested that motor-function changes may arise before memory changes become apparent (see Very Early Signs and Symptoms on page 28 for more on this research).

All of the 300 study participants are 80 years or older or have a spouse of a similar age, and live independently in Portland-area retirement communities. Wireless, infrared motion sensors, like those used to automatically open grocery store doors, have been placed strategically throughout the participants’ homes to gather data about changes in their walking or dressing speed over time. Special software also has been installed on each participant’s home computer to measure motor skills and speed in typing or using a mouse. The sensors and computer software collect data about motion, not what the volunteer is actually doing. Privacy is largely not a concern therefore, because the volunteers are not directly observed and no video or photographs are taken.

The 3-year study began in early 2007, so results are not yet available. However, a small pilot study using the same type of sensors showed a clear difference in the walking speeds of people age 65 and older who had MCI, compared with cognitively healthy people of the same age, over time periods of nearly a year. These data suggest that a remote sensing system like this is a feasible technology and is potentially sensitive enough to distinguish accurately between affected and unaffected people.
USING TECHNOLOGY TO COLLECT DATA AT HOME

Researchers at nearly 30 sites nationwide are comparing various ways of collecting data, including the use of an in-home “kiosk” that combines a touch-screen computer monitor with a telephone handset, an interactive voice-response system, and traditional mail and telephone. All three methods gather the same data about several areas known to be important in early detection of cognitive decline: memory; language skills; attention and concentration; activities of daily living; quality of life; health care and resource use; and changes in “global” well-being as measured by self-rating of health, cognition, and mood. This study is looking at questions such as how likely people are to complete the questions using each method, which method is the most efficient, and how sensitive each method is.

Having a data collection system that is easy to use and that collects data accurately and completely may encourage wider participation in AD clinical trials. It also may reduce the expense and burden of conducting AD research. Early results from this study show that the older participants were skeptical at first about using the kiosk, but once they learned how to use it, they became enthusiastic and excited about participating.

This photo shows ORCATECH study participants at home. The small device between the photographs on the wall is an infrared motion sensor.
The Search for New Treatments

More and more, scientists are able to think about ways to treat, slow, or perhaps even prevent AD at a number of possible points during the years-long continuum of disease progression. This continuum begins with the very earliest disease stage, even before symptoms are evident, moves to the first signs of memory and cognitive problems, then continues through the mild and moderate stages, and ends with the very late stages and the person’s death.

As a result, researchers who focus on developing AD treatments think a lot about the importance of timing: When would it be best to intervene and what interventions are most appropriate at which time? These questions are similar to those asked with other conditions, such as heart disease. For example, a physician would prescribe different treatments for a patient who is seemingly healthy but who is at risk of having future heart disease than for a patient who is actually having a heart attack or whose heart disease is well established. The same decision process now can be applied to AD.

It has become clear that there probably is no single “magic bullet” that will, by itself, prevent or cure AD. Therefore, investigators are working to develop an array of options from which physicians can choose. For people who already have AD, the most immediate need is for treatments to control cognitive loss as well as problem behaviors, such as aggression, agitation, wandering, depression, sleep disturbances, hallucinations, and delusions. Safe medications that remain effective over time are needed to ease a broad range of symptoms and to improve a person’s cognitive function and ability to carry out activities of daily living. Scientists also are investigating treatments that combine medications with lifestyle strategies to lessen the risk of developing cognitive decline or AD. Eventually, scientists hope to develop treatments that attack the earliest manifestations and underlying causes of AD, thereby slowing, delaying, or preventing the disease from progressing and damaging cognitive function and quality of life. Scientists use clinical trials to pursue all these goals.

Today, NIA, other NIH institutes, and private industry are conducting many clinical trials of AD interventions (see page 59 for more about clinical trials). These studies focus on several key areas:

- Helping people with AD maintain their mental functioning
- Managing symptoms
- Slowing, delaying, or preventing AD
HELPING PEOPLE WITH AD MAINTAIN THEIR MENTAL FUNCTIONING

In the mid-1970s, scientists discovered that levels of a neurotransmitter (a chemical that carries messages between neurons) called acetylcholine fell sharply in people with AD. This discovery was one of the first that linked AD with biochemical changes in the brain. Scientists found that acetylcholine is a critical player in the process of forming memories. It is used by neurons in the hippocampus and cerebral cortex, which are areas of the brain important to memory function. This discovery was an important initial breakthrough in the search for drugs to treat AD.

Four medications, tested in clinical trials, have been approved by the FDA for use in treating AD symptoms. Donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®) are prescribed to treat mild to moderate AD symptoms. Donepezil was recently approved to treat severe AD as well. These drugs, known as cholinesterase inhibitors, act by stopping or slowing the action of acetylcholinesterase, an enzyme that breaks down acetylcholine. They help to maintain higher levels of acetylcholine in the brain. In some people, the drugs maintain abilities to carry out activities of daily living. They also may maintain some thinking, memory, or speaking skills, and can help with certain behavioral symptoms. However, they will not stop or reverse the underlying progression of AD and appear to help people only for months to a few years. The newest approved AD medication is memantine (Namenda®), which is prescribed to treat moderate to severe AD symptoms. This drug appears to work by regulating levels of glutamate, another neurotransmitter involved in memory function. Like the cholinesterase inhibitors, memantine will not stop or reverse AD.
MANAGING SYMPTOMS

“My father is often agitated. He paces up and down, wringing his hands and crying. I know he’s sad or anxious about something but he can’t tell me what’s bothering him. Asking him about it just makes him more upset.”

“Last week, I visited Mom in the nursing home. We had a great time. Then yesterday, I went to see her again. When I walked into her room, she didn’t know me. She thought I was her sister.”

“My husband used to be such an easy going, calm person. Now, he suddenly lashes out at me and uses awful language. Last week, he got angry when our daughter and her family came over and we sat down to eat. I never know when it’s going to happen. He’s changed so much—it scares me sometimes.”

“Gran hums all the time. She used to be a singer. Is she trying to relive her past?”

As AD begins to affect memory and mental abilities, it also begins to change a person’s emotions and behaviors. Between 70 and 90 percent of people with AD eventually develop one or more behavioral symptoms. These symptoms include sleeplessness, wandering and pacing, aggression, agitation, anger, depression, and hallucinations and delusions. Some of these symptoms may become worse in the evening (a phenomenon called “sundowning”) or during daily routines, especially bathing.

The damage of AD affects many different parts of the brain. This presents a problem because even small tasks require the brain to process signals that often involve more than one region of the brain. If this processing is disrupted because of AD, the person may not be able to do the task or may act in a strange or inappropriate way.

In light of our growing understanding about the effects of AD on the brain, behaviors like the ones highlighted above suddenly make sense or even provide a loving opportunity for caregivers:

For a man who can no longer distinguish between past and present, the anguish caused by the death of a parent may be as real today as it was many years before.

Sitting down to a family meal may produce intense anxiety when a person has no idea what to do with the knife and fork in front of him and all the conversation and activity feel overwhelming.

Memories of favorite songs from long ago resurface and provide a compelling link to a happy time in the past.

Behavioral symptoms, often emotional and upsetting, are one of the hardest aspects of the disease for families and other caregivers to deal with. They are also a visible sign of the terrible change that has taken place in the person with AD. Researchers are slowly learning more about why behavioral symptoms occur and are conducting clinical trials on new treatments—both drug and non-drug—to deal with difficult behaviors.
SLOWING, DELAYING, OR PREVENTING AD

AD research has developed to the point where scientists are looking beyond treating symptoms to addressing the underlying disease process. Slowing the progress of AD could do much to maintain the functioning of people with AD and reduce physical and emotional stress on caregivers. Delaying AD’s effects also could help to postpone or prevent placement in an assisted living facility or nursing home, and reduce the financial costs of the disease. Preventing AD altogether is, of course, the ultimate long-term goal.

NIA and pharmaceutical companies support treatment clinical trials that are aimed at slowing, delaying, or preventing AD. The advances in our knowledge about the mechanisms and risk factors associated with AD have expanded the types of interventions under study. These trials are examining a host of possible interventions, including cardiovascular treatments, hormones, type 2 diabetes treatments, antioxidants, omega-3 fatty acids, immunization, cognitive training, and exercise, among others.

For example, NIA funds pilot trials to learn whether treating one or another aspect of type 2 diabetes will affect cognitive health and AD progression. A pilot trial is a relatively small clinical trial that collects initial data on the safety, effectiveness, and best dosage of a potential treatment. This information helps investigators decide which treatments should be tested in larger, full-scale trials. One 4-month pilot trial has examined the effects on AD of administering a nasal-spray form of insulin. This trial is founded on evidence that AD is associated with reduced levels of insulin in cerebrospinal fluid and that treatment with insulin improves memory performance. The trial will provide useful data on the safety, feasibility, and potential effectiveness of this innovative treatment approach. Investigators may be able to use the results to plan future full-scale clinical trials.

Beyond pilot studies, investigators also are conducting full-scale AD clinical trials of various interventions. One of these trials, the Alzheimer’s Disease Cooperative Study (ADCS), is testing whether one omega-3 fatty acid (DHA), found in the oil of certain fish, can slow the progression of cognitive and functional decline in people with mild to moderate AD. During the 18-month clinical trial, investigators will measure the progress of the disease using standard tests for functional and cognitive change. Researchers also will evaluate whether taking DHA supplements has a positive effect on possible physical and biological markers of AD, such as brain atrophy...
and proteins in blood and spinal fluid. The ADCS is a federally established consortium conducting clinical trials on AD, with sites across the United States and Canada.

Full-scale AD prevention trials are underway as well. One such trial, Prevention of Alzheimer’s Disease with Vitamin E and Selenium (PREADVISE), is being conducted in conjunction with a National Cancer Institute-funded trial called the Selenium and Vitamin E Cancer Prevention Trial (SELECT). SELECT is evaluating whether taking selenium and/or vitamin E supplements can prevent prostate cancer in healthy men older than 60 years. PREADVISE is evaluating whether these supplements can help prevent memory loss and dementia by protecting brain cells from oxidative
Rapid advances in our knowledge about AD have led to the development of many promising new drugs and treatment strategies. However, before these new strategies can be used in clinical practice, they must be shown to work in people. This means that clinical trials—and volunteer participants—are an essential part of AD research. Advances in prevention and treatment are possible thanks to volunteers who participate in clinical trials.

Clinical trials are the primary way that researchers find out if a promising treatment is safe. Clinical trials tell researchers which treatments are the most effective and for which people they may work best. Trials can take place in various settings, such as private research facilities, teaching hospitals, specialized AD research centers, and doctors’ offices. FDA approval is necessary before scientists can begin a clinical trial.

Participating in a clinical trial is a big step for anyone, including people with AD and their caregivers. That is why physicians and clinical trials staff spend time talking with participants about what it is like to be in a trial and the pros and cons of participating. It is also why they get a signed informed consent form before a person enrolls in a trial. Here are some facts that potential participants might want to know about clinical trials.

**WHAT KIND OF TRIALS ARE THERE?**
Treatment trials with existing drugs or behavioral strategies assess whether an intervention already approved for other purposes may be useful in treating age-related cognitive decline or AD. For example, trials have tested whether drugs used to lower cholesterol help slow progression of AD.

Treatment trials with experimental drugs or strategies show whether a new drug or treatment approach can help improve cognitive function or lessen symptoms in people with AD, slow the progression to AD, or prevent it. Interventions tested in these trials are developed from knowledge about the mechanisms involved in the AD process. Experimental drugs, for example, are first tested in tissue culture and in animals to determine their actions in the body. Safety and effectiveness studies are also conducted in animals before the compounds are tested in humans.

**WHAT ARE THE PHASES OF CLINICAL TRIALS?**
During Phase I trials, a research team gives the treatment to a small number of participants and examines its action in the body and its safety. The main goals of Phase I trials are to establish the highest dose of a new drug that people can tolerate and to define the dose at which people may begin to experience harmful side effects. These trials generally last only a few months.

If results show that the treatment appears to be safe, it will go on to Phase II and Phase III clinical trials. Phase II trials involve larger numbers of people studied over longer periods of time than Phase I trials. In these trials, the study team wants to know whether the treatment is safe and effective at changing the course of the disease. Phase II trials occasionally also involve the use of a placebo (an inactive substance that looks like the study drug). Results from Phase II trials give study staff an indication of the effective dose to take into Phase III trials. Phase III trials are large studies that compare an experimental treatment with a placebo or standard treatment to determine safety and efficacy (whether the treatment has the power to produce an effect).

After these phases are complete.

*Continued on next page*
and investigators are satisfied that the treatment is safe and effective, the study team may submit its data to the FDA for approval. FDA experts review the data and decide whether to approve the drug or treatment for use in patients with the disease under study.

WHAT HAPPENS WHEN A PERSON SIGNS UP FOR A CLINICAL TRIAL?
First, it is important to learn about the trial. Staff at the clinical research center explain the trial in detail to potential participants and describe possible risks and benefits. Staff also talk about the participants’ rights as research volunteers, including their right to leave the trial at any time. Participants and their family members are entitled to have this information repeated and explained until they feel they understand the nature of the trial and any potential risks.

After all questions have been answered, participants who are still interested in joining the trial are asked to sign an informed consent form. In some cases, a participant may no longer be able to provide informed consent because of problems with memory and thinking. In such cases, it is still possible for an authorized representative (usually a family member) to give permission for the person to participate. Laws and regulations regarding informed consent differ across States and research institutions, but all are intended to ensure that participants are protected and well cared for.

Next, people go through a screening process to see if they qualify to participate in the trial. If they qualify and can safely participate, then they are enrolled in the trial.

WHAT HAPPENS DURING A TRIAL?
If participants agree to join the trial and an evaluation process shows they meet all the criteria for participation, then a “baseline” visit is scheduled with the trial staff. This visit generally involves cognitive and physical tests. This gives the team information against which to measure future mental and physical changes.

In most clinical trials, participants are randomly assigned to different study groups so that each study group has people in it of about the same average characteristics (such as age, sex, educational level, or cognitive ability). One group, the test group, receives the experimental drug or intervention. Other groups may receive a different drug, a placebo, or a different intervention. Comparing results for different groups gives researchers confidence that changes in the test group are the result of the experimental treatment and not some other factor, such as the placebo effect (this is when people feel an effect because they think they are getting the test medication even though they are really getting a placebo). In many trials, no one—not even the research team—knows who is getting the treatment and who is getting the placebo or other intervention. This means that the participant, family member, and the staff are “blind” to the treatment being received. This kind of trial is called a double-blind, placebo-controlled trial.

As the trial progresses, participants and family members usually must follow strict medication or treatment instructions and keep detailed records of symptoms. Every so often, participants visit the clinic or research center to have physical and cognitive exams, give blood and urine samples, and talk with trial staff. These visits allow the investigators to collect information on the effects of the test drug or treatment, see how the disease is progressing, and see how the participant and the caregiver are doing.
WHAT SHOULD PEOPLE CONSIDER BEFORE PARTICIPATING IN A CLINICAL TRIAL?

People who have participated in AD clinical trials say that it’s a good idea to consider the following issues before deciding to join a trial.

- **Expectations and motivations.** The test drug or treatment may relieve a symptom, change a clinical measurement, or reduce the risk of death, but clinical trials generally do not have miraculous results and participants may not receive any direct benefit. With a complex disease like AD, it is unlikely that one treatment will cure or prevent the disease. Some people choose not to participate or decide to drop out of a study because this reality does not meet their expectations. Others choose to stay in a trial because they realize that even if they get no or only a slight benefit, they are making a valuable contribution to knowledge that will help people in the future.

- **Uncertainty.** Some families have a hard time with the uncertainties of participation—for example, not knowing whether the person is taking the test treatment, a placebo, or a control treatment, not being able to choose which study group to be in, or not knowing for a long time whether the study was successful. Ongoing and open communication with study staff can help to reduce this frustration.

- **Finding the right clinical trial.** Some clinical trials involve participants who are cognitively healthy or have only mild symptoms because they are testing a drug that might delay a decline in cognitive function. Other trials involve participants who have more advanced AD because they are testing a treatment that might lessen behavioral symptoms. Or, a trial may be testing new strategies to help caregivers. Even if a participant is not eligible for one trial, another trial may be just right.

- **The biggest benefit of all.** Many families find that the biggest benefit of participating in a clinical trial is the regular contact with the study team. These visits provide an opportunity to get state-of-the-art AD care and to talk regularly with AD experts who have lots of practical experience and a broad perspective on the disease. The study team understands and can provide advice about the emotional and physical aspects of the person with AD and the caregivers’ experience. Team members can suggest ways to cope with the present and give insights into what to expect in the future. They also can share information about support groups and other helpful resources.

**FOR MORE INFORMATION**

To learn more about AD clinical trials, visit the Alzheimer’s Disease Education and Referral (ADEC) Center’s Clinical Trials Database website (www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials). This NIA website includes a list of AD and dementia clinical trials currently in progress at research centers throughout the United States. It also provides information about the phases of clinical trials and how to participate, explains the drug development process, and provides links to other useful websites. Also, visit the clinical trials websites of the National Institutes of Health (www.clinicaltrials.gov) or the Alzheimer’s Association (www.alz.org).
One of the greatest costs of AD can be the physical and emotional toll on family members, caregivers, and friends of people with the disease. The changes in a loved one’s personality and mental abilities; the need to provide constant, loving attention for years on end; and the demands of bathing, dressing, and other caregiving duties in the later stages of the disease can be hard to bear. Many caregivers must assume new and unfamiliar roles in the family, and these changes can be both difficult and sad. Not surprisingly, caregivers of people with dementia spend significantly more time on caregiving tasks than do caregivers of people with other types of illnesses.

One of the hardest decisions that many families face is whether and when to place a loved one with AD in a nursing home or other type of care facility. Once this decision is made, families must decide what type of care is best for the person and the family. Many investigators are working to identify strategies that can lead to improved quality of care in various facilities, including adult day care centers, assisted living facilities, continuing care retirement communities, nursing homes, and special care units (separate areas within nursing homes or assisted living facilities designed especially for people with dementia).

Who Are AD Family Caregivers?

Many primary caregivers are family members, and NIA-funded research has shown that the value of informal family caregiving of people with cognitive impairment adds up to billions of dollars every year. Who are these family caregivers?

**Spouses:** This is the largest group of caregivers. Most are older, too, and many have their own health problems.

**Daughters:** The second largest group of primary caregivers is daughters. Many are married and raising children of their own. Juggling two sets of responsibilities is often tough for these members of the “sandwich generation.”

**Daughters-in-law:** Many women in this group help take care of an older person with AD. They are the third largest group of family caregivers.

**Sons:** Although many are involved in the daily care of a parent with AD, sons often focus on the financial, legal, and business aspects of caregiving.

**Brothers and sisters:** Siblings may assume primary responsibility for care if they live close by. Many of these caregivers also are older and may be coping with their own frailties or health problems.

**Grandchildren:** Older children may become major helpers in caring for a grandparent with AD. Grandchildren may need extra support if their parents’ attention is heavily focused on the ill grandparent or if the grandparent with AD lives in the family’s home.
Although research on family caregiver support is still in its early days, we have already learned much about the unique aspects of caregivers’ personalities and situations. For example, it is well established that AD caregivers often experience stress, anxiety, depression, and other mental health problems as a result of the continuing and demanding nature of AD care. This chronic stress can have detrimental effects on the physical health of caregivers. The physical and emotional effects of AD caregiving can last a long time, even after the death of the person with AD.

On the other hand, research also has shown that caregiving can have important positive effects, including:

- A new sense of purpose or meaning in life
- Fulfillment of a lifelong commitment to a spouse
- An opportunity to give back to a parent some of what the parent has given to them
- Renewal of religious faith
- Closer ties with people through new relationships or stronger existing relationships

AD caregivers do not all have the same psychological and physical response to caregiving. For example, caregivers who have strong support systems and well-developed coping skills may be able to weather the stresses of caring for a loved one with AD. Others who have few breaks from caregiving responsibilities and/or have preexisting illnesses may be more vulnerable to the physical and emotional stresses associated with dementia care. Caregiver research is beginning to discover effective ways to ease the burden of caregiving. Researchers have learned that:

- The information and problem-solving needs of caregivers evolve over time as AD progresses.

Therefore, support programs should be tailored to the needs of the caregiver at various stages of caregiving. Programs can respond by offering
services and information geared to different stages of the disease.

- **Traditions and attitudes about caregiving vary across cultural groups.** For example, some researchers have found that African-American caregivers use fewer formal in-home services than do white caretakers. Some populations may find it difficult to publicly admit that a family member has AD and may be reluctant to seek help with caregiving issues. Therefore, programs and services for caregivers must be culturally appropriate and sensitive to factors that positively and negatively influence caregivers’ attitudes and ability to carry out their responsibilities.

- **Use of multiple types of support over an extended period of time helps caregivers.** For example, the Resources for Enhancing Alzheimer’s Caregiver Health (REACH) clinical trial showed that caregivers who received 6 months of intensive help with caregiving strategies had significant improvements in overall quality of life. They also had lower rates of clinical depression compared to caregivers who did not participate in the program. The caregiving strategies included information sharing, instruction, role plays, problem-solving, skills training, stress-management techniques, and telephone support groups. Caregivers reported that taking part in REACH helped them feel more confident in working with their loved ones, made life easier for them, improved their caregiving ability, improved the care recipient’s life, and helped them keep their loved one at home.

- **Developing ways to help caregivers become educated about AD, improve flexibility in responding to caregiving demands, and learn a variety of practical strategies can help.** Studies are teaching caregivers how to read the emotional and physical cues of the person with AD and to understand the sequence of events that often leads to inappropriate behaviors. They are also helping caregivers respond to the needs of the person with AD in a variety of creative ways, such as maintaining flexibility in the face of many demands, becoming educated about the disease, learning practical strategies, using available
Helping caregivers deal with the complicated issue of whether and when to place a loved one in a nursing home is an important aspect of caregiver support. People with dementia are at much greater risk of nursing home placement than are other older people of the same age. Placing a loved one in a nursing home may relieve some of the burden of caregiving, but it does not necessarily reduce caregiver stress or emotional distress. Moreover, nursing home costs now average more than $70,000 per year.

One clinical trial tested the effects of an enhanced counseling and support program on nursing home placement and caregiver health. This program for caregivers consisted of six sessions of individual and family counseling, support group participation, and on-demand telephone counseling. Participants in the program were able to delay placement of their loved ones in nursing homes by about 18 months. Researchers attributed the effects of the program to greater tolerance for memory and behavior problems in the person with AD, improved satisfaction with the support provided by family and friends, and fewer symptoms of depression. Moreover, it appears that the extra time at home did not come at the expense of the caregivers’ sense of well-being.

Helping caregivers stay physically active has big benefits. Researchers have found that regular moderate exercise is an important stress reliever for caregivers. Exercise helps to reduce blood pressure increases due to stress, improves sleep quality, and reduces psychological distress and depression.

EARLY-STAGE AD SUPPORT GROUPS: A VITAL SOURCE OF HELP

For families and friends who care for a person with AD, talking with others who are going through the same experience can be a vital lifeline. AD support groups provide a place where caregivers can seek respite, express concerns, share experiences, get tips, and receive emotional comfort. NIA-funded Alzheimer’s Disease Centers, the Alzheimer’s Association, and many other organizations sponsor in-person and online AD support groups all around the country.

Improved diagnostic tests and increasing awareness of AD mean that more and more people are now being diagnosed at early stages of AD. People
in the early stages often still have good coping skills and are intensely aware of themselves and their symptoms. They also may feel considerable distress, embarrassment, and isolation because of a perceived stigma associated with the disease. As a result, a growing number of people with early-stage AD and their family members are looking for coping strategies, meaningful activities, and mental stimulation. They are eager to educate themselves about AD, share common experiences, and break the potential barriers and isolation caused by their diagnosis. This has led to the formation of early-stage support groups specifically designed to meet their needs.

Some early-stage support groups follow a structured model, with 1- to 2-hour sessions scheduled over 6 to 8 weeks. The sessions are led by a facilitator and discussion topics are determined in advance. Guest speakers provide information and help on specific topics such as legal and financial planning. In some programs, the person with AD and the caregiver meet in separate groups; in others, people with AD and their caregivers are together for part of the session and apart for the remainder.

Other types of early-stage support groups are less structured. Members discuss topics of their own choosing, and the groups meet regularly over an extended time. Members with AD may stay in the group as long as they are able to meaningfully take part in the discussion and activities.

Early-stage support groups are not for everyone. Some people with early AD and their families may not benefit because of family conflict, denial, cognitive impairment, or discomfort with the intimacy of a group experience. However, most participants report positive outcomes, such as a greater sense of control over their lives and feelings that they are not alone. Many participants find early-stage support groups helpful because they instill a spirit of camaraderie, build coping skills, and forge relationships and emotional support that continue to help the person with AD and the caregiver even after the sessions end.
Taking Care of Mom or Dad at a Distance

Taking care of a parent with AD who lives hundreds of miles away is a real worry facing many adults. “How can we make sure Mom gets the best care possible if we’re not there all the time?” “What can I do to help Dad live at home for as long as possible?”

That was the dilemma facing Ken Nixon and his two brothers in 2001. Their mother lived in an Arkansas farming community and wanted to stay there. Ken and his brothers lived 3 to 5 hours away—close, but not close enough.

With funding from NIA, Ken and his brothers created a multi-purpose, Internet-based system called AttentiveCare that is currently available to others faced with the same long-distance caregiving challenges. Back in 2001, broadband Internet service had just become available in their mother’s community, so the brothers decided to see whether videoconferencing could be a way to keep in touch with her. They installed a computer with a video camera in her home so they could check on her daily, helping fulfill her wish to continue living independently on the family farm while assuring themselves that she was faring well.

“We had a need, and we patched the system together at first,” says Ken. “It exceeded our expectations in being able to keep our mother independent and connected to the family. We could call and have coffee with her every morning, and it got her day started off right. She had something to look forward to every day—one or two of her boys was going to visit.”

After 6 months of using the home-grown system, Nixon decided to develop it to help other caregivers. In 2003, he applied for and received a grant from NIA to refine the AttentiveCare prototype and test its feasibility in providing informal, long-distance care to people with AD.

He later received another grant to evaluate the software, services, and caregiver usage and benefits of the system in a variety of caregiving situations. The participants in this study are distance caregivers of persons with early- to moderate-stage AD who had the AttentiveCare system installed in their own homes and the homes of their family members with AD.

AttentiveCare now features videoconferencing, multimedia reminders to help care recipients function independently, and slide shows to keep care recipients connected with family. The system’s journal and data logging capability also allows family caregivers to maintain and share information about the care recipient’s health and well-being, whether they are across the street or thousands of miles away.

Ken Nixon and his grandson use AttentiveCare to check in with Ken’s mother.
Conclusion

The future builds upon the events and experiences of the past. That’s certainly true of AD research. Our knowledge of AD is advancing rapidly, and we have much to celebrate in our scientific successes.

At the same time, we cannot forget that AD remains an urgent problem for our Nation. The challenge is to continue building on these discoveries so that we can create a brighter future in which the potential of successfully managing AD or even preventing this terrible disease can become a reality.
Acetylcholine—a neurotransmitter that plays an important role in many neurological functions, including learning and memory.

Amygdala—an almond-shaped structure involved in processing and remembering strong emotions such as fear. It is part of the limbic system and located deep inside the brain.

Amyloid plaque—a largely insoluble deposit found in the space between nerve cells in the brain. Plaques are made of beta-amyloid, other molecules, and different kinds of nerve and non-nerve cells.

Amyloid precursor protein (APP)—the larger protein from which beta-amyloid is formed.

Apolipoprotein E—a protein that carries cholesterol in blood and that appears to play some role in brain function. The gene that produces this protein comes in several forms, or alleles: ε2, ε3, and ε4. The APOE ε2 allele is relatively rare and may provide some protection against AD (but it may increase risk of early heart disease). APOE ε3 is the most common allele and appears to play a neutral role in AD. APOE ε4 occurs in about 40 percent of all people with AD who develop the disease in later life; it increases the risk of developing AD.

Axon—the long extension from a neuron that transmits outgoing signals to other cells.

Beta-amyloid—a part of the amyloid precursor protein found in plaques, the insoluble deposits outside neurons.

Brain-derived neurotrophic factor (BDNF)—a growth factor that stimulates survival, growth, and adaptability of some neurons.

Brain stem—the portion of the brain that connects to the spinal cord and controls automatic body functions, such as breathing, heart rate, and blood pressure.

Capillary—a tiny blood vessel. The brain has billions of capillaries that carry oxygen, glucose (the brain's principal source of energy), nutrients, and hormones to brain cells so they can do their work. Capillaries also carry away carbon dioxide and cell waste products.

Cerebellum—the part of the brain responsible for maintaining the body's balance and coordination.

Cerebral cortex—the outer layer of nerve cells surrounding the cerebral hemispheres.

Cerebral hemispheres—the largest portion of the brain, composed of billions of nerve cells in two structures connected by the corpus callosum. The cerebral hemispheres control conscious thought, language, decision making, emotions, movement, and sensory functions.
Cerebrospinal fluid—the fluid found in and around the brain and spinal cord. It protects these organs by acting like a liquid cushion and by providing nutrients.

Chromosome—a threadlike structure in the nucleus of a cell that contains DNA. DNA sequences make up genes. Most human cells have 23 pairs of chromosomes containing approximately 30,000 genes.

Clinical trial—a research study involving humans that rigorously tests safety, side effects, and how well a medication or behavioral treatment works.

Cognitive functions—all aspects of conscious thought and mental activity, including learning, perceiving, making decisions, and remembering.

Computed tomography (CT) scan—a diagnostic procedure that uses special x-ray equipment and computers to create cross-sectional pictures of the body.

Corpus callosum—thick bundles of nerve cell fibers that connect the two cerebral hemispheres.

Dementia—a broad term referring to a decline in cognitive function to the extent that it interferes with daily life and activities.

Dendrite—a branch-like extension of a neuron that receives messages from other neurons.

DNA (deoxyribonucleic acid)—a long, double-stranded molecule within the nucleus of the cell that forms chromosomes and genes.

Early-onset Alzheimer’s disease—a rare form of AD that usually affects people between ages 30 and 60. It is called familial AD (FAD) if it runs in the family.

Entorhinal cortex—an area deep within the brain where damage from AD often begins.

Enzyme—a protein that causes or speeds up a biochemical reaction.

Free radical—a highly reactive molecule (typically oxygen or nitrogen) that combines easily with other molecules because it contains an unpaired electron. The combination with other molecules sometimes damages cells.

Gene—the biologic unit of heredity passed from parent to child. Genes are segments of DNA and contain instructions that tell a cell how to make specific proteins.

Genetic risk factor—a variant in a cell’s DNA that does not cause a disease by itself but may increase the chance that a person will develop a disease.
Glial cell—a specialized cell that supports, protects, or nourishes nerve cells.

Hippocampus—a structure in the brain that plays a major role in learning and memory and is involved in converting short-term to long-term memory.

Hypothalamus—a structure in the brain under the thalamus that monitors activities such as body temperature and food intake.

Late-onset Alzheimer’s disease—the most common form of AD. It occurs in people aged 60 and older.

Limbic system—a brain region that links the brain stem with the higher reasoning elements of the cerebral cortex. It controls emotions, instinctive behavior, and the sense of smell.

Magnetic resonance imaging (MRI)—a diagnostic and research technique that uses magnetic fields to generate a computer image of internal structures in the body. MRIs are very clear and are particularly good for imaging the brain and soft tissues.

Metabolism—all of the chemical processes that take place inside the body. In some metabolic reactions, complex molecules are broken down to release energy. In others, the cells use energy to make complex compounds out of simpler ones (like making proteins from amino acids).

Microtubule—an internal support structure for a neuron that guides nutrients and molecules from the body of the cell to the end of the axon.

Mild cognitive impairment (MCI)—a condition in which a person has memory problems greater than those expected for his or her age, but not the personality or cognitive problems that characterize AD.

Mutation—a permanent change in a cell’s DNA that can cause a disease.

Myelin—a whitish, fatty layer surrounding an axon that helps the axon rapidly transmit electrical messages from the cell body to the synapse.

Nerve growth factor (NGF)—a substance that maintains the health of nerve cells. NGF also promotes the growth of axons and dendrites, the parts of the nerve cell that are essential to its ability to communicate with other nerve cells.

Neurodegenerative disease—a disease characterized by a progressive decline in the structure, activity, and function of brain tissue. These diseases include AD, Parkinson’s disease, frontotemporal lobar degeneration, and dementia with Lewy bodies. They are usually more common in older people.
**Neurofibrillary tangle**—a filamentous collection of twisted and hyperphosphorylated tau found in the cell body of a neuron in AD.

**Neuron**—a nerve cell.

**Neurotransmitter**—a chemical messenger between neurons. These substances are released by the axon on one neuron and excite or inhibit activity in a neighboring neuron.

**Nucleus**—the structure within a cell that contains the chromosomes and controls many of its activities.

**Oxidative damage**—damage that can occur to cells when they are exposed to too many free radicals.

**Positron emission tomography (PET)**—an imaging technique using radioisotopes that allows researchers to observe and measure activity in different parts of the brain by monitoring blood flow and concentrations of substances such as oxygen and glucose, as well as other specific constituents of brain tissues.

**Single photon emission computed tomography (SPECT)**—an imaging technique that allows researchers to monitor blood flow to different parts of the brain.

**Synapse**—the tiny gap between nerve cells across which neurotransmitters pass.

**Tau**—a protein that helps to maintain the structure of microtubules in normal nerve cells. Abnormal tau is a principal component of the paired helical filaments in neurofibrillary tangles.

**Thalamus**—a small structure in the front of the cerebral hemispheres that serves as a way station that receives sensory information of all kinds and relays it to the cortex; it also receives information from the cortex.

**Transgenic**—an animal that has had a gene (like human APP) inserted into its chromosomes. Mice carrying the mutated human APP gene often develop plaques in their brains as they age.

**Ventricle**—a cavity within the brain that is filled with cerebrospinal fluid.

**Vesicle**—a small container for transporting neurotransmitters and other molecules from one part of the neuron to another.
INFORMATION AND SUPPORT RESOURCES

Alzheimer’s Disease Education and Referral (ADEAR) Center
P.O. Box 8250
Silver Spring, MD 20907-8250
800-438-4380 (toll-free)
www.nia.nih.gov/Alzheimers

This service of the National Institute on Aging (NIA) offers information and publications on diagnosis, treatment, patient care, caregiver needs, long-term care, education and training, and research related to Alzheimer’s disease. Staff members answer telephone, email, and written requests and make referrals to local and national resources. The ADEAR website offers free, online publications in English and Spanish; email alerts and online Connections newsletter registration; an AD clinical trials database; the AD Library database; and more.

Alzheimer’s Association
225 North Michigan Avenue, Suite 1700
Chicago, IL 60601-7633
800-272-3900 (toll-free)
www.alz.org

The Alzheimer’s Association is a national, non-profit organization with a network of local chapters that provide education and support for people diagnosed with AD, their families, and caregivers. Chapters offer referrals to local resources and services and sponsor support groups and educational programs. Online and print publications are also available. The Association also funds AD research.

Alzheimer’s Foundation of America
322 Eighth Avenue, 7th Floor
New York, NY 10001
866-232-8484 (toll-free)
www.alzfdn.org

The Alzheimer’s Foundation of America provides care and services to individuals confronting dementia and to their caregivers and families, through member organizations dedicated to improving quality of life. Services include a toll-free hotline, consumer publications and other educational materials, and conferences and workshops.

Dana Alliance for Brain Initiatives
745 Fifth Avenue, Suite 900
New York, NY 10151
212-223-4040
www.dana.org/danaalliances

The Dana Alliance for Brain Initiatives, a non-profit organization of more than 265 leading neuroscientists, helps advance public awareness about the progress and promise of brain research and disseminates information about the brain.
CAREGIVING SUPPORT AND SERVICES

Children of Aging Parents
P.O. Box 167
Richboro, PA 18954-0167
800-227-7294 (toll-free)
www.caps4caregivers.org

This nonprofit organization provides information and referrals for nursing homes, retirement communities, elder-law attorneys, adult day-care centers, insurance providers, respite care, assisted living centers, support groups, and State and county agencies. It also offers fact sheets, a newsletter, and conferences and workshops.

Eldercare Locator
800-677-1116 (toll-free)
www.eldercare.gov

Eldercare Locator is a nationwide, directory-assistance service helping older people and their caregivers locate local support and resources. It is funded by the U.S. Administration on Aging, whose website at www.aoa.gov also features AD information for families, caregivers, and health professionals.

Family Caregiver Alliance
180 Montgomery Street, Suite 1100
San Francisco, CA 94104
800-445-8106 (toll-free)
www.caregiver.org

The Family Caregiver Alliance is a nonprofit organization that offers support services and information for people caring for adults with AD, stroke, traumatic brain injuries, and other cognitive disorders.

National Family Caregivers Association
10400 Connecticut Avenue, Suite 500
Kensington, MD 20895-3944
800-896-3650 (toll-free)
301-942-6430
www.thefamilycaregiver.org

The National Family Caregivers Association helps educate and support people who care for loved ones with chronic illness, disability, or the frailties of old age. The Association offers an online library of information and educational materials, workshops, and other resources.

National Hospice and Palliative Care Organization
1700 Diagonal Road, Suite 625
Alexandria, VA 22314
800-658-8898 (toll-free)
www.nhpco.org

This nonprofit organization works to enhance the quality of life for people who are terminally ill. It provides information, resources, and referrals to local hospice services, and offers publications and online resources.

Well Spouse Association
63 West Main Street, Suite H
Freehold, NJ 07728
800-838-0879 (toll-free)
www.wellspouse.org

The nonprofit Well Spouse Association gives support to spouses and partners of people who are chronically ill and/or disabled. It offers support groups and a newsletter.
RESEARCH AND CLINICAL TRIALS

Alzheimer’s Disease Cooperative Study
University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92039-0949
858-622-5880
www.adcs.org

The Alzheimer’s Disease Cooperative Study (ADCS) is a cooperative agreement between NIA and the University of California, San Diego, to advance research in the development of drugs to treat AD. The ADCS is a consortium of medical research centers and clinics working to develop clinical trials of medicines to treat behavioral symptoms of AD, improve cognition, slow the rate of decline caused by AD, delay the onset of AD, or prevent the disease altogether. The ADCS also develops new and more reliable ways to evaluate patients enrolled in clinical trials.

Alzheimer Research Forum
www.alzforum.org

The Alzheimer Research Forum, an online community and resource center, offers professionals and the general public access to an annotated index of scientific papers, research news, moderated discussions on scientific topics, libraries of animal models and antibodies, and directories of clinical trials, conferences, jobs, and research-funding sources.

ClinicalTrials.gov
www.ClinicalTrials.gov

ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world. Users can search for clinical trials and find information about each trial’s purpose, who may participate, locations, and phone numbers for more details.

RECOMMENDED READING

The ADEAR Center offers fact sheets; easy-to-read materials; booklets about topics such as being diagnosed with early-stage AD, caregiving, home safety, and comfort and care at the end of life; and more. See the ADEAR Center listing under “Information and Support Resources” above for contact information.

Consumers and professionals interested in AD also may wish to refer to the following materials:

Ballard, E.L., & Poer, C.M. Lessons Learned: Shared Experiences in Coping. Durham, NC: The Duke Family Support Program, 1999. Available for $7 from the ADEAR Center, P.O. Box 8250, Silver Spring, MD 20907-8250; 800-438-4380; www.nia.nih.gov/Alzheimers. This book documents the experiences of people caring for loved ones with AD. Filled with short stories and advice, it is intended for caregivers who wish to take comfort and learn from the experiences of others. Caregivers discuss the caregiving process, such as getting a diagnosis, finding support services, making decisions about treatment and living arrangements, and coping with stress and caregiver burden.


This concise volume provides an overview of recent findings regarding the causes, diagnosis, and treatment of AD. It is designed to help caregivers and family members gain a better understanding
of AD and the available options for coping with and managing this illness. Sixteen chapters answer questions about topics such as the definition of AD and dementia, AD versus other causes of dementia, treatments for behavioral symptoms and other complications of AD, and practical issues for the patient and family. Illustrations, a glossary, and a list of resources are also included.


This book, by a physician and social worker at Duke University, offers information about how to get an early and accurate AD diagnosis and why it matters, life after the diagnosis, state-of-the-art treatments, coping with behavioral and emotional changes through the early and middle stages of AD, accessing the latest clinical trials, and understanding the future of AD.


With increased awareness of the symptoms of AD and improved diagnostic techniques, more people are learning that they or a family member have a memory disorder. This book, written by experts at Rush University Alzheimer’s Disease Center in Chicago, helps readers understand and find ways to cope with the early stages of the disease. It also includes an extensive resource list of websites, organizations, and references to consumer and professional literature.


This book offers guidance and comfort for families caring for loved ones with AD, other dementias, and memory loss in later life. The fourth edition includes chapters on topics such as getting medical help for the person with dementia, behavioral symptoms of dementia, nursing homes and other living arrangements, and research in dementia. New information discusses diagnostic evaluation, caregiver resources, legal and financial information, nursing homes and other communal living arrangements, and the latest updates on research, medications, and the biological causes and effects of dementia. Available in a large-print version.


In simple, easy-to-read language, this book addresses issues such as setting boundaries, managing anger positively, and risk factors for anger in AD care. It offers tangible action steps for responding appropriately, rather than abusively,
when feeling angry. Participants in Alzheimer’s support groups share helpful techniques and coping mechanisms, as well as enlightening anecdotes about caring for a loved one with AD. Caregivers, family members of AD patients, clergy, and health professionals all may benefit from this publication. Two companion booklets are also available from the AD/EA Center: “Hit Pause”: Helping Dementia Families Deal with Anger (for health professionals; $3.00) and Wait a Minute! When Anger Gets Too Much (for families and caregivers; $2.00).


This volume brings together the important discoveries in the AD field since the disease’s original description by Dr. Alois Alzheimer a century ago. It traces how the importance of AD as the major cause of late-life dementia came to light and narrates the evolution of the concepts related to AD throughout the years. Fifty papers are organized into sections on historical perspective, neuropathology, synaptic changes, amyloid, tau, disease mechanisms, genetics, and diagnosis and treatment.


This guide is designed to help nonprofessionals understand dementia and its effects on the mind, the differences between dementia and changes associated with normal aging, and how to improve memory and maintain good mental function. It includes information about changes that occur in normal aging; the process of diagnosing dementia; non-AD forms of dementia; how AD develops, and AD stages, diagnosis, and treatment. New information about mild cognitive impairment, ways to stay mentally sharp, and research trends, along with an action guide for caregivers, are also included.

This companion to the PBS documentary takes the reader on a fascinating journey through the developing brain, from infancy and childhood through adulthood and old age. The author examines brain disorders and mechanisms of brain repair and healing.


An eloquent and moving description of AD, *The Forgetting* is an exploration of, and meditation on, the nature of memory and perceptions of self. It is a readable, accessible description of the history of AD, research, and the human impact of the disease. Calling AD a “death by a thousand subtractions,” the author describes the science of AD in clear and easy-to-understand terms.


This book describes the participants and findings from the Nun Study, a long-term project examining aging and AD in a unique population of 678 Catholic sisters. The nuns gave Dr. Snowdon access to their medical and personal records and agreed to donate their brains upon death. The book discusses the relationship of early linguistic ability to risk of AD, the association of stroke and depression with AD, and the role of heredity and lifestyle in healthy aging.


This book examines every major aspect of AD—clinical, epidemiologic, structural, chemical, genetic, molecular, and therapeutic. This edition includes expanded coverage of related dementing disorders, including prion diseases, Pick’s disease, frontotemporal disorders, an in-depth discussion of transgenic models, and the biochemistry of presenilins. It also discusses treatment of symptoms with therapeutic drugs and AD clinical trials. The broad coverage of AD in this book will be of special interest to clinicians, educators, investigators, and health administrators.


This book combines information from researchers, experts, and families in a comprehensive guide for AD caregivers. It offers personal accounts of three families caring for a loved one from the earliest stages to the last stages, illustrating the commonalities and differences among AD patients and the ways their families handle the most difficult challenges. It also provides information to help families cope with the psychological aspects of AD, behavior problems, and communication difficulties. The book covers such topics as the stages of AD, Medicare, Medicaid, long-term care insurance, geriatric care management, the diagnosis of AD, causes and prevention, and drug treatments.
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Alzheimer’s disease (AD) is an age-related brain disorder that develops over many years. Its symptoms typically first appear after age 60. The course of AD varies from person to person, but in most people, the first symptom is memory loss. Memory decline becomes more serious as the disease progresses, and people often begin having problems with other cognitive functions, such as decision making (including financial) and language skills. People with Alzheimer’s may also experience behavior and personality changes. Eventually, the loss of mental function becomes so severe that it impairs daily living and the ability to recognize family and friends. These losses are related to the breakdown of the connections between different classes of neurons (nerve cells) in the brain and the associated death of many of these cells.

Although AD was first described by Dr. Alois Alzheimer more than 100 years ago, scientific study of the disease began in earnest only in the early 1970s. Since then, a broad and increasingly productive research program led by the National Institute on Aging (NIA) at the National Institutes of Health (NIH) has revealed much about the basic biology of the disease and the factors that influence its development and progression. This program applies the expertise of many scientific disciplines in an attempt to answer complex questions: What causes AD? How can it be diagnosed early and accurately? How can it be treated? How might it ultimately be prevented? A current focus of research seeks to accelerate the pace of “translational research”—the transfer of knowledge gained in the laboratory to the clinical arena.

An Urgent National Health Priority

The search for more effective ways to treat or prevent AD is increasingly urgent. Today, it is estimated that 2.4 million to 5.1 million people in the United States have AD. While estimates vary, depending on how AD is measured, scientists agree that without scientific breakthroughs in prevention or early treatment of the disease, the number of people with AD will increase significantly as society ages.

Studies suggest that the number of people with the disease doubles for every 5-year age interval beyond age 65. The U.S. Census Bureau estimates that the 65-and-older population will double to about 72 million during the next 20 years, starting with the oldest “baby boomers” who turn 65 in 2011. The ranks of the very elderly, those 85 years old and older and at the highest risk of AD, will increase as well, potentially tripling their numbers by 2050.

The costs of AD are at the same time deeply personal and broadly societal. Families, friends, and caregivers experience emotional, physical, and financial stress as they watch a loved one become more and more forgetful, frustrated, confused, and lost. As the disease runs its course and the person with AD loses the ability to live or function independently, family members and other caregivers face difficult decisions about long-term care. Frequently, they turn to assisted living facilities, then nursing homes, for care and support. The number of caregivers—and their need for practical and psychological support—is expected to escalate rapidly as the population ages and the number of people with AD grows.
The U.S. investment in Alzheimer’s disease (AD) research through the National Institutes of Health (NIH) has resulted in accelerating progress on several research fronts and has laid the groundwork for future discovery. This report highlights key AD research findings and activities in 2009, conducted or supported by public funding for the National Institute on Aging (NIA) at NIH and other NIH Institutes and Centers. NIA leads the Federal Government’s research effort to understand and combat this devastating disease and is mandated by Congress to prepare this report.

### 2009 Highlights

#### New AD Genes

International teams studying AD genetics have identified three new genes that are associated with increased risk of late-onset AD. Two of these genes contain instructions for the synthesis of proteins that may be involved in clearing beta-amyloid from the brain and preventing its interference with communication among brain cells, which is thought to be a major factor in the development of AD. These genetic discoveries come at a time when researchers are increasingly interested in harnessing the brain’s own beta-amyloid clearance mechanisms as a therapeutic strategy. (See the sections New human AD genes identified, page 23, and Clearing out beta-amyloid, page 37.)

#### Earlier AD Diagnosis

Researchers from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) showed that changes in the levels of certain proteins in cerebrospinal fluid (CSF) may correlate with the risk and progression of AD. These biomarkers may be used in the future to identify individuals at risk of developing AD. In addition, measuring amyloid in the brain may prove promising as a diagnostic tool. A preliminary study showed that the presence of high levels of brain amyloid in cognitively normal people is linked with greater risk of later cognitive decline. (For details, see the sections Biomarkers and ADNI, page 33, and Brain Amyloid an Early Warning Sign of Possible Cognitive Decline in “Normal” Individuals, page 19.)

#### Vascular Disease Linked to AD

AD is typically a disease of old age, which means that many people with AD also suffer from other age-related diseases and conditions, such as high blood pressure, cerebrovascular disease, or diabetes. Researchers are learning that these “co-morbid” conditions may increase the risk of AD and speed its clinical progression. For example, there is now a growing body of evidence that the cellular abnormalities associated with vascular disease feed into and exacerbate those associated with AD. Researchers are exploring in clinical trials whether the therapeutic interventions known to reduce risk of heart disease and diabetes may also reduce risk of AD. Reports published in
This Progress Report highlights key 2009 Alzheimer’s disease research findings and activities supported by public funding.

2009 suggest that the Mediterranean diet, exercise, and controlling high blood pressure may be associated with reduced risk of AD. (See the sections Links with Other Diseases, page 14; Interactions Between AD and Vascular Disease, page 28; and AD Clinical Trials, page 38.)

Cognitive Exercise and Successful Cognitive Aging

The popularly held belief that brain exercise can improve cognitive function in older people is now being tested. In two different clinical trials, significant cognitive performance gains were seen in people over 65 who received training interventions aimed at improving either attention or speed and accuracy of verbal information processing. (See Clinical Trials to Maintain or Improve Cognitive Function with Age, page 46.) However, as in previous trials, there was no evidence that training in one dimension improved function in another, so questions remain about the overall usefulness of this type of training in real-world settings.

AD Is Not Just a Memory Disorder

Our view of AD is undergoing a transformation. In the past, AD was seen primarily as a memory disorder, and intervention focused on memory symptoms. However, mood and behavioral problems, such as depression, anxiety, and displays of socially inappropriate behavior, are increasingly recognized as co-occurring conditions with AD. Mood and behavioral disturbances also appear to be associated with more rapid progression from mild cognitive impairment (MCI) to dementia, and early treatment of these symptoms may help slow that progression. For example, treatment with the drug donepezil reduced the risk of progression to AD among MCI patients with depressive symptoms. (See the sections Other Early Signs and Symptoms, page 32, and Slowing progression to AD in people with MCI and depression, page 39.)

Sleep and AD

AD may also be linked to sleep problems. Many people with AD suffer from sleep disturbances, which can contribute to cognitive impairment through a variety of mechanisms. Researchers are starting to study the possibility that therapeutic interventions to improve sleep quality may help alleviate some symptoms of AD.

AD Caregiving

Two clinical trials, REACH I and REACH II, were previously funded to develop and test strategies for helping caregivers manage the stress and emotional burden of caring for people with dementia. The REACH OUT Program is beginning to implement these strategies through local social service agencies. The first such study showed a significant improvement in caregivers’ sense of burden, social support, depression, and health, as well as in care recipients’ behavior problems and mood.
Recovery Act Funds Advance Research on AD and Age-Related Cognitive Decline

In 2009, the American Recovery and Reinvestment Act (ARRA) provided a novel opportunity to spark additional Alzheimer’s disease research. NIA targeted promising areas of research in awarding more than 100 Alzheimer’s or Alzheimer’s-related ARRA research grants, totaling $77 million. Projects conducted within a short timeframe (2009-2010) included both new and ongoing studies to understand the biological mechanisms of the disease, identify additional risk-factor genes associated with Alzheimer’s, improve diagnostic tools, find biomarkers, develop therapies, conduct clinical trials, and explore preventive measures. ARRA funding also provided an opportunity to support research on age-related cognitive decline, a condition even more prevalent than AD in the older population.

Basic Research

Basic research to better understand the development and progression of AD will lay the foundation for new prevention and treatment interventions. ARRA-supported researchers are:

- Investigating how AD and vascular disease may influence and exacerbate one another. Findings may suggest strategies for preventing dementia.
- Investigating how amyloid, a protein implicated in AD brain changes, contributes to the formation of clots in the brain and blood vessels.
- Examining how energy metabolism influences brain aging by looking for correlations among the loss of brain volume, metabolic measures, and dementia status in aging and in people with AD.

Genetic and Other Risk Factors

The ability to identify people at risk for AD is increasingly important as preventive measures are developed and as we learn more about how those at risk may reduce their odds of developing the disease. ARRA-supported investigators are:

- Using genome-wide association studies to compare the entire genomes of individuals with and without the disease to identify potential genetic risk factors for cognitive decline and AD.
- Investigating whether changes to the brain “histone code,” which helps determine the activity of specific genes, can mediate the effect of life experiences on the development of age-related cognitive decline and AD.
- Exploring the association of AD with vascular risk factors (e.g., high blood pressure), markers of inflammation, and pathology pathways in diverse populations.

Biomarkers for Detection and Diagnosis

Research suggests that the earliest AD damage begins to develop in the brain long before clinical symptoms appear. Finding ways to diagnose AD as early as possible is critical so that researchers can test interventions and, ultimately, treat the disease as early as possible. ARRA-supported investigators are:

- Building on the highly successful ADNI to determine the clinical, cognitive, imaging, genetic, and biochemical biomarker characteristics of MCI, often a precursor to AD.
- Identifying best practices for collecting samples of CSF and its analysis for proteins that may be associated with AD onset and progression, with the goal of identifying biomarkers that appear before cognitive symptoms do.
The American Recovery and Reinvestment Act (ARRA) provided a novel opportunity to spark additional Alzheimer’s disease research.

Comparing the effectiveness of brain imaging and blood biomarkers to diagnose AD.

Possible Prevention and Treatment Strategies
ARRA-supported investigators are studying a range of potential strategies to prevent MCI or AD. This research includes:

- Evaluating the drug levetiracetam in a clinical trial as a treatment for MCI, potentially preventing progression to AD by reducing the hyperactivity of neurons in the hippocampus, a part of the brain important to learning and memory.
- Evaluating the effects of exercise in combination with two dietary supplements—the omega-3 fatty acid DHA and curcumin—on AD biomarkers and cognition in an animal model.
- Testing whether blocking a key inflammation pathway alleviates the consequences of high cholesterol on the brain in mouse models of AD. High cholesterol is believed to increase AD risk by triggering inflammation pathways that ultimately damage brain cells.
- Studying how the outer shell, or capsid, of certain viruses might be used to carry protective or therapeutic molecules into the brains of AD patients. This early work is being carried out in a mouse model of AD and, if successful, might be used in other neurodegenerative diseases as well.
- Studying the drug methylphenidate as a treatment for apathy, one of the most common behavioral symptoms of AD and one for which there is currently no effective treatment.
- Closely following participants who were enrolled in the Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT) to assess the long-term effects of naproxen and celecoxib on cognitive health.

Understanding Normal Aging and Preventing Loss of Cognitive Function
A growing body of evidence suggests that various interventions may exert a protective effect on the brain in older age, but little is known about the underlying mechanisms and more intervention testing is needed. ARRA-supported researchers are working to:

- Understand the role that neurotrophic factors (proteins that promote the development of new neurons and the repair of damaged ones) play in healthy and abnormal brain aging. Animal and human studies have shown that circulating levels of neurotrophic factors increase with exercise and also with a calorie-restricted diet or one rich in fruits and vegetables.
- Elucidate the neural mechanisms that contribute to robust age-related decline in prospective memory—the act of remembering to carry out an intention such as sending a grandchild a birthday card, paying bills on time, or taking needed medication.
- Develop automated technologies to map functional activity of brain networks, which will help expand our understanding of the neural basis of episodic and semantic memory and how this function changes with normal aging.
- Test a home-technology based cognitive health coaching approach to improve function and quality of life for older adults.
A Brief Primer on Alzheimer’s Disease and the Brain

The healthy human brain is made up of tens of billions of neurons that are connected through chemical and electrical signals. The function of these neurons is supported and regulated by other brain cells, called glial cells, and by the brain’s rich supply of blood vessels. A typical neuron has a cell body, an axon, and many dendrites. The cell body contains the cell’s nucleus. As in other cell types, the nucleus contains the neuron’s genetic blueprint and helps regulate changes in the neuron’s activity, metabolism, and structure in response to signals from outside and inside the cell. The axon is a cable-like structure that extends from one end of the neuron’s cell body and transmits messages to other neurons. Dendrites are branch-like structures that radiate from the other side of the neuron’s cell body and receive messages from the axons of other neurons.

The function and survival of neurons depends on several interdependent processes:

- **Communication.** When a neuron receives enough messages from surrounding cells, an electrical charge is generated that travels from the cell body to the end of the axon. There, it triggers the release of chemicals called neurotransmitters that move across a gap, or synapse, to the dendrites of neighboring neurons. The neurotransmitters bind to specific receptor sites on the dendrites of neighboring neurons, triggering chemical or electrical changes in those neurons. In some cases, neurotransmitter binding stimulates a neuron. In others, it inhibits the neuron’s activity. Scientists estimate that at any one time the average neuron makes 7,000 synaptic connections to other neurons.

- **Metabolism.** This process encompasses all the chemical reactions that take place in the cell. These reactions require chemical energy in the form of oxygen and glucose, which is supplied by the brain’s blood circulation. The brain has an exceptionally high energy demand and so has one of the richest blood supplies of any organ.

- **Repair.** Unlike many short-lived cells in the body, neurons have evolved to live a long time—more than 100 years in humans—so they must constantly maintain and repair themselves. Neurons also continuously remodel themselves—for example, by breaking down synaptic connections with one neighboring neuron and forming new ones with a different neighbor.

How Does AD Affect the Brain?

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

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

What Are the Main Characteristics of the AD Brain?

Many changes take place in the brain of a person with AD. Some of these changes can be observed under the microscope after death. The three abnormalities most evident in the brains of people who have died with AD are:

- **Amyloid plaques.** Found in the spaces between neurons, plaques consist of largely insoluble deposits of a protein fragment called beta-amyloid, which is generated from a protein called amyloid precursor protein (APP). Plaques also contain other proteins, remnants of degenerating neurons and glia, and other cellular material. Scientists used to think that amyloid plaques were the primary...
cause of the damage to neurons seen in AD. Now, however, many think that more soluble forms of beta-amyloid, seen earlier in the plaque formation process, may be the major culprits.

- **Neurofibrillary tangles.** Found inside neurons, neurofibrillary tangles are abnormal aggregates of a protein called *tau*. Healthy neurons are internally supported in part by structures called microtubules, which help guide nutrients and molecules from the cell body to the end of the axon. Normally, *tau* binds to microtubules and helps stabilize them. In AD, *tau* undergoes abnormal chemical changes that cause it to disengage from microtubules and come together with other threads of *tau*, eventually forming neurofibrillary tangles. The microtubules disintegrate, and the neuron’s transport system collapses. As with beta-amyloid, some scientists think that early soluble forms of abnormal *tau* may cause the most damage to neurons.

- **Loss of neuronal connections and cell death.** In AD, the synaptic connections between certain groups of neurons stop functioning and begin to degenerate. This feature of AD likely results from the accumulation of beta-amyloid and abnormal *tau*. When neurons lose their connections, they cannot function properly and eventually die. As neuronal injury and death spreads through the brain, connections between neurons break down, and affected regions begin to shrink in a process called brain *atrophy*. By the final stage of AD, damage is widespread, and brain tissue has shrunk significantly.

### What Causes AD?

In some rare cases, people develop AD in their 40s or 50s. This form of the disease, called “early-onset” AD, often runs in families and is caused by a mutation in one of three genes that a person has inherited from a parent. The causes of other early-onset cases are not yet understood.

More than 90 percent of AD cases occur in people older than 60. The development and pathology of this “late-onset” form of the disease are very similar to those of early-onset AD. The causes of late-onset AD are not yet completely understood, but they probably include a combination of genetic, environmental, and lifestyle factors. The importance of any one of these factors in increasing or decreasing the risk of developing AD may differ from person to person.

Much basic research in AD has focused on the genes that cause early-onset AD, and how mutations in these genes disrupt cellular function and lead to disease. Scientists hope that what they learn about early-onset AD can be applied to the late-onset form of the disease.

Perhaps the greatest mystery is why AD largely strikes people of advanced age. Why does it take 60 to 80 years or more for people to develop signs of the disease? Research on how the brain changes normally as people age will answer this important question, as will studying the disease itself.

### How Is AD Diagnosed?

Clinicians use a range of tools to diagnose “possible AD” (dementia that could be due to another condition) or “probable AD” (no other cause of dementia can be found). Some people with memory problems have a condition called amnestic mild cognitive impairment (MCI) that often precedes AD. People with MCI have more memory problems than normal for people their age, but their symptoms are not as severe as those seen in AD. Importantly, not all people with MCI develop AD.

Tools for diagnosing AD include a medical history, a physical exam and tests—preferably over time—that measure memory, language skills, and other abilities related to brain functioning. The physician may also perform a brain scan. Information provided by family members or other caregivers about changes in a person’s day-to-day function and behavior also help in diagnosis. At this time, AD can be diagnosed conclusively only by an autopsy of the brain after death. However, in specialized research facilities such as the NIA-funded Alzheimer’s Disease Centers, clinicians can diagnose AD in a living person with up to 90 percent accuracy.

Early, accurate diagnosis is crucial because it tells people whether they have Alzheimer’s or whether their symptoms are
caused by something else. Stroke, tumor, Parkinson’s disease, sleep disturbances, or side effects of medications are all known to affect cognitive function and memory, and some of these conditions are reversible. When AD is diagnosed, knowing early on can help families plan for the future while the person with AD can still participate in making decisions. Researchers are developing increasingly accurate diagnostic tests for telltale biomarkers that may one day be used in general medical practice to detect the disease before memory loss or cognitive impairment is evident.

**How Is AD Treated?**

Only a few medications have been approved by the U.S. Food and Drug Administration (FDA) to help control the cognitive loss that characterizes AD. Donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®, formerly known as Reminyl® and now available as a generic drug) are prescribed to treat mild to moderate AD symptoms. Donepezil also is approved to treat severe AD. These drugs act by stopping or slowing the action of acetylcholinesterase, an enzyme that breaks down acetylcholine (a neurotransmitter that helps in memory formation). The drugs maintain some patients’ abilities to carry out everyday activities and may slow down symptoms related to thinking, memory, or speaking skills. They also may help with certain behavioral symptoms. However, they do not stop or reverse AD and appear to help patients only for months to a few years.

Another type of medication, memantine (Namenda®), is prescribed to treat moderate to severe AD symptoms. This drug appears to work by blocking receptors for glutamate, another neurotransmitter involved in memory function. Studies in animals suggest that memantine may have disease-modifying effects, although this has not yet been demonstrated in humans.

In addition to these medications, physicians may use other drugs and nondrug approaches to treat behavioral and psychiatric problems associated with AD. These problems include agitation, verbal and physical aggression, wandering, depression, sleep disturbances, and delusions. (It is important to note, however, that since no drugs are specifically approved by the FDA to treat behavioral or psychiatric symptoms in dementia, this practice constitutes “off-label” usage.)

**NIA’s ADEAR Center Offers Free AD Information and Resources**

Efforts to educate and inform people with AD, their families, the public, providers, and others interested in the disease complement NIH’s research initiatives.

The NIA Alzheimer’s Disease Education and Referral (ADEAR) Center provides free information and publications for families, caregivers, and professionals on research, diagnosis, treatment, patient care, caregiver needs, long-term care, and education and training related to AD. For example, the publication *Alzheimer’s Disease: Unraveling the Mystery* explains the disease, highlights ongoing research, and describes efforts to support caregivers of people with AD. An animated companion video brings to life the latest knowledge about AD and the brain.

Other ADEAR Center publications include *Can Alzheimer’s Disease be Prevented?,* which summarizes the latest research findings on AD risk factors and potential prevention strategies, and *Caring for a Person with Alzheimer’s Disease: Your Easy-to-Use Guide from the National Institute on Aging,* which provides caregiving information and advice. ADEAR fact sheets cover a variety of topics, including basic information, AD genetics, and participating in AD clinical trials and studies. Many ADEAR publications also are available in Spanish.

ADEAR staff members answer telephone, email, and written requests and can suggest local and national resources. In addition, the ADEAR Center website offers email alerts, the online *Connections* newsletter, an AD clinical trials database, and the AD Library database.

To read and order these publications, view the AD video, and take advantage of many other resources, visit the ADEAR Center at [www.nia.nih.gov/Alzheimers](http://www.nia.nih.gov/Alzheimers) or call the Center toll-free at 800-438-4380.
The NIH scientific portfolio for AD covers a wide range of disciplines and research programs. In 2009, NIH-supported researchers forged new understanding of the disease that could lead to future breakthroughs in how to prevent, treat, and cope with its impact. The following pages highlight important findings and explore their potential relevance to the field.

1 Recognizing the Scope of AD

A first step toward curing or preventing a disease is to get a clear picture of how the disease appears in individuals and across large populations. Critical questions for physicians, research scientists, and public policy makers involved in AD treatment and prevention include: How widespread (or prevalent) is the disease? Is it more or less common in certain populations? What is the relationship of AD to other chronic or age-related diseases? How is it different from normal cognitive aging?

Prevalence of Dementia

As the average age of the U.S. population rises, developing a reliable estimate of the current and future prevalence of AD becomes increasingly urgent. Knowing how many people have or are likely to develop AD can help manage private and public health resources in the coming years. For example, the number of people living to 100 or beyond is expected to be 15 times greater in 50 years than it is today. Since the risk of AD increases with age, pertinent questions are: What proportion of centenarians will be affected by AD? How many more relatives will be impacted?

Data are available on the current prevalence of AD in a number of communities and on a national level, but specific data are lacking for the over-97 age group, or “oldest old,” living in rural communities. Compared with those living in and near cities, people living in rural communities are relatively isolated and may have different lifestyles, decreased access to some resources, and potentially different rates of dementia. Researchers at Oregon Health & Science University in Portland assessed dementia prevalence in a sample of people aged 97 or older living in the Klamath Basin, a large rural region in southern Oregon (Kaye et al., 2009). The study showed this population to be within the typical range for people of advanced age. Sixty-one percent of the sample had dementia, 29 percent suffered from MCI, and 10 percent were still cognitively intact. Better understanding of factors that enable nearly 40 percent of people age 97 and older to remain dementia-free could help identify strategies for preventing progress to dementia in younger elders.

Additional advance in estimating prevalence:

Wilson et al. (2009a) Biracial population study of mortality in mild cognitive impairment and Alzheimer disease. Rush Alzheimer’s Disease Center. Supported by NIA and NIEHS.

Links with Other Diseases

Plaques and tangles are usually the most obvious disease features seen under the microscope in brain tissue from deceased AD patients. However, individuals diagnosed with AD also often suffer from other diseases affecting the brain, such as vascular disease. In a postmortem study of 349 people who had been diagnosed before death with either AD or MCI, neuropathologists at the Rush University Alzheimer’s Disease Center in Chicago, IL, found evidence of other disease processes in almost half of the AD brains and 20 percent of the MCI brains.
(Schneider JA et al., 2009). Most common were microinfarcts—small spaces in brain tissue where cells have died due to blockage of blood vessels that once nourished them—which are associated with cerebrovascular disease. The next most common disease signature was Lewy bodies in the cortex. Lewy bodies are abnormal clumps of protein often found in the brains of older people that differ in structure and composition from plaques and tangles. They are associated with dementia with Lewy bodies, and are also found in the brains of people with Parkinson’s disease.

A key finding was that people whose brains showed “mixed” disease (plaques and tangles plus microinfarcts, for example) were more cognitively impaired when they died than those whose brains contained only comparable levels of plaques and tangles. Microinfarcts and Lewy bodies may compound the negative effects of plaques and tangles on neural function, so that fewer plaques and tangles are required to produce noticeable cognitive decline. This study highlights the need to understand how other disease processes contribute to brain dysfunction in people diagnosed with AD. In addition, the finding that microinfarcts seem to exacerbate the negative impact of plaques and tangles on neural function is consistent with increasing evidence of overlap between risk factors for AD and vascular disease (see Interactions Between AD and Vascular Disease, page 28).

Diabetes is another disease that often coexists with AD in older adults. Neuropathologists at the University of Washington in Seattle found that the brains of people who had died with diabetes and dementia had more neuroinflammation and more microinfarcts than those with dementia alone (Sonnen et al., 2009). This finding is not surprising, given that diabetes is a risk factor for cerebral atherosclerosis (accumulation of fatty deposits inside brain blood vessels that restrict or block blood flow). Interestingly, the people who had diabetes in addition to dementia actually carried less amyloid on average at the time of their deaths than did nondiabetics with dementia. The brains of nondiabetics with dementia also had higher levels of free radical damage. These different patterns of injury suggest different underlying mechanisms of pathology and may have implications both for mechanisms of disease development and possible therapies.

2 Deciphering AD Biology

Scientists believe that the accumulation of beta-amyloid fragments around neurons and blood vessels interferes with communications between cells. This communication breakdown is followed by loss of synapses and death of neurons (see A Brief Primer on Alzheimer’s Disease and the Brain, page 11). Much research has focused on exactly how beta-amyloid disrupts intercellular communication. Key questions to be answered include:

- With which molecules does beta-amyloid interact at the synapse?
- With which specific cellular processes does beta-amyloid interfere?
- Which brain “circuits” (systems of interconnected neurons) are most affected by beta-amyloid and why?
- What mechanisms support normal cognitive function in older individuals who also display substantial levels of brain amyloid?
There is also increasing research interest in apparent points of overlap between cellular and molecular changes occurring in AD and in “normal” brain aging.

Synaptic Dysfunction

How beta-amyloid interferes with memory formation

One mechanism the brain uses to store memories is a process called “long-term potentiation” (LTP). LTP is a strengthening of the synaptic connection between two neurons that allows the second neuron to fire more readily. This process is thought to contribute to memory formation.

Beta-amyloid has been shown to interfere with this process. Understanding how it does might reveal potential molecular targets for AD drug development. In particular, researchers would like to identify the proteins involved in LTP-beta-amyloid interactions. Reports from the University of Southern California Alzheimer’s Disease Research Center, State University of New York at Buffalo, and Harvard University identified three different synaptic proteins interacting with beta-amyloid (Williams et al., 2009; Gu et al., 2009; Li et al., 2009). All three are involved in signaling by the neurotransmitter glutamate.

Another study suggests an alternative or additional beta-amyloid “receptor”: cellular prion protein (PrPc). Prion protein in its abnormal form causes mad cow disease in cattle and Creutzfeldt-Jacob disease in humans. Scientists at Yale University in New Haven, CT, supported by NIA and NINDS found that beta-amyloid binds to hippocampal nerve-cell membranes at or near sites where PrPc is found. Moreover, binding to PrPc appears to be necessary for beta-amyloid to disrupt LTP (Laurén et al., 2009). If it is ultimately shown that PrPc is the receptor through which beta-amyloid binds to nerve cells and disrupts LTP, then drugs that block beta-amyloid binding to PrPc could be pursued aggressively as potential AD therapeutics.

Beta-amyloid and synapse loss

Beta-amyloid appears not only to disrupt LTP, but to cause the collapse of dendritic spines (specialized protrusions on the surfaces of dendrites that receive input from other neurons). Loss of dendritic spines is evident around amyloid plaques in both human AD and transgenic mouse models of AD. Scientists at the Massachusetts General Hospital Alzheimer’s Disease Research Center in Boston sought to discover whether this loss is caused by the plaque itself or by soluble beta-amyloid shed from the plaque. Using a new microscopic imaging technique, the researchers were able to see amyloid plaques and nearby dendritic spines in greater detail than had previously been possible. They discovered that plaques are surrounded by halos of soluble beta-amyloid, and that spines first begin to collapse upon contact with these halos (Koffie et al., 2009). Thus, plaques may serve as a reservoir for soluble beta-amyloid, which in turn triggers collapse of spines and loss of synaptic contacts.

Other advances related to synaptic dysfunction:
- Polyedor et al. (2009) Age-dependent impairment of cognitive and synaptic function in the htau mouse model of tau pathology. Albert Einstein College of Medicine. Supported by NINDS.

Selective Neuronal Death

AD affects neurons sooner and more severely in certain brain regions than in others. Particularly vulnerable are neurons in the entorhinal cortex, hippocampus, and certain other cortical regions. A key question is, Why are neurons in certain regions especially vulnerable to AD? In some cases, it may be because these neurons experience higher-than-average levels of functional activity (see Cortical “Hubs” and Amyloid, page 17).

Neurons may also be more affected in AD because they synthesize certain proteins that render them vulnerable. An example is neurons in the basal forebrain, a brain region severely affected in AD. These neurons synthesize high levels of a receptor for nerve growth factor, which usually helps ensure their survival. However, investigators at the Buck Institute for Age Research in Novato, California, supported by NIA and NINDS, showed that when the receptor is bound by APP, two toxic events take place: the APP is cleaved into beta-amyloid, and neurons die (Fombonne et al., 2009).

Additional advance related to selective neuronal death:
Cortical “Hubs” and Amyloid

If there were a map of the neural connections within the brain’s cortex, it would look something like an airline route map, with airport “hubs” such as Atlanta, Chicago, and Dallas serving many different routes and showing much higher activity levels than other points in the system. Human brain hubs include hot spots in several regions of the cortex. They can be observed using functional magnetic resonance imaging (fMRI), an imaging technique that monitors levels of nerve-cell activity in different brain regions. Some cortical hubs are busier when a person is at rest, others when a specific task is being performed.

Researchers at Harvard University compared patterns of this activity to patterns of amyloid deposition in people with AD. They found that the regions of highest amyloid accumulation coincided with the locations of highly active cortical hubs (Buckner et al., 2009). The study suggests that these amyloid-associated hubs are active both at rest and during task performance, consistent with mounting evidence that the presence and deposition of amyloid is associated with high neuronal activity levels.

Amyloid and Sleep

The idea that amyloid deposition is correlated with high levels of neuronal activity has received further support from a study showing increased beta-amyloid deposition after sleep deprivation. Active neurons are known to secrete beta-amyloid into the fluid surrounding them. Investigators at Washington University in St. Louis, supported by NIA, NINDS, and NIMH, measured beta-amyloid levels in AD model mice at different points in the sleep-wake cycle. They found levels to be highest at the end of the wakeful period and decreased during sleep (Kang et al., 2009). A similar pattern was seen for beta-amyloid levels in the CSF of human volunteers (10 young healthy males). Additional studies in AD model mice showed that beta-amyloid levels and plaque deposition were increased by chronic sleep deprivation and by orexin, a neurohormone that promotes wakefulness. Treating mice with a drug that blocks orexin receptors blocked the daily rise in beta-amyloid.

The possibility that chronic sleep deprivation exacerbates amyloid deposition is especially interesting given evidence that sleep disturbances, such as sleep apnea, are common in the elderly and cause damage to certain brain regions. This study provides further impetus for testing whether measures that promote healthy sleep also reduce risk of brain dysfunction and AD. (Read about a sleep apnea treatment study, page 39.)

Additional advance related to amyloid and sleep:

- O’Hara et al. (2009) Sleep apnea, apolipoprotein epsilon 4 allele, and TBI: mechanism for cognitive dysfunction and development of dementia. Sierra-Pacific Mental Illness Research, Education, and Clinical Center (MIRECC), Stanford University. Supported by NIMH.

Cellular Energy Deficits

Neurons need exceptionally high levels of energy to support their signaling. Indeed, although the brain represents only about 2 percent of the body weight of an average adult human, it uses about 20 percent of the body’s energy. Neurons are also especially sensitive to energy deficits. Failures in energy-generating mechanisms that occur as neurons age may contribute to the development of AD.
Mitochondrial fission and fusion

Often called the cellular “powerhouses,” mitochondria are responsible for energy production. Mitochondria are highly dynamic—they move around inside cells and can fuse with one another or break apart into smaller pieces (fission). If the balance between mitochondrial fusion and fission tips too much toward fission, the result is abnormally small, malformed mitochondria that may not function properly. Such abnormal mitochondria have been observed in the brains of people with AD.

Researchers at Case Western Reserve University in Cleveland, OH, found that the proteins responsible for mitochondrial fission and fusion are abnormally regulated in the AD brain. They also found that applying beta-amyloid to rat hippocampal neurons caused the mitochondria in the neurons’ dendrites to break apart (Wang X. et al., 2009). Thus, abnormal mitochondrial dynamics may be a link between beta-amyloid and synaptic degeneration.

In related work, a research team at the Burnham Institute for Medical Research in La Jolla, California, supported by NICHD, NEI, NIEHS, and NINDS, showed that nitric oxide (NO), thought to be a key mediator of beta-amyloid’s neurotoxic effects, stimulates the activity of an enzyme that accelerates mitochondrial fission (Cho et al., 2009). Drugs that inhibit activity of this fission-accelerating enzyme might therefore be useful to explore as a possible therapeutic for AD.

Changes in brain metabolism in normal aging and AD

Since age is the best known risk factor for AD, it seems likely that some of the cellular changes that occur with aging contribute to the development of AD. One such change, depressed mitochondrial function, was examined by scientists at the University of Southern California in Los Angeles, supported by NIA and NIMH. The researchers investigated the possible link between mitochondrial dysfunction and events in the AD disease pathway using a mouse model of AD. They found an age-dependent decline in mitochondrial function in both normal and AD model mice, which preceded the onset of amyloid plaque formation (Yao et al., 2009). Thus, mitochondrial dysfunction might contribute to amyloid deposition, as well as vice versa.

Another finding also points to the impact of normal aging and AD on cellular energy production. While nerve cells usually use glucose as their main energy source, researchers at the University of Kentucky in Lexington, studying the brains of aging rats, observed a shift to other fuel sources, such as fats and amino acids. This metabolic shift was accompanied by the breakdown of myelin, the fat- and protein-rich sheath that insulates axons. The earliest stages of cognitive impairment in rats coincided with the changes in myelin metabolism. The investigators hypothesize that these processes damage neuron structure and deplete energy needed for cell-to-cell signaling (Kadish et al., 2009).

Insulin-like growth factor-1 (IGF-1) is a hormone that promotes cell growth. The brain IGF signaling pathway also appears to be involved in aging, as blocking this pathway prolongs lifespan in organisms ranging from worms to mammals. The pathway may also contribute to AD. Investigators at the Salk Institute for Biological Studies in La Jolla, CA, discovered that reducing IGF signaling in AD model mice prevented the development of AD-like disease symptoms, including brain inflammation, behavioral impairment, and neuronal death. Of great interest, the beta-amyloid plaques in the brains of these mice differed from those normally seen in AD: the fibrils making up the plaques were more orderly and tightly packed than usual. These more tightly packed beta-amyloid aggregates are less likely to shed the soluble form of beta-amyloid, and are therefore less likely to be toxic to neurons (Cohen E. et al., 2009).

Additional advances in brain metabolism, normal aging, and AD:

- Cohen AD et al. (2009b) Basal cerebral metabolism may modulate the cognitive effects of Abeta in mild cognitive impairment: an example of brain reserve. University of Pittsburgh. Supported by NIA.
Brain Amyloid an Early Warning Sign of Possible Cognitive Decline in “Normal” Individuals

The year 2009 saw intense investigation of the relationship between brain amyloid deposits and cognitive function. It has been known for many years that some cognitively normal individuals had high levels of brain amyloid at autopsy. More recently, methods became available for imaging amyloid in the brains of living people using positron emission tomography (PET) and radioactive Pittsburgh Compound B (PiB) as an amyloid marker. Subsequent imaging studies supported by NIA and NIMH funding at the University of Pittsburgh, Mayo Clinic, and Banner Alzheimer’s Institute produced an important result: Amyloid deposits were found in the brains not only of people with MCI and AD, but also in some older people who were cognitively normal (Aizenstein et al., 2008; Jack et al., 2009; Reiman et al., 2009). In fact, the percentage of nondemented older adults with significant levels of brain amyloid ranged from 20 to 50 percent in different studies.

Questions to Explore
These findings opened the door to exploring the future implications of differences in amyloid levels among cognitively normal people. Could some older people who have high brain amyloid nonetheless maintain good cognitive function for decades to come? Or, if one scrutinized these apparently normal people more rigorously, would they show the very earliest signs of cognitive loss and eventually develop AD? The weight of evidence from studies supports the second scenario. Many cognitively normal people with high brain amyloid levels exhibit other abnormalities associated with cognitive decline. Further longitudinal studies will be needed to distinguish between those who will progress and those who will not.

Imaging of neuronal activity patterns in individuals with high levels of brain amyloid in three studies at Washington University, Harvard University, and Massachusetts General Hospital indicated abnormalities in the brain’s “default network,” a system of brain regions that is most active when a person is not performing a task, but rather focused inward (e.g., during daydreaming, envisioning or planning the future, or recollecting the past) (Sheline et al., 2010; Sperling et al., 2009; Hedden et al., 2009). The pattern of network disruption seen in these cognitively normal, high amyloid load-bearing individuals is similar to that seen in people with clinical AD. It involves cortical “hubs” that participate in memory formation (see Cortical “Hubs” and Amyloid, page 17).

PIB-PET Scans Key
Most importantly, several studies in 2009 found that cognitively normal people with high amyloid loads were more likely to suffer eventual cognitive decline than peers with low amyloid levels. For example, one research team at the Washington University Alzheimer’s Disease Research Center (ADRC) in St. Louis, MO, longitudinally studied 135 cognitively normal people who had annual cognitive testing starting in 1985 and PiB-PET scans starting in 2004. All of these individuals scored within the normal range on cognitive tests when they first entered the study. PiB-PET scans showed that 29 participants had high brain amyloid loads. This group also showed shrinkage of brain areas typically affected by AD, as seen in MRI scans, and declining performance on visuospatial, episodic, and working memory tasks over time (Storandt et al., 2009).

In a related study, the Washington University ADRC showed that positive PiB-PET scans at baseline were predictive of developing very mild AD but not of other causes of dementia up to 5.5 years later (Morris et al., 2009). This study was limited by the small number of people who developed AD and the short followup time.

Together, the studies suggest the following sequence of disease events in AD:
- Amyloid deposition occurs first, and in its earliest stages is not associated with cognitive impairment.
- Loss of synapses, neurons, and brain volume occurs next, and is accompanied or shortly followed by loss of cognitive function (see AD Progression figure, page 30).

More studies are needed to determine the best ways of accurately predicting who will go on to develop AD and who will not before clinical symptoms emerge. This scenario may seem discouraging but in fact offers hope. Because significant amyloid deposition seems to occur years before clinical diagnosis of AD, there may be a window of time in which therapeutic intervention might prevent disease progression. Accumulation of brain amyloid could serve as a warning sign that additional testing is necessary and therapeutic intervention should be considered. Thus, just as people are now routinely checked for high cholesterol and counseled about lifestyle changes and medications to reduce their risk of heart disease and stroke, in the future they may also be checked for brain amyloid and counseled about AD prevention.

Another encouraging finding is that it is possible for a person to have a lot of amyloid in his or her brain without significant cognitive decline. Thus, in some people the brain somehow compensates for the presence of beta-amyloid, at least for some period of time. The brain’s capacity to compensate for AD pathology, called “cognitive reserve,” is also being intensively studied.

Additional advance:
- Mormino et al. (2009) Episodic memory loss is related to hippocampal-mediated beta amyloid deposition in elderly subjects. University of California, Berkeley. (ADNI)
**What Is Normal Aging?**

The close association between age and risk of AD raises the question of whether AD is an inevitable consequence of aging, especially since many older people with normal cognition have substantial levels of brain beta-amyloid. Is there any such thing as “normal” cognitive aging and, if so, what does it look like?

Understanding what constitutes normal brain aging and age-related cognitive decline is an important focus of research. Cognitive decline associated with aging can compromise quality of life for older people and looking at brain aging in this way may help promote healthy cognitive outcomes. It is anticipated that such research, both in animal models and in humans, can provide critically important insight into effects of normal aging, distinct from AD, as well as providing a biological context for the abnormal brain changes in AD. More detailed descriptions of normal aging will also help in developing early and sensitive AD diagnostic tools.

Investigators at NIA’s intramural Laboratory of Personality and Cognition in Baltimore, MD, carried out an exceptionally detailed analysis of brain changes over time in 138 people who were 64 to 86 years of age and nondemented at the beginning of the study. Brain scans were conducted every year for up to 10 years, and cognitive status was evaluated. Some participants developed MCI over the course of the study, while others remained cognitively normal. Both groups experienced atrophy (shrinkage) of certain brain areas over time, but the specific patterns of atrophy differed. For example, the group who remained cognitively normal showed more atrophy in certain areas of the frontal cortex (the portion of the cortex closest to the forehead), whereas the group who developed MCI had more prominent atrophy in temporal areas (the regions on the sides of the brain, closer to the ears) (Driscoll et al., 2009).

These results suggest that there is a specific trajectory of brain changes that occurs during normal aging, distinct from that occurring in AD. Brain changes in cellular mitochondria and energy production also occur during normal aging (see Changes in brain metabolism in normal aging and AD, page 18). Moreover, a review from the University of Virginia in Charlottesville suggests that declines in certain aspects of cognitive function, such as memory and speed of processing, may begin as early as a person’s 20s or 30s (Salthouse, 2009). These observations appear to be dependent on the type of study conducted, cross-sectional or longitudinal, and debate continues as to the point at which measurable and meaningful change occurs.

**Additional advance in understanding normal aging:**

Discovering New Genetic Mechanisms

In the early days of AD research, scientists realized that some cases of the disease ran in families. When it did, it appeared quite early, in the 40s or early 50s. By analyzing the patterns of inheritance of these early-onset cases of AD, researchers proved that these particular forms of the disease had a genetic basis. Those findings opened an entire area of AD research that continues to be highly productive today. Research into the genetics of early-onset AD has revealed much about the biological basis of the disease, the interrelationship of genetic and environmental factors in causing it, and molecular pathways that might be targeted to prevent or treat both early- and late-onset AD. As medical science moves toward individualized medicine based on a person’s unique genetic makeup, identification of other genes contributing to the development and progression of AD—including those that may be involved in sporadic, late-onset disease, the most common form of AD—may help determine which preventive and treatment strategies are best suited to particular individuals.

The Search for New Genes

Four genes affecting the development of AD have been known for many years. Mutations in three of them—the APP gene found on chromosome 21, the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1—cause the rare early-onset forms of familial AD. The AD-associated mutations in each of these genes promote the breakdown of the large APP protein along a pathway that generates more harmful forms of beta-amyloid.

The fourth gene, apolipoprotein E (APOE), found on chromosome 19, is linked to late-onset AD. Late-onset AD is not “inherited” in the same sense that the early-onset mutations actually cause AD, but genes involved in late-onset AD can affect the risk of developing it. APOE was the first gene to be identified as influencing late-onset AD. APOE has three forms, or alleles: ε2, ε3, and ε4. The ε2 form may provide some protection against AD, and ε3 is thought to play a neutral role. The ε4 form can increase a person’s risk of developing AD.

Research shows that additional genes likely influence the development of late-onset AD, either as risk factors or protective factors. Geneticists worldwide are searching for these genes.

AD Gene Discovery Timeline

- First published GWAS
- First Transgenic mouse models
- First published GWAS confirmed by GWAS
- Five additional genes discovered confirmed by GWAS

If the genes involved in AD are so troublesome, then why do humans have them in the first place? Usually, genes remain in human or animal populations only if they have a useful biological function and confer a survival advantage. For example, there is evidence that the presenilins, particularly PS1, play a role in the earliest stages of the development of the nervous system. Better understanding the normal or “good” biological functions of the proteins encoded by AD genes could shed light on how mutations or variations in these genes lead to disease.

Several findings, including those from investigators at Georgetown University in Washington, DC, supported by NIA and NINDS, and Baylor College in Houston, TX, supported by NIA and NICHD, indicate a role for APP in the development of synaptic connections between nerve cells (Hoe et al., 2009a; Wang Z. et al., 2009). In particular, APP appears to promote the growth of dendrites, the branch-like structures through which neurons receive input from the axons of other neurons. APP is also necessary for neurons to form orderly synaptic contacts with other neurons or muscle cells. In both cases, APP seems to act in part by promoting cell-to-cell adhesion, a process in which certain proteins on the membrane of one cell bind to proteins on a neighboring cell and help “glue” the two cells together.

The presenilins have long been recognized as important to the development of neurons. New evidence suggests they also regulate the strength and flexibility of synaptic connections in the hippocampus. Researchers at Harvard University supported by NINDS found that inactivating the presenilin genes in mice reduced the process of hippocampal long-term potentiation (LTP) (Zhang C. et al., 2009). Another research group at NIA’s Laboratory of Neurosciences in Baltimore, MD, found that, instead of PS1s enhancing the use of an important chemical neurotransmitter acetylcholine on hippocampal LTP, the PS1 mutation impaired synaptic connections. (Wang Y. et al., 2009).

Recent work from the Nathan S. Kline Institute in Orangeburg, NY, indicates yet another role for normal PS1 in neuronal function. It seems to participate in a process called “macroautophagy,” in which cells dispose of internal debris. Many cellular proteins and structures wear out with time and cease to function properly. Most cells have the capacity to target their worn-out components and break them down into smaller pieces, which are either reused or discarded. This process involves lysosomes, parts of cells containing enzymes that digest cellular debris. Mutations in PS1 that cause early-onset AD disrupt metabolism in the lysosomes, so that they can no longer digest cellular debris. This debris then accumulates and may contribute to neuronal death (Lee et al., 2010).

Like APP, the ApoE protein promotes the growth of dendrites and their spines. However, a genetic study in human ApoE model mice from Georgetown University in Washington, DC, suggests that the ε4 form of APOE, which is associated with higher AD risk in humans, is less effective in promoting dendrite and spine growth than the other forms of APOE (Dumanis et al., 2009). This finding may help explain how the APOE ε4 allele increases risk of AD.

Additional advances in understanding AD genes:

- Hoe et al. (2009b) The effects of amyloid precursor protein on postsynaptic composition and activity. Georgetown University. Supported by NIA and NINDS.
- Maji et al. (2009) Functional amyloids as natural storage of peptide hormones in pituitary secretory granules. Zurich, Switzerland. Supported by NIDDK.
New human AD genes identified

Genetics research has helped to reveal much about the basis of AD, the interrelationship of genetic and environmental factors in causing AD, and pathways amenable to prevention or treatment. Complicating the study of AD genetics is the fact that the risk of late-onset AD is probably influenced by many genetic risk factors, each likely contributing a small risk distributed across different genes affecting a variety of biochemical pathways. These genetic factors may influence the age at onset, the risk of getting the disease, or disease progression.

Technological developments in genetic analysis over the last few years have played a huge role in pushing this area of research forward. Genome-wide association study (GWAS) technologies let scientists use sophisticated software and hours of computing time to find links between individual gene variations and observable traits, such as the presence of AD. For just a few hundred dollars, scientists can now rapidly test 500,000 to a million sites in an individual's DNA using a gene chip the size of a postage stamp.

This year, a large GWAS search “struck gold” with the discovery of two new late-onset AD genes, CLU and PICALM. Variants of these genes that correlated with the development of late-onset AD were identified in a collaborative study led by researchers at Cardiff University, Wales (Harold et al., 2009). The group analyzed more than 16,000 samples collected by dozens of laboratories across Europe and the United States, including several funded by NIA and other NIH Institutes.

Sometimes newly discovered disease genes are mysterious entities of unknown biological function. Fortunately, a substantial body of knowledge is already available about CLU and PICALM because the proteins encoded by these genes have roles in well-studied cellular pathways. CLU (ApoJ/clusterin) is another apolipoprotein and, like ApoE, may play a role in clearing beta-amyloid out of the brain and into the blood (see Clearing out beta-amyloid, page 37). PICALM (phosphatidylinositol-binding clathrin assembly protein) appears to be involved in recycling of cell membrane proteins at synapses. Identification of these two new genes should help researchers home in on novel specific biological processes that are disrupted in AD.

A third gene, CR1 (complement receptor 1), identified by the Cardiff University investigators, was confirmed as a “hit” in a smaller collaborative GWAS led by French investigators (Lambert et al., 2009). CR1 is an immune system protein involved in inflammation responses and like CLU, may be involved in clearing beta-amyloid from the brain. The French study also identified CLU, confirming its potential role in AD.

A recently published analysis in an independent data set has confirmed that CR1, CLU, and PICALM are AD susceptibility genes in another population of European ancestry (Jun et al., 2010).

Investigators at Massachusetts General Hospital supported by NIMH identified a fourth potential AD gene, ADAM10. They discovered two rare mutations in this gene in individuals from seven different late-onset AD families. ADAM10 is an alpha-secretase, an enzyme that cleaves APP in a way that eliminates its potential to form beta-amyloid. A mutation could disrupt this cleavage and add to AD risk (Kim M. et al., 2009).

Research in animal models as well as humans can suggest potential human AD genes. An international team of researchers, supported by NIA and NINDS and led by the Burnham Institute in La Jolla, CA, and Xiamen University, China, identified a new gene in mice—Rps23r1—that reduces levels of both beta-amyloid and phosphorylated tau (another major hallmark of AD) when it is turned on either in AD model mice or in human cells in tissue culture (Zhang Y.W. et al., 2009). This gene may protect mice against the development of AD-like changes in the brain. If this gene or one like it is present in humans, therapeutics might be designed to mimic its protective effects.

How are people affected by knowing their risk for AD?

As new genetic risk factors for AD are discovered, measures to assess individual risk will be developed. Currently, APOE ε4 is the most robust risk marker available for late-onset AD, and requests for APOE genotyping are increasingly common. The REVEAL study group led by researchers at Boston University with support from NHGRI and NIA studied the psychological consequences of disclosure of APOE genotype test results in a group of 162 symptom-free adults who had a parent with AD. This study found that people who had
the highest genetic risk for AD and were told their test results did not suffer significantly greater anxiety or depression during the weeks or months after the test than did people who either tested negative or who did not learn their test results (Green et al., 2009).

Additional advance in effects of genetic susceptibility testing:
- Ashida et al. (2009) Disclosing the disclosure: factors associated with communicating the results of genetic susceptibility testing for Alzheimer's disease. NHGRI Intramural Program.

**Epigenetics: Nature Meets Nurture**

Until recently, scientists believed that genes and environmental factors acted independently to influence an individual's biological makeup, including a person's predisposition to different diseases. Now we realize that “nature and nurture” are not so easily untangled. Genes can be affected by environmental factors, such as diet or smoking, which a person may be exposed to, even in the womb.

The study of these interactions is called *epigenetics*, and it is emerging as a new frontier of science. Diet and exposure to environmental chemicals, among other factors, throughout all stages of human development can cause epigenetic changes that may turn on or turn off certain genes. Changes in the regulation of genes could make people more or less susceptible to developing a disease, such as AD, later in life.

Unlike gene mutations, epigenetic modifications of genes do not involve changes to the genetic code. They involve chemical alterations that make genes more or less accessible to interactions with enzymes responsible for “reading” each gene's code and cranking out the protein for which it codes. Environmental factors leave their mark on the genome by altering the epigenetic signature of genes. Like gene mutations, epigenetic changes can be passed from one cell to its daughter cells during cell division, and so can persist for an individual's lifetime. If the cells involved are egg or sperm cells, the changes can also be passed to the next generation. (The old phrase “You are what you eat” now could be revised to say, “You are what you eat and what your mother ate.”)

The epigenome can mark DNA in two ways, both of which play a role in turning genes off or on. The first occurs when certain chemical tags called methyl groups attach to the backbone of a DNA molecule. The second occurs when a variety of chemical tags attach to the tails of histones, which are spool-like proteins that package DNA neatly into chromosomes. This action affects how tightly DNA is wound around the histones. (Source: NHGRI, www.genome.gov)

There is some evidence that epigenetic mechanisms contribute to AD. That may help explain why one individual in a family develops AD while another does not. One study, by scientists at the Sun Health Research Institute in Sun City, AZ, looked at certain chemical modifications in brain tissue samples from deceased identical twins. The comparison examined levels of DNA methylation, a chemical modification that can reduce the level at which a gene is expressed. One twin had developed AD at age 60 and deteriorated until his death at age 76; the other died cognitively intact at age 79. Methylated DNA levels were significantly lower in the brain tissue from the twin who had AD than in that of his brother (Mastroeni et al., 2009). The twin with AD had experienced extensive pesticide exposure during his lifetime as result of his profession. Pesticides are one environmental factor believed to cause epigenetic changes, although it is not known if they were a causative factor in this case.

Recent scientific evidence also points to the involvement of epigenetic mechanisms in memory formation and maintenance. One such mechanism involves enzymes that chemically modify histones (proteins...
around which DNA is wrapped inside chromosomes) and results in the remodeling of chromosomes, the individual coils of DNA and protein storing genetic information inside cells. Two papers from the Massachusetts Institute of Technology in Boston and Columbia University in New York, NY, supported by NINDS, suggest an involvement of histone-modifying enzymes in memory formation and AD and point to these enzymes as possible targets for therapeutic development (Guan et al., 2009; Francis et al., 2009).

Additional 2009 advance in epigenetics:
- Debette et al. (2009) Association of parental dementia with cognitive and brain MRI measures in middle-aged adults. Boston University. Supported by NIA, NINDS, NHLBI.

4 Preventing AD and Promoting Healthy Brain Aging

Genetic factors cannot fully account for why some people develop AD and others do not. There is mounting evidence that a number of nongenetic factors, such as diet, lifestyle, and exposure to certain environmental agents, may increase or reduce one’s risk of developing AD. Understanding these nongenetic risk factors will point the way to potential therapies or lifestyle changes that can help prevent AD.

Potential AD Risk Factors

Advancing age and serious head injury are well-established risk factors for developing AD. Scientists are exploring a wide range of other possible factors.

Estrogen

The hormone estrogen has important effects on the brain, many of which are potentially relevant to cognitive aging and AD. For example, animal studies have shown that estrogen protects neurons against a wide spectrum of toxic insults, some of which are linked to AD. Estrogen can also reduce formation of beta-amyloid and can counteract some of the effects of normal aging on cognition when administered to nonhuman primates.

In humans, some large observational studies have suggested a possible protective effect of estrogen for women. Clinical trials and studies have attempted to assess whether estrogen therapy can protect women against age-associated cognitive decline. In the largest trial to date, reported in 2003, data from the Women’s Health Initiative Memory Study (WHIMS) showed that prolonged treatment with a common type of hormone therapy (conjugated equine estrogens) increased the risk of dementia and adversely affected cognition in women age 65 and older.

However, in the WHI trial, postmenopausal hormone therapy was usually started many years after normal reproductive cycles had stopped and involved synthetic hormones. Further, hormone treatment also increased the risk of stroke, suggesting that impaired cerebrovascular function may have been a factor in participants’ cognitive decline.
To try to understand why hormone therapy impaired cognitive function in the WHIMS study, researchers at Wake Forest University and NIA’s Laboratory of Personality and Cognition in Baltimore, MD, used MRI to look for brain degeneration in a group of women, ages 79 to 89, who had participated in the 2003 WHI trial. The women who had received hormone therapy showed more shrinkage of the hippocampus and frontal cortex than those who did not. (These brain regions are important for memory and planning, and also show shrinkage in AD.) Many of the women who received hormone therapy also showed evidence of varying degrees of brain damage due to cerebrovascular disease, but the extent of that damage was not significantly higher compared with women who had received a placebo (Coker et al., 2009). This finding suggests that the adverse effects of hormone therapy on cognition were not due to an increase in cerebrovascular disease (Resnick et al., 2009).

The human clinical data highlight the substantial gaps in our understanding of ovarian hormone influences on neurocognitive aging, as recently summarized from an NIA-sponsored workshop convened to address these issues (Asthana et al., 2009). One of these questions is about timing. Animal studies have shown that estrogen has positive effects on the brain, but only if administered during or immediately after withdrawal of ovarian steroids. Thus, estrogen may protect cognition in humans only if administered at a particular age or for a specific amount of time after menopause. Two NIA-funded clinical trials in progress will compare the effects of early and late hormone therapy on cognition, and other endpoints: the Kronos Early Estrogen Prevention–Cognitive and Affective Study (KEEPS–CA) and the Early versus Late Intervention Trial with Estrogen (ELITE) (see AD Clinical Trials, page 38).

**General anesthetics**

An estimated 200 million patients worldwide have surgery with anesthesia each year. Several studies have linked general anesthesia in surgery with an increased risk of AD later in life. Researchers at Massachusetts General Hospital and Harvard University in Boston, supported by NIGMS, NIA, and NINDS, looked at the most commonly used inhalation anesthetic (sevoflurane) and found increases in beta-amyloid levels and cell death when it was applied to a glial tumor cell line in culture. In addition, mice anesthetized for 2 hours showed increased beta-amyloid deposition in the frontal cortex (Dong et al., 2009). It is important to note that no evidence to date with this or any other inhalation anesthetic shows similar results in humans, but further study of effects of anesthetics on development of brain pathology may be warranted.

**Lead**

A pilot study of 47 healthy subjects, 55 to 67 years old, provided additional support for previous research suggesting a link between lead exposure and memory impairment. Investigators at the University of Rochester, NY, supported by NIEHS, found that higher lead levels in bone, which indicate accumulated lead exposure over time, were associated with impaired performance on two memory tests used to detect MCI (van Wijngaarden et al., 2009).

**Additional advance related to AD risk factors:**

Lifestyle and Successful Cognitive Aging

Many individuals stay mentally sharp to age 90 and beyond, and there has been increasing research emphasis on finding out why. Epidemiological–observational–studies such as those described below are important to identify associations between certain lifestyle factors and the risk of developing AD. However, even if substantial evidence is found for a potential association, observational studies alone cannot establish a cause-and-effect relationship. To be useful in the clinic, associations between some factor and AD risk must be able to yield an intervention that can be randomly assigned to individuals in a clinical trial, as randomized trials remain the gold standard for identifying successful treatments (see AD Clinical Trials, page 38).

Researchers for the Health ABC Study at the University of California, San Francisco, and the NIA Intramural Research Program identified several factors associated with continued cognitive health. In a group of 2,509 older people who were functioning well when they entered the study (at ages 70 to 79), factors contributing to enhanced or intact cognitive function included at least a high school level of education, not smoking, and engaging in moderate to vigorous exercise on a weekly basis (Yaffe et al., 2009). Similar associations have been found in a variety of studies.

Social interaction

A number of studies have found that social interaction, whether through work, volunteering, or living with someone, is associated with maintaining cognitive health. It has not been clear, though, whether this correlation is due to the increased intellectual stimulation and physical activity that generally accompany social interaction or whether it was the social interaction itself that was beneficial. Researchers at the Rush University Alzheimer’s Disease Center in Chicago, IL, addressed this question in a large study of nondemented older people (average age, 80). Consistent with previous studies, they found that better cognitive function was correlated with more frequent participation in social activities, as well as with the subjects’ own perception of being well-supported socially. This correlation was significant even after accounting for higher levels of intellectual and physical activity (Krueger et al., 2009).

Exercise

Building evidence from epidemiological studies and several small clinical trials in healthy adults have shown that aerobic exercise may help prevent age-associated cognitive decline, at least in the short term. Studies in animals suggest that exercise may strengthen cognition in part by supporting the hippocampus, a brain structure critical for learning and memory that is one of the first to deteriorate during both normal brain aging and in AD. A report from investigators at the University of Pittsburgh, PA, and the University of Illinois, Urbana-Champaign, suggests that exercise supports hippocampal function in humans as well. They assessed cardiorespiratory fitness in 165 older adults using a treadmill test, and found that higher fitness levels were associated not only with better performance on a spatial memory test but also with greater hippocampal volumes (Erickson et al., 2009).

Work by researchers at Washington University, St. Louis, MO, supported by NIA and NIMH, suggests some forms of exercise are more beneficial than others, at least in one animal model. In AD model mice, voluntary exercise was superior to forced exercise in reducing plaque deposition and improving memory (Yuede et al., 2009). Another study, supported by NIA and NIAMS, from the University of California, Irvine, on AD model mice bearing different forms of the APOE gene suggested that exercise is especially beneficial for cognitive function in mice with the APOE ε4 form (Nichol et al., 2009).

Additional advance related to exercise and AD risk:

- McAuley et al. (2009) Trajectory of declines in physical activity in community-dwelling older women: social cognitive influences. University of Illinois, Urbana-Champaign. Supported by NIA.
The brain has one of the richest supplies of blood vessels of any organ. Cognitive health depends very much on the health of the brain’s blood vessels. Aging is often accompanied by problems in cardiovascular and/or cerebrovascular function. Two of the most common are high blood pressure and clogging of blood vessels that supply the brain, which can cause stroke. Vascular disease, in turn, can cause cognitive impairment.

It has become clear in recent years that AD and vascular disease-associated cognitive impairment are closely intertwined. For example, a large proportion of people diagnosed with AD also have brain damage due to vascular disease (see Links with Other Diseases, page 14). In addition, two analyses of data from NIA’s Baltimore Longitudinal Study of Aging and the Honolulu-Asia Aging Study found that many of the major risk factors for vascular disease may also be risk factors for AD. These findings suggest common cellular mechanisms for the two diseases (Wendell et al., 2009; Stewart et al., 2009).

The overlap between vascular disease and AD may be important because drugs and lifestyle modifications known to be effective in preventing vascular disease may also help prevent AD. In 2009, the following epidemiological and animal studies found that some factors known to reduce vascular disease are also associated with reduced risk of AD.

### Controlling high blood pressure
A postmortem study of brains of people who had hypertension while living, from Mount Sinai School of Medicine, New York, NY, found significantly fewer plaques and tangles in those who had taken medication to control their blood pressure than in those who had not (Hoffman et al., 2009).

### Mediterranean diet
A large study by Columbia University researchers in a multiethnic New York community showed that people who maintained a Mediterranean diet had a 28 percent lower risk of developing MCI and a 48 percent lower risk of progressing from MCI to AD. A Mediterranean diet includes vegetables, legumes, fruits, cereals, fish, monounsaturated fats such as olive oil, mild to moderate amounts of alcohol, and low intake of saturated fats, dairy products, meat, and poultry (Scarmeas et al., 2009a).

### Physical activity
Another Columbia University study in the same multiethnic New York population showed that people who reported regular engagement in “some” physical activity had a 29 to 41 percent lower risk of developing AD, compared to participants who said they were not physically active. Engaging in “much” physical activity was associated with a 37 to 50 percent lower risk (Scarmeas et al., 2009b).

### Cholesterol-reducing drugs
Investigators at the University of Alabama, Birmingham, supported by NIA and NHLBI, treated AD model mice with a drug that imics apolipoprotein A-1 (the major protein in high density lipoprotein, or HDL, the “good” form of cholesterol) together with a statin for controlling cholesterol. The mice treated with this combination of drugs showed improved cognitive function, reduced amyloid, and reduced inflammation compared with untreated AD model mice (Handattu et al., 2009).

**Additional 2009 advance related to vascular disease and AD:**
- Schuff et al. (2009a) Cerebral blood flow in ischemic vascular dementia and Alzheimer’s disease, measured by arterial spin-labeling magnetic resonance imaging. University of California, San Francisco/VA Medical Center. Supported by NIA.
Mounting epidemiological and animal-study findings point to interesting possibilities for preventing AD and cognitive decline. What can scientists say definitively now about what works to prevent Alzheimer’s and age-related cognitive decline? To examine this critical question, the NIH Office of Medical Applications of Research and NIA convened a State-of-the-Science Conference, held April 26-28, 2010, with co-sponsorship from NICHD, NCCAM, NIMH, NINDS, NINR, and the Office of Dietary Supplements.

An independent, 15-member panel was convened to review questions and evidence. Panel members were not currently involved in Alzheimer’s research and represented the fields of preventive medicine, geriatrics, internal medicine, neurology, neurological surgery, psychiatry, mental health, human nutrition, pharmacology, genetic medicine, nursing, health economics, health services research, and family caregiving.

Experts from pertinent fields were invited to present data to the panel and conference audience. The panel also received a systematic evidence review from the Evidence-based Practice Center at Duke University’s Clinical Research Institute, prepared under contract with the Agency for Healthcare Research and Quality. Conference participants also provided oral and written comments in response to the conference questions. The panel considered all of this evidence when preparing its consensus statement.

The panel concluded that cognitive decline and AD are major causes of morbidity and mortality worldwide and are substantially burdensome to the people affected, their caregivers, and society in general. Extensive research during the past 20 years has provided important insights on the nature and extent of AD and cognitive decline. Currently, however, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or AD. Further, evidence is insufficient to support the use of any pharmaceutical agent or dietary supplement to prevent cognitive decline or AD.

However, promising research is underway, the panel noted. These efforts need to be increased and added to by new insights and innovations. For example, the panel indicated that ongoing studies, including those of antihypertensive medications, omega-3 fatty acids, physical activity, and cognitive engagement, may provide new avenues for the prevention or delay of cognitive decline or AD.

NIA’s ongoing research programs are actively investigating and testing a variety of strategies to prevent or delay AD and cognitive decline. Research includes clinical trials investigating exercise, statins and blood pressure and diabetes medications, hormones, antioxidants, cognitive training, and other interventions (see AD Clinical Trials, page 38).

Further large-scale population-based studies and randomized clinical trials are needed to investigate strategies to maintain cognitive function in individuals at risk for decline, to identify factors that may delay the onset of AD in people at risk, and to identify factors that may slow the progression of AD in people already diagnosed.

As this research continues, there are very good reasons for adults to adopt or maintain lifestyle choices and treatments known to promote healthy aging and reduce the risk of diseases like diabetes or cardiovascular disease.

Detecting Disease Earlier

Many researchers believe that therapeutic interventions for AD are more likely to be effective if initiated early in the disease process. Since we now know that the brain damage caused by AD can begin long before cognitive impairment becomes evident, intensive effort has been aimed at developing methods to detect this damage at its earliest stages.

Scientists are currently exploring three main approaches to early diagnosis: cognitive testing, brain imaging, and measurement of biomarkers in CSF. In addition, there is a growing body of research on other early symptoms and changes that may signal the onset of AD.

Cognitive Testing

Extensive cognitive testing has been a key diagnostic tool in AD, refined over many years. Many existing tests were designed to diagnose relatively later stages of the disease—for example, in people who come to the doctor’s office already complaining of memory problems. What is currently lacking are tests that can detect and track the earliest, most subtle stages of the disease and tests that can identify who is at risk of eventually developing the disease. Research efforts now concentrate on the development of a new generation of cognitive tests that are more sensitive to changes in cognition and more reliably discriminate between normal aging, early stages of AD, and cognitive impairment due to other diseases, such as cerebrovascular disease or Lewy body disease. Progress toward establishing a detailed account of normal neurocognitive aging will importantly inform this effort.

MCI is often a transitional stage between normal aging and AD. Sensitive, accurate diagnostic tests for MCI are critical to identify people at risk of developing AD and to predict the likely progression of symptoms. There has been considerable variability in assessing how common MCI is in the population and the rate at which people with MCI progress to AD, due in part to the use of different criteria for diagnosing MCI. Researchers at the University of California, Los Angeles Alzheimer’s Disease Center assessed 115 people with amnestic or nonamnestic MCI using a battery of tests for different neuropsychological functions, such as memory, attention, and visuospatial processing, then followed their progress for 16 months. (In amnestic MCI, memory is the dominant problem; in nonamnestic MCI, other cognitive impairments dominate, such as problems with language, visuospatial processing, and attention. People with amnestic MCI are more likely to progress to AD than those with nonamnestic MCI.) In both the amnestic and nonamnestic groups, the percentage of people who had performance deficits differed significantly for different tests. However, the people who were most impaired on memory tests at the beginning of the study were also the most likely to have persistent memory deficits over the long term (Teng et al., 2009).
The Mini Mental State Examination (MMSE) was designed in 1975 and remains the most widely used screening test for dementia. The MMSE is not sensitive to mild cognitive changes, nor is it very useful for distinguishing between AD and other forms of dementia. It has remained in use in part because it is simple, quick to administer, and can be used in any doctor’s office. Most clinical trials use MMSE scores to help determine who is eligible to participate. A number of new tests are under development that retain those virtues but provide more sensitive and accurate diagnoses. For example, researchers at Mount Sinai Medical Center in Miami, FL, reported on the Florida Brief Memory Screen, which shows high sensitivity for detection of MCI and takes only 3 to 4 minutes to administer. The test is available in Spanish and English, an important feature, as linguistic issues can compromise test performance (Loewenstein et al., 2009).

Several computer-based tests have also been developed, most of which can be used with a standard personal computer. Most of these tests have to be administered and scored by a clinician, as is also true for pen and paper-based tests like the MMSE. University of Pittsburgh researchers reported on a new computer-based test, Computer Assessment of Mild Cognitive Impairment (CAMCI), that is both self-administered and automatically scored. The researchers reported a good sensitivity for detection of MCI (Saxton et al., 2009).

Additional 2009 advance related to cognitive testing:

- Schneider LS et al. (2009) Characteristics and performance of a modified version of the ADCS-CGIC CIBIC+ for mild cognitive impairment trials. University of Southern California. Supported by NIA, NCRR.

Ethnicity and AD diagnosis

Several reports have suggested racial and ethnic differences in the prevalence of AD. Studies seeking to explain these differences have found that cultural factors and variations in education quality, for example, can affect performance on standardized cognitive tests. Another source of diagnostic information, used in conjunction with cognitive tests, is reports from family members and other caregivers about how well a person is functioning in day-to-day life. However, these informant reports, too, may be affected by ethnic and cultural differences. Investigators from Duke University in Durham, NC, found that family member/caregiver reports were less likely to predict cognitive impairment without dementia in African Americans than in whites (Potter et al., 2009). These results are consistent with previous studies suggesting that African Americans are less likely than whites to report cognitive changes in family members. This difference may reflect different cultural perceptions of “normal” aging. For example, a research team at the University of Michigan and Boston University Alzheimer’s Disease Centers studied a group of 301 people in the Boston area, most of whom had personal experience with AD as a caregiver and/or relative. Significantly more of the African American than white participants believed that memory impairment is an expected part of aging (Connell et al., 2009).

Looking to the Future: Cognitive Testing

The AD field is moving toward much earlier diagnosis. More sensitive measures that assess different cognitive domains in more diverse populations are needed. To explore these issues, NIA held a workshop in spring 2010, “Assessment of Cognition in Early Dementia.” The purpose was to review a range of computerized cognitive assessments to determine gaps and opportunities for further development, evaluate novel assessment methods and cognitive domains (e.g., spatial orientation, prospective memory), and determine the best ways to assess cognition in diverse populations. Information from this meeting will be used in the near future to decide which cognitive measures will be incorporated into particular research studies.
Other Early Signs and Symptoms

The clinical picture of AD is changing considerably. For many years since AD was first described in 1906, clinicians believed that it was a rare disease affecting middle-aged adults. In the 1960s, at about the same time larger numbers of people were living past age 65, it became evident that a similar disease occurred in older adults. At the time, the clinical description of AD focused on the symptom of memory loss, specifically, loss of the ability to form and recall memories of recent events. Now there is growing recognition that, even in its earliest stages, AD can affect other cognitive skills and disrupt mood and behavior, sometimes even before memory is affected. Scientists are also increasingly aware that the symptoms and course of AD can vary considerably from person to person, depending in part on whether an individual has other common diseases and conditions of old age, such as vascular disease or diabetes.

Sensory Changes

Cognitive changes in the early stages of AD may include deficits in the ability to process sensory information. NIA-supported research published in 2008 showed that some people with AD begin losing their sense of smell early in the course of the disease (see 2008 Progress Report on Alzheimer’s Disease; also additional references below). Research reported in 2009 suggests that visuospatial skills also may falter early on.

Visuospatial skills allow us to perceive objects and the spatial relationships among them and to judge how close or far away we are from objects in our environment. These skills are crucial for navigating city streets, our own homes, or an assisted living facility. Researchers at the Washington University Alzheimer’s Disease Center in St. Louis, MO, studied 444 older people, all of whom were cognitively normal at the start of the study. About 30 percent of them subsequently developed AD. In this group, performance on tests of visuospatial skill began to decline 3 years earlier on average than performance on memory tests (Johnson et al., 2009).

Investigators at the University of Rochester, NY, provided further evidence that visuospatial skills can decline while memory remains relatively intact (Duffy, 2009). The team studied navigational problems associated with AD, specifically, the question of why people with AD tend to get lost in familiar environments. They found that the brain’s electrical responses to navigation are reduced in people with early AD, and that this ability can be impaired even in people with no measurable memory deficits.

Another report this year from the University of Alabama, Birmingham Alzheimer’s Disease Center found that in everyday life, people with MCI have worse driving performance than their cognitively normal peers (Wadley et al., 2009). The MCI group did not have worse visual acuity (sharpness of vision) than the control group. Thus, it is possible that the MCI group’s impaired driving performance reflected deficits in cortical visuospatial processing, similar to the navigation deficits observed by the Rochester researchers. On the other hand, this impaired level of driving performance could reflect changes in executive function (e.g., the ability to rapidly choose the appropriate action once you have detected a potentially dangerous situation), given the complexity of driving.

Looking to the Future: Sensory and Motor Changes

These studies and others suggest that examining sensory and motor changes in the context of AD may offer fresh perspectives regarding the course, early detection, assessment, and treatment of AD. To further explore these new avenues for research, NIA held an exploratory workshop in August 2010, “Sensory and Motor Dysfunctions in Aging and Alzheimer’s Disease (AD),” focusing on recent findings in sensory and motor changes occurring early in the course of AD, gaps in knowledge, and strategies for advancing this area of research. Participants included experts from the fields of AD as well as leading researchers in the relevant sensory and motor fields.

Additional advances in sensory changes:

- Murphy et al. (2009) Olfaction in aging and Alzheimer’s disease: event-related potentials to a cross-modal odor-recognition memory task discriminate ApoE epsilon4+ and ApoE epsilon 4- individuals. San Diego State University. Supported by NIA and NIDCD.
- Wilson et al. (2009b) Olfactory impairment in presymptomatic Alzheimer’s disease. Rush University Alzheimer’s Disease Center. Supported by NIA.
Behavioral and Mood Problems

Many people with AD experience behavioral and mood disturbances, including depression, irritability, and disinhibition (displays of socially inappropriate behavior). Indeed, such “neuropsychiatric” symptoms are the primary reason caregivers consider moving family members with AD to nursing homes.

Behavioral and mood disturbances also appear to be associated with more rapid progression from MCI to dementia. Researchers at the Instituto Universitario CEMIC in Buenos Aires, Argentina, in collaboration with Johns Hopkins University Alzheimer’s Disease Center scientists, studied 239 people with MCI, of whom 36 percent had persistent neuropsychiatric symptoms in addition to cognitive symptoms. They also progressed more rapidly to dementia. During the period of the study, 44 percent of the people with both MCI and neuropsychiatric symptoms converted to AD, and 18 percent converted to frontotemporal dementia (FTD), a degenerative dementia affecting the frontal and temporal lobes of the brain and causing changes in personality, behavior, language, and movement. In contrast, only 18 percent of the people who had MCI without neuropsychiatric symptoms converted to AD, and none to FTD (Taragano et al., 2009).

Biomarkers and ADNI

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) was launched in 2004 to determine which imaging methods and fluid biomarkers can best track and predict clinical change over time (more information on ADNI, page 54). As of fall 2010, ADNI scientists had collected 3 years of longitudinal data from more than 800 participants (about 200 normal, 400 with MCI, and 200 with AD) at 59 U.S. and Canadian sites. In 2009, ADNI helped identify a number of precisely measurable, clinically relevant biomarkers that will enable more accurate diagnosis and prediction of disease course and also speed and cut the cost of clinical trials.

Structural MRI

During the course of AD, certain regions of the brain shrink due to the degeneration of synapses and death of neurons. Researchers have been using brain scans to try to detect such changes very early, before people have significant cognitive impairment. A collaborative team of investigators from the University of Pennsylvania in Philadelphia and NIA’s Laboratory of Personality and Cognition in Baltimore, MD, developed a pattern detection program to analyze MRI scans obtained from ADNI participants. The program compared patterns of brain area loss over time in people with AD with those of cognitively normal people the same age. Based on differences in these patterns, the program generated a kind of “search image” for AD-like changes, called the “spatial patterns of abnormality for recognition of early AD (SPARE-AD).” The researchers then used the program to analyze people enrolled in NIA’s Baltimore Longitudinal Study of Aging neuroimaging study. In that investigation, people who had either MCI or memory decline with otherwise normal cognition had the highest SPARE-AD scores (Davatzikos et al., 2009). The study suggests that sophisticated pattern detection methods with MRI imaging may help identify cognitively normal individuals who are likely to show cognitive decline.

A 1-year structural MRI study of 449 participants by ADNI investigators at the University of California, San Francisco, found that people with AD and MCI lost volume in the hippocampus more quickly than did cognitively normal people. The losses were associated with deteriorating scores on cognitive assessments. In people with AD, higher rates of loss in hippocampal volume also
In 2009, ADNI helped identify a number of precisely measurable, clinically relevant biomarkers.

correlated with the presence of the ApoE ε4 gene, a risk factor for Alzheimer’s. In people with MCI, higher rates of hippocampal loss were associated with lower levels of the peptide beta-amyloid 1-42 (Aβ1-42) in CSF. The finding of accelerating hippocampal loss is important for understanding the natural history of the disease and emphasizes the need for early diagnosis and therapeutic intervention, the study report noted (Schuff et al., 2009b).

Other ADNI studies, including one published by researchers at the Mayo Clinic in Rochester, MN, have shown that PET imaging holds potential for a different use: the identification of people with AD pathology who have not yet developed dementia. Detection of brain beta-amyloid could potentially be used as a risk factor to predict future decline to AD (Jack et al., 2009).

Cerebrospinal fluid

Researchers took a major step forward in developing a test to diagnose early-stage AD by measuring two biomarkers—tau and beta-amyloid proteins—in CSF. Previous imaging studies had shown that AD-like changes can occur in the brain years before any cognitive symptoms appear. However, CSF testing costs less than brain imaging, so researchers have sought CSF biomarker changes correlated with the development and progression of AD. A report from the ADNI Biomarker Core at the University of Pennsylvania School of Medicine in Philadelphia provided strong evidence that changes in CSF tau and beta-amyloid signal the onset of mild AD. Researchers also established a method for standardized testing for these biomarkers (Shaw et al., 2009). These results may open the door to the discovery of an entire panel of CSF biomarkers that will predict who is at risk of developing AD and how the disease responds to therapies. Like all ADNI results, these findings have been posted to a publicly accessible database available to qualified researchers worldwide.

Additional advances in neuroimaging:

- Dickerson et al. (2009) The cortical signature of Alzheimer’s disease: regionally specific cortical thinning relates to symptom severity in very mild to moderate AD dementia and is detectable in asymptomatic amyloid-positive individuals. Massachusetts General, Harvard University. Supported by NIA, NINDS, and NCRR.

Additional advances in biomarkers:

- Fagan et al. (2009a) Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer’s disease. Washington University. Supported by NIA, NINDS, and NCRR.
- Fagan et al. (2009b) Decreased cerebrospinal fluid Abeta(42) correlates with brain atrophy in cognitively normal elderly. Washington University. Supported by NIA, NINDS, and NCRR.
- Okereke et al. (2009) Ten-year change in plasma amyloid beta levels and late-life cognitive decline. Harvard University. Supported by NIA and NCCAM.
Developing Novel Therapeutic Approaches

Translational research is a multidisciplinary effort that enables the transfer of information between basic-science laboratory studies and clinical research for the purpose of developing novel therapies. The discovery and development of new drugs for neurological disorders is extremely challenging and very expensive. On average, it takes more than 13 years and costs $1.78 billion from the discovery of a new therapeutic target to the time a new drug receives FDA approval for use in the general patient population (Paul et al., 2010). At each step of the translational process, there is a very high failure rate.

In recognition of the difficulties in moving basic scientific knowledge toward drug development, NIA's Division of Neuroscience instituted a series of funding initiatives aimed at creating a robust AD translational research program. The aim is to increase the number of investigational new drugs that can then be tested in humans.

NIA's Alzheimer's Disease Translational Research Program

During the last 5 years, NIA launched a series of funding initiatives to support early drug discovery and preclinical therapy development for AD. The funding opportunity PAS 10-151 supports exploratory drug discovery research using the R21 grant mechanism, and the funding opportunity PA 10-205 supports the preclinical development of promising candidate therapeutics through a cooperative agreement mechanism (U01). In addition, NIA participates in drug discovery funding opportunities initiated by other Institutes (PAR 10-001 and PAR 10-002). The U01 program in conjunction with toxicology services provided through an NIA contract enable researchers involved in preclinical development of candidate therapeutics to secure an Investigational New Drug (IND) status from the FDA. Once a compound has received an IND status, the multiple steps of testing in humans (clinical development) can be pursued either by the pharmaceutical industry or through NIA's clinical trial funding opportunities or clinical trial consortium (ADCS).
**Drug Discovery and Preclinical Development**

NIA support provides critical investments in the riskiest early steps of AD drug discovery and preclinical drug development, which the pharmaceutical industry is unlikely to pursue. The NIA Translational Research Program funds a diverse portfolio of more than 60 projects, ranging from early drug discovery to preclinical development of novel therapeutic compounds aimed at a variety of targets (see Petanceska et al., 2009, for a detailed summary).

To date, this Program includes more than a dozen preclinical drug development projects focused on 1) preclinical optimization of novel therapeutic candidates, 2) repurposing and/or reformulation of drugs currently in use to treat other disease conditions, and 3) preclinical development of naturally occurring compounds. Following are examples of new candidate therapeutics for each of these three areas.

**Novel compounds**

**Tau aggregation inhibitors.** One of the hallmarks of AD is the abnormal clustering of the tau protein into neurofibrillary tangles (see *A Brief Primer on AD and the Brain*, page 11). Tau has emerged as an attractive therapeutic target for AD and other neurodegenerative diseases, commonly known as tauopathies. A multidisciplinary team from the University of Pennsylvania in Philadelphia reported the discovery in mice of two candidate compounds that are effective inhibitors of tau aggregation and can penetrate the blood brain barrier after being orally administered (Ballatore et al., 2010). The Translational Research Program is supporting the further preclinical optimization of these compounds.

**Hsp90 inhibitors.** Heat shock protein 90 (Hsp90) is a member of a large family of molecules that help regulate the transformation of healthy cells to diseased ones. Until recently, Hsp90 was mostly known for its involvement in malignant transformation in cancer. But several laboratories have now provided evidence that Hsp90 plays a role in maintaining the stability of abnormally folded neuronal proteins, allowing the accumulation of toxic aggregates (Luo et al., 2010). Previous research has shown that agents that inhibit Hsp90 can protect neurons against beta-amyloid toxicity as well as tau aggregation. A drug discovery research team from the University of Kansas in Lawrence involved in the design of novel Hsp90 inhibitors for AD reported that three new analogues of the Hsp90 inhibitor novobiocin provide excellent neuroprotection, with little, if any, toxicity in a cell culture model of beta-amyloid (Lu Y et al., 2009).

**Old drug, new purpose**

Memory is governed by long-term changes in nerve cell firing patterns, which in turn require changes in the expression of certain neuronal genes. Regulation of gene expression is the business of proteins called “transcription factors.” The activity of one such factor, CREB (which seems to be particularly important in memory formation) can be increased using the drug sildenafil (*Viagra®*). When scientists at Columbia University in New York, supported by NIA and NINDS, applied sildenafil to hippocampal cells from AD model mice in tissue culture, they saw immediate and long-lasting improvements in synaptic function. In addition, short-term (2- to 3-week) administration of sildenafil to living AD model mice significantly improved their performance in memory tests up to 3 months later. Interestingly, the drug also reduced beta-amyloid levels in these mice, perhaps through its effects on gene expression (Puzzo et al., 2009).

**Nature to the rescue**

Data from epidemiological studies and laboratory experiments suggest that gonadal steroid hormones (sex steroids) and their metabolites can promote neuronal health, while their decline or absence is associated with higher risk of neurodegenerative disease, including Alzheimer’s (see *Estrogen*, page 25). One of the steroids that declines in the aged brain, and in AD brains in particular, is allopregnanolone. Previous experimental evidence demonstrated the ability of this neurosteroid to stimulate the production of neuronal progenitor cells (cells that ultimately develop into functional neuronal cells in the brain) in rodent models. A multidisciplinary team from the University of Southern California in Los Angeles initiated a translational project focused on the preclinical development of allopregnanolone as a regenerative AD therapeutic. The team reported that allopregnanolone can rescue the loss of neurogenic potential in a
transgenic mouse model of AD and reverse associated cognitive decline (Wang JM et al., 2010). The USC team is currently identifying a formulation and dosing regimen for allopregnanolone that will result in an optimal efficacy and safety profile for testing in future clinical trials in humans.

Additional advances in drug discovery and preclinical drug development:

- Cohen AD et al. (2009a) Anti-amyloid effects of small molecule Abeta-binding agents in PS1/APP mice. University of Pittsburgh. Supported by NIA.
- Ma QL et al. (2009) Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling; suppression by omega-3 fatty acids and curcumin. University of California, Los Angeles. Supported by NIA and NCCAM.

New Therapeutic Targets

As scientists continue to learn more about the complexity of the processes and mechanisms of AD, they are also discovering potential new targets for attacking the disease and new approaches for treating it. These basic research findings are the stepping stones for translational research efforts that ultimately may lead to new, effective drug therapies.

Nourishing the brain with its own growth factor

Brain-derived neurotrophic factor (BDNF), a growth factor produced by neurons, is essential for early brain development and healthy brain function in adulthood. Among other actions, BDNF supports nerve cell growth and survival and promotes synaptic outgrowth and plasticity. In people with AD, BDNF levels are abnormally low in certain brain regions where neurons are dying. To test the possible therapeutic effects of BDNF, researchers at the University of California, San Diego used a gene therapy approach in several animal models of AD and aging. They found that BDNF had beneficial effects in all of the models. In AD model mice, it induced recovery of synapses and synaptic signaling markers and improved spatial memory. In rats, BDNF prevented the death of cortical nerve cells that were exposed to beta-amyloid in tissue culture. BDNF gene therapy also had positive effects on spatial learning and memory in the aged rats, as well as in nonhuman primates (Nagahara et al., 2009). These findings indicate that BDNF has multiple protective effects on the neuronal systems that deteriorate during AD and suggest that therapeutic delivery of BDNF or other means of stimulating BDNF activity holds promise as a therapeutic approach for the disease.

Stem cell therapy for AD

Neural stem cells—cells present in both embryonic and adult neural tissue that have the capacity to develop into neurons—have received less consideration as therapy for AD than for other neurodegenerative disorders like Parkinson’s disease and stroke. Because AD affects a wide variety of cell types across widespread regions of the brain, it seemed implausible that many different cells could be replaced using stem cells. Recently, however, scientists have realized that stem cells can improve brain function not only by replacing lost cells, but also by promoting the survival and function of remaining cells.

Researchers at the University of California, Irvine, supported by NIA and NIAMS, took neural stem cells from newborn normal mice and transplanted them into the hippocampal regions of aged AD model mice with widespread plaques and tangles. The transplanted neural stem cells reversed spatial learning and memory deficits in the older mice. They did so not by reducing plaques or tangles in their brains, but by promoting the growth of new synapses in surrounding brain tissue. The beneficial effect of these stem cells turned out to be due to their secretion of the growth factor BDNF (Blurton-Jones et al., 2009). This study is important because it suggests the potential of neural stem cell therapy in AD and shows its beneficial effects in old transgenic mice with substantial AD-like pathology in their brains.

Clearing out beta-amyloid

A number of potential new therapeutic targets are emerging from studies of the multiple mechanisms by which beta-amyloid is removed or cleared from the brain. Beta-amyloid clearance is accomplished by proteins on brain blood vessels that bind beta-amyloid and transport it out of the brain and into the blood. A research team at Washington University in St. Louis, supported by NIA and the NIH Neuroscience Blueprint, showed that by experimentally increasing levels of the beta-amyloid transport protein LRP-1 in the mouse brain, it was possible to dramatically enhance beta-amyloid clearance and reduce its accumulation (Kim J et al., 2009).

Work by another team of investigators at the University of Rochester, NY, supported by NIA,
NINDS, and NHLBI, raised the possibility that beta-amyloid clearance by the same transport protein is disrupted in some forms of AD. They found that LRP-1 production is suppressed by two gene regulatory proteins (SRF and myocardin) present in abnormally high levels in the brain blood vessels of some people with AD. Levels of these regulatory proteins in turn are stimulated by low blood oxygen levels, a condition associated with AD (Bell et al., 2009).

Additional advances related to translational research and beta-amyloid clearance:

- Oddo et al. (2009) Genetically altering Abeta distribution from the brain to the vasculature ameliorates tau pathology. University of California, Irvine. Supported by NIA.
- Persaud-Sawin et al. (2009) Raft aggregation with specific receptor recruitment is required for microglial phagocytosis of Abeta42. NIEHS Intramural Program.

Looking to the Future: Translational Research

Although NIA’s AD Translational Research Program has built significant momentum, much remains to be done. To this end, NIA held an advisory panel workshop on “Alzheimer’s Disease Preclinical Therapy Development” in October 2010. This meeting convened leading therapy development experts from academia, biotechnology and pharmaceutical companies, and disease-focused foundations to develop recommendations for continued improvements in translational research efforts.

Testing Therapies for Prevention and Treatment

AD Clinical Trials

Clinical trials, which compare a potential new treatment with a standard treatment or a placebo (an inactive substance), are the only way to demonstrate whether a drug or other type of treatment is safe and effective in humans. The first stage of human trials, Phase I, involves testing a new treatment in a small group of healthy people to evaluate safety and tolerability. In Phase II, the treatment is given to a larger group of people with the disease to see if it is effective and to further evaluate safety. In Phase III, the last stage before a treatment is approved by the FDA, the treatment is given to a large group of people with the disease to confirm its effectiveness and monitor safety. Phase III trials are complex and expensive, involving hundreds or even thousands of people and often conducted over long periods of time.

In AD, some clinical trials focus on treatment—strategies to preserve cognitive function for as long as possible and alleviate behavioral or psychiatric problems. Other trials aim to delay progression from MCI to AD (secondary prevention). Still others focus on primary prevention—strategies to help cognitively healthy people reduce the risk of developing AD in the future.

NIA provides both infrastructure and funding opportunities for clinical development of AD therapeutics. The major clinical trial programs are the Alzheimer’s Disease Cooperative Study (ADCS) and the AD Pilot Clinical Trials Initiative (see additional information, pages 53 and 56). These programs are in addition to continued support of investigator-initiated clinical trials for AD, MCI, and age-related cognitive decline.

Results from completed AD clinical trials

Two trials published in 2009 support the notion that AD progression can be slowed by targeting symptoms other than memory loss (for example, depression or sleep apnea, in the trials reported here). A third study argues against the popular belief that gingko biloba is effective in preventing cognitive decline. Eleven additional clinical trials reached completion this year; the results are still being analyzed and/or awaiting publication.
Two trials found that AD progression can be slowed by targeting symptoms other than memory loss, such as depression or sleep apnea.

Slowing progression to AD among people with MCI and depression
People with MCI are at higher risk for progressing to AD if they also have neuropsychiatric symptoms such as depression, apathy, or anxiety. The Alzheimer's Disease Cooperative Study (ADCS) examined the effects of depression on progression from amnestic MCI to AD in 208 people who had depression and 548 who did not. Symptoms of depression were assessed as a secondary outcome measure as part of the ADCS trial of donepezil (Aricept®), vitamin E, and placebo in participants with MCI. Study investigators reported that depressed patients were more likely to progress from MCI to AD than nondepressed patients. Also, the proportion of depressed patients progressing to AD was significantly lower for the donepezil group than for the combined vitamin E/placebo group for a little more than 2 years and remained marginally lower for up to 2.7 years. Nondepressed MCI patients who received donepezil initially exhibited a slower rate of progression compared to the vitamin E and placebo groups, but by 2 years there was no difference between the groups. These findings demonstrate that donepezil can reduce the increased risk of progression to AD in MCI patients with depressive symptoms (Lu PH et al., 2009).

Treatment of sleep apnea may slow cognitive decline
Obstructive sleep apnea is common among people with AD. The condition reduces brain oxygen levels and disrupts normal sleep patterns and thus may exacerbate cognitive and behavioral problems in people with AD. Researchers at the University of California, San Diego, supported by NIA and NCRR, evaluated the long-term effects of continuous positive airway pressure (CPAP) treatment in a small sample of 10 people who had participated in a larger 6-week randomized controlled trial of CPAP in AD patients with obstructive sleep apnea. Five of the participants had continued CPAP use for a little more than a year after the larger trial ended, and the other five had not. Those who continued CPAP use showed less cognitive decline and daytime sleepiness, greater stabilization of depressive symptoms, and better sleep quality than those who discontinued CPAP use. Importantly, caregivers of people in the CPAP group reported that their sleep was better and that the patients’ behavioral disturbances improved (Cooke et al., 2009). The results of this small study suggest that long-term CPAP treatment for patients with AD and obstructive sleep apnea may slow cognitive decline and produce lasting improvements in sleep and mood. Larger randomized controlled trials are needed to test these findings.

Gingko not effective in reducing risk of AD or cognitive decline
Gingko biloba is a widely marketed supplement used by people hoping to improve their cognitive health. The largest double-blind, randomized controlled trial to date, the Ginkgo Evaluation of Memory (GEM) study, included 3,069 community-dwelling older adults aged 72 to 96 years who had either normal cognition or MCI. The study, funded by NCCAM, NIA, and NHLBI, was conducted in six academic medical centers in the United States between 2000 and 2008. The primary analysis demonstrated that gingko was not effective in reducing risk of either AD or dementia overall. To learn if ginkgo has more subtle effects on cognitive health, GEM investigators analyzed additional data from this trial. They found no significant effect on cognitive decline or on more specific measures of memory, attention, visuospatial skill, language, and executive functioning (Snitz et al., 2009).
Research Advances

Recently Completed Trials

The following clinical trials supported by NIA were recently completed and are undergoing data analysis:

- **ACCORD–MIND** (Action to Control Cardiovascular Risk in Diabetes—Memory in Diabetes)—NIA-funded primary prevention add-on trial to NHLBI's ACCORD trial
  Principal Investigator (PI): Lenore Launer, NIA Intramural Research Program
- **ESPRIT** (Evaluating Simvastatin’s Potential Role in Therapy)
  PI: Cynthia Carlsson, University of Wisconsin
- **RECALL** (Rosiglitazone Effects on Cognition for Adults in Later Life)
  PI: Suzanne Craft, University of Washington/VA Medical Center
- **SNIFF 120** (Study of Insulin to Fight Forgetfulness, 120 Days)
  PI: Suzanne Craft, University of Washington/VA Medical Center
- **SHARP-P** (Seniors Health and Activity Research Program Pilot)
  PI: Mark Espeland, Wake Forest University
- **Transdermal Nicotine Treatment of MCI**
  PI: Paul Newhouse, University of Vermont

Investigators are preparing and submitting results for publication from the following completed clinical trials supported by NIA:

- **Huperzine A in Alzheimer's Disease**—ADCS
  PI: Paul Aisen, University of California, San Diego
- **VALID** (Valproate in Dementia)—ADCS
  PI: Pierre Tariot, Banner Alzheimer's Institute
- **CLASP** (Cholesterol Lowering Agent to Slow Progression of Alzheimer's Disease Study)—ADCS
  PI: Mary Sano, Mount Sinai
- **Antioxidant Trial** (Vitamins E and C, alpha lipoic acid, coenzyme Q)—ADCS
  PI: Douglas Galasko, University of California, San Diego
- **PREPARE** (Prevention of Postmenopausal Alzheimer Disease and Cognitive Loss with Replacement Estrogen)
  PI: Mary Sano, Mount Sinai

Observational studies on treatments

There has been increasing interest in combination therapy for AD—simultaneous administration of two or more drugs or behavioral interventions. Investigators at the University of Pittsburgh Alzheimer's Disease Research Center looked at the effects of combined treatment with drugs from each of the two major classes currently approved to treat AD, cholinesterase inhibitors and an NMDA receptor blocker (memantine). They studied data from 943 probable AD patients at the Center from April 1983 to December 2004 who had been treated with a cholinesterase inhibitor alone, a cholinesterase inhibitor plus memantine, or no medication. The researchers found that those treated with two drugs delayed admission to a nursing home significantly longer than those who took just one drug (Lopez et al., 2009).

Cholinesterase inhibitors may ameliorate some types of behavioral symptoms in AD patients, but what happens when those drugs are stopped? Researchers at Brown University in Providence, RI, found that discontinuation of cholinesterase medications in nursing home residents with dementia who had been treated for 3 to 9 months was associated with some worsening behavioral changes and less time engaged in leisure-related activities compared to residents who received longer-term treatment (greater than 9 months) (Daiello et al., 2009).

Ongoing clinical trials

Alzheimer's Disease Cooperative Study

The ADCS, a large clinical trials consortium with sites throughout the United States and Canada, is a major initiative for AD clinical trials in the Federal Government. It addresses treatments for cognitive and behavioral symptoms (see additional information on page 53). The ADCS mission is to advance research in the development of clinical trial designs, instruments, and interventions that might be useful for treating patients with AD, particularly interventions that might not be developed by industry.

The most recent round of new ADCS studies, funded in October 2006, explore a variety of approaches:

- **Docosahexaenoic acid (DHA)**. This completed trial examined whether treatment with DHA, an omega-3 fatty acid found in fish, would slow cognitive decline in people with AD. Observational studies associate high fish consumption with reduced risk of AD in people, and studies in mouse models of AD show that dietary DHA reduces
Research advances brain levels of beta-amyloid, oxidative damage associated with beta-amyloid, and neurotoxicity. The manuscript of the results has been accepted for publication in the *Journal of the American Medical Association* (JAMA).

- **Intravenous immunoglobulin (IVIg).** IVIg, a blood product that is administered intravenously, contains naturally occurring antibodies against beta-amyloid. Preliminary studies have shown that IVIg may improve cognition, and research has demonstrated that IVIg increases levels of anti-beta-amyloid antibodies in plasma and promotes clearance of beta-amyloid from CSF. This ongoing Phase III, double-blind randomized controlled trial will demonstrate whether IVIg is effective in treating AD.

- **Home-based assessment.** This ongoing study, conducted in people aged 75 and older, will examine the development and use of three types of home-based assessments: 1) a low-technology telephone assessment, 2) a high-technology automated telephone assessment, and 3) a high-technology computer assessment. Cognition, daily functioning, mood, and other factors will be evaluated in each of the methods. These innovative assessment and data collection tools will be compared to traditional in-person measures. The findings from this study will provide information on how home-based assessments might be used in prevention trials. Such methods could significantly reduce the cost and increase the feasibility of participation in long-term clinical trials.

- **Resveratrol.** This Phase II, double-blind randomized controlled trial, scheduled to begin in 2011, will evaluate the impact of resveratrol treatment on AD biomarkers and clinical outcomes in patients with mild to moderate AD. Resveratrol, a compound found in grapes and wine, has been shown in animal studies to be neuroprotective, and observational studies have shown that moderate consumption of red wine is associated with a lower incidence of AD.

NIH currently supports 37 active clinical trials, including pilot and large-scale trials, of a wide range of interventions to prevent, slow, or treat AD and/or MCI (see Table 1 and Table 2). In particular, the NIA is currently funding seven primary prevention and six secondary prevention trials (Table 1). Of the primary prevention trials, two are NIA-funded cognitive/AD measure add-ons to large NIH primary prevention trials that address a variety of other primary outcomes. One such trial is NHLBI’s Systolic Blood Pressure Intervention Trial (SPRINT), which will evaluate the health effects of lowering systolic blood pressure from 140 mmHg to 120 mmHg. The add-on study, SPRINT-MIND, funded by NIA and NINDS, will assess the effect of lowering systolic blood pressure on cognitive decline and development of MCI and AD. The study will also use brain imaging to measure treatment effects on brain structure, including white matter lesions typical of vascular disease.

A number of the prevention trials are focusing on lifestyle interventions, including exercise, cognitive training, and a combination of the two. Other prevention trials examine how treatments for diabetes might reduce risk of AD. Diabetes is associated with the development of AD, and insulin regulation has been shown to be disrupted in AD. Two trials are examining the effect of the diabetes medications metformin and pioglitazone on cognition and progression to AD in MCI subjects who are also obese. The trial using pioglitazone compares the effects of the medication and exercise (endurance training) as well as a placebo.

Another recently completed diabetes-related trial (SNIFF-120) examined the effects of intranasal insulin in people with MCI or early AD. The idea is that restoring normal insulin function in the brain may provide cognitive benefit and slow disease progression. Administering insulin through the nose does not result in increased peripheral insulin levels, and the drug enters the brain within 15 minutes. Data analysis is ongoing for this trial.

Table 2 summarizes treatment trials to delay the progression of AD and to treat the behavioral disturbances typical of the disease. It also summarizes several trials that are testing biomarkers and performing feasibility studies. Taken together, the trials test a wide range of potential therapies. Several are due to be completed in the next 2 years; other longer trials will not finish data collection until 2014 or later. It is important to note that the year the trial is completed does not include the additional time necessary for analysis of data and publication of findings.
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/ Institution</th>
<th>Intervention</th>
<th>Population</th>
<th>Type of Trial</th>
<th>Anticipated Completion Date</th>
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</thead>
<tbody>
<tr>
<td>PREADVISE (Prevention of Alzheimer’s Disease by Vitamin E and Selenium)*</td>
<td>Frederick Schmitt, Univ. of Kentucky</td>
<td>Vitamin E, Selenium, Vitamin E + Selenium</td>
<td>Men age 60-90</td>
<td>Primary Prevention</td>
<td>2014</td>
</tr>
<tr>
<td>Vitamin E in Aging Persons with Down Syndrome</td>
<td>Arthur Dalton, NY State Inst. for Basic Research in Developmental Disabilities</td>
<td>Vitamin E</td>
<td>People age 50+ with Down syndrome, at high risk of developing AD</td>
<td>Primary Prevention</td>
<td>2012</td>
</tr>
<tr>
<td>AREDS2 (Age-Related Eye Disease Study 2)†</td>
<td>John Paul San Giovanni (Study Director), NEI</td>
<td>Macular xanthophylls (lutein and zeaxanthin) and/or omega-3 fatty acids (DHA and EPA)</td>
<td>People age 50-85 with age-related macular degeneration (AMD) in both eyes or advanced AMD in one eye</td>
<td>Primary Prevention</td>
<td>2015</td>
</tr>
<tr>
<td>SPRINT-MIND (Systolic Blood Pressure Intervention Trial-MIND)*</td>
<td>David Reboussin, Wake Forest Univ.</td>
<td>Blood pressure lowering to &lt;140 mmHg versus &lt;120 mmHg</td>
<td>Adults age 55+ with systolic blood pressure of 130 mmHg or higher, history of cardiovascular disease, high risk for heart disease</td>
<td>Primary Prevention</td>
<td>2017</td>
</tr>
<tr>
<td>ELITE (Early Versus Late Intervention with Estradiol)</td>
<td>Howard Hodis, Univ. of Southern California</td>
<td>17β-estradiol</td>
<td>Healthy early (less than 6 years) or late (10 years+) menopausal women</td>
<td>Primary Prevention</td>
<td>2014</td>
</tr>
<tr>
<td>SMART (Somatotrophics, Memory, and Aging Research Trial)</td>
<td>Michael Vitiello, Univ. of Washington</td>
<td>Growth hormone releasing hormone (GHRH)</td>
<td>People with MCI and healthy older adults age 55-80</td>
<td>Secondary Prevention</td>
<td>2011</td>
</tr>
<tr>
<td>Testosterone Supplementation in Men with MCI</td>
<td>Monique Cherrier, Univ. of Washington</td>
<td>Testosterone</td>
<td>Older men with MCI and low testosterone</td>
<td>Secondary Prevention</td>
<td>2011</td>
</tr>
<tr>
<td>Trial Name</td>
<td>Principal Investigator/ Institution</td>
<td>Intervention</td>
<td>Population</td>
<td>Type of Trial</td>
<td>Anticipated Completion Date</td>
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<tr>
<td>Metformin in Amnestic MCI</td>
<td>Jose Luchsinger, Columbia Univ.</td>
<td>Metformin</td>
<td>Overweight/obese older adults with MCI</td>
<td>Secondary Prevention</td>
<td>2012</td>
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<tr>
<td>Pioglitazone &amp; Exercise Effects on Older Adults with MCI and Metabolic Syndrome</td>
<td>Robert Schwartz, Univ. of Colorado, Denver</td>
<td>Pioglitazone</td>
<td>Overweight/obese older adults with MCI</td>
<td>Secondary Prevention</td>
<td>2012</td>
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<tr>
<td>Exercise Versus Cognitive Interventions for Elders at Risk for Dementia</td>
<td>David Loewenstein, Mount Sinai Medical Center, Miami</td>
<td>Cognitive training, aerobic exercise training, cognitive training + aerobic exercise training</td>
<td>People with MCI</td>
<td>Secondary Prevention</td>
<td>2012</td>
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<tr>
<td>Lifestyle Interventions and Independence for Elders (LIFE)</td>
<td>Marco Pahor, Univ. of Florida</td>
<td>Aerobic exercise, resistance, and flexibility exercises</td>
<td>Adults age 70+</td>
<td>Primary Prevention</td>
<td>2015</td>
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<tr>
<td>Memory Training Intervention in Mild Cognitive Impairment</td>
<td>Miriam Mintzer, Johns Hopkins Univ.</td>
<td>Repetition lag training procedure (RLTP)</td>
<td>People with MCI</td>
<td>Secondary Prevention</td>
<td>2014</td>
</tr>
</tbody>
</table>

**Note:** For information on new and currently recruiting trials, visit: [www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials](http://www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials) or [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).

* NIA-funded primary prevention add-on trials: PREADVISE (add-on to National Cancer Institute's SELECT trial); SPRINT-MIND (add-on to National Heart, Lung, and Blood Institute's and National Institute of Diabetes and Digestive and Kidney Diseases' SPRINT trial; co-funded with the National Institute of Neurological Disorders and Stroke).

† Co-funded primary prevention trial: AREDS2 (National Eye Institute, lead institute).
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/ Institution</th>
<th>Intervention</th>
<th>Population</th>
<th>Anticipated Completion Date</th>
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<tr>
<td><strong>Cardiovascular</strong></td>
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<tr>
<td>Effects of Simvastatin on CSF AD Biomarkers in Cognitively Normal Subjects</td>
<td>Gail Li, Univ. of Washington</td>
<td>Simvastatin</td>
<td>Cognitively normal adults age 45-64</td>
<td>2013</td>
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<tr>
<td>Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for AD</td>
<td>Cynthia Carlsson, Univ. of Wisconsin, Madison</td>
<td>Simvastatin</td>
<td>Adults at high risk of AD (family history, APOE4) age 45-65</td>
<td>2013</td>
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<tr>
<td><strong>Hormones</strong></td>
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<tr>
<td>Alzheimer's Disease: Potential Benefit of Isoflavones</td>
<td>Carey Gleason, Univ. of Wisconsin, Madison</td>
<td>Novasoy (soy isoflavones–phytoestrogens)</td>
<td>People with AD</td>
<td>2010</td>
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<tr>
<td>Estrogen Receptor-beta phytoSERMs for Management</td>
<td>Lon Schneider, Univ. of Southern California</td>
<td>ER2-selective phytoestrogens (phytoSERMs–selective estrogen receptor modulators)</td>
<td>Postmenopausal women age 50-59</td>
<td>2014</td>
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<td>Raloxifene for Women with Alzheimer's Disease</td>
<td>Victor Henderson, Stanford Univ.</td>
<td>Raloxifene</td>
<td>Older women with AD</td>
<td>2012</td>
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<td><strong>Exercise, Cognitive Training</strong></td>
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<td>Aerobic Fitness in Slowing the Progression of AD</td>
<td>Jeffrey Burns, Univ. of Kansas</td>
<td>Aerobic exercise training</td>
<td>People with AD</td>
<td>2014</td>
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<tr>
<td>Conversational Engagement as a Means to Delay AD Onset</td>
<td>Hiroko Dodge, Oregon Health &amp; Science Univ.</td>
<td>Internet-based conversational engagement</td>
<td>Adults age 75+</td>
<td>2014</td>
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<td>Effects of Standardized Aerobic Exercise Training on Neurocognition and Neurodegeneration</td>
<td>Thomas Obisesan, Howard Univ.</td>
<td>Aerobic exercise training</td>
<td>African Americans with AD</td>
<td>2012</td>
</tr>
<tr>
<td>MCI: Cerebrovascular Dysfunction and Exercise Training</td>
<td>Rong Zhang &amp; Hanzhang Lu, Univ. of Texas Southwestern</td>
<td>Endurance exercise training</td>
<td>People with MCI</td>
<td>2014</td>
</tr>
<tr>
<td>Neural Effects of Exercise, Cognitive, or Combined Training in AD At-Risk Elders</td>
<td>Stephen Rao, Cleveland Clinic</td>
<td>Cognitive training, aerobic exercise training, cognitive training + aerobic exercise training</td>
<td>Healthy adults age 65-85</td>
<td>2012</td>
</tr>
<tr>
<td>Trial Name</td>
<td>Principal Investigator/ Institution</td>
<td>Intervention</td>
<td>Population</td>
<td>Anticipated Completion Date</td>
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<td>AAV-NGF Gene Delivery in Alzheimer's Disease</td>
<td>Paul Aisen, Univ. of California, San Diego</td>
<td>Nerve growth factor (NGF) gene delivery</td>
<td>People with AD</td>
<td>2014</td>
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<tr>
<td>ADMIT (Alzheimer's Disease Multiple Intervention Trial)</td>
<td>Chris Callahan, Indiana Univ.</td>
<td>Home-based occupational therapy</td>
<td>People with AD</td>
<td>2016</td>
</tr>
<tr>
<td>fMRI Activation in Mild Cognitive Impairment</td>
<td>Michela Gallagher, Johns Hopkins Univ.</td>
<td>Levetiracetam</td>
<td>People with MCI</td>
<td>2012</td>
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<tr>
<td>Glucose Regulation and Memory in Alzheimer's Disease</td>
<td>Suzanne Craft, Univ. of Washington</td>
<td>Improved insulin resistance, 3 studies: diet, triglyceride emulsion, rosiglitazone</td>
<td>People with AD and age-matched healthy older adults</td>
<td>2016</td>
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<tr>
<td>Intravenous Immunoglobulin (IVig) for Treatment of AD (passive immunization)*</td>
<td>Norman Relkin, Weill Medical College, Cornell Univ.</td>
<td>IVig</td>
<td>People with AD</td>
<td>2013</td>
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<tr>
<td>Lipoic Acid and Omega-3 Fatty Acids in AD</td>
<td>Lynne Shinto, Oregon Health &amp; Science Univ.</td>
<td>Lipoic acid and/or omega-3 fatty acids (DHA and EPA)</td>
<td>People with AD</td>
<td>2014</td>
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<tr>
<td>Thalidomide as BACE1 Inhibitor in AD</td>
<td>Marwan Sabbagh, Banner Sun Health Research Inst.</td>
<td>Thalidomide</td>
<td>People with AD</td>
<td>2012</td>
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<td>Therapeutic Effects of Cataract Removal in AD</td>
<td>Grover Cleveland Gilmore, Case Western Reserve Univ.</td>
<td>Cataract removal surgery</td>
<td>People with AD</td>
<td>2014</td>
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<td><strong>Behavioral Disturbance Interventions</strong></td>
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<td>ADMET (Apathy in Alzheimer's Disease Methylphenidate Trial)</td>
<td>Jacobo Mintzer, Medical Univ. of South Carolina; Krista Lanctot, Sunnybrook Health Sciences Center; Paul Rosenberg, Johns Hopkins Univ.</td>
<td>Methylphenidate</td>
<td>People with AD</td>
<td>2012</td>
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<td>Antipsychotic Discontinuation in AD</td>
<td>Davangere Devanand, NYSP/Columbia Univ.</td>
<td>Risperidone</td>
<td>People with AD</td>
<td>2011</td>
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<td>CITAD (Citalopram Treatment for Agitation in Alzheimer Dementia)</td>
<td>Constantine Lyketsos, Johns Hopkins Univ.</td>
<td>Citalopram</td>
<td>People with AD</td>
<td>2014</td>
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<tr>
<td>Light Treatment for Sleep/Wake Disturbances in AD</td>
<td>Jerome Yesavage, Stanford Univ.</td>
<td>Light treatment</td>
<td>People with AD and their caregivers</td>
<td>2010</td>
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<tr>
<td>Prazosin Treatment for Disruptive Agitation in Alzheimer's Disease</td>
<td>Elaine Peskind, Univ. of Washington</td>
<td>Prazosin</td>
<td>People with AD</td>
<td>2013</td>
</tr>
<tr>
<td>TREA (Treatment Routes for Exploring Agitation)</td>
<td>Jiska Cohen-Mansfield, Research Inst. on Aging</td>
<td>TREA-systematic approach to individualizing nonpharmacological interventions for persons with dementia</td>
<td>Nursing home residents with AD/dementia</td>
<td>2012</td>
</tr>
</tbody>
</table>

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*Alzheimer's Disease Cooperative Study trial
A d clinical trials have progressed from a focus on symptomatic treatment to disease modification to halting the progression from MCI to AD (secondary prevention) to preventing MCI/AD (primary prevention). Many researchers believe that prevention trials that are started before AD pathology has taken hold have the best chance of a positive result. However, the conduct of prevention trials needs to become more efficient by reducing the time and/or number of subjects involved, each of which would reduce the cost. It is clear from completed AD prevention trials, such as ADAPT (AD Anti-Inflammatory Prevention Trial) and GEMS (Ginkgo Evaluation of Memory Study), that using as endpoints the progression from normal cognition to a clinical diagnosis of MCI/AD or changes in cognition takes 8 to 10 years and costs tens of millions of dollars.

Based on the results of ADNI and similar imaging and fluid biomarker studies, the AD clinical trials community is starting to consider the use of biomarkers as potential endpoints in prevention trials. Biomarkers such as structural MRI, amyloid PET imaging, FDG PET, and CSF protein concentrations may ultimately provide a window into the course of the disease in the living brain. Their use in clinical trials may show whether a particular intervention affects underlying brain pathology more quickly than traditional clinical/neuropsychological outcome measures would. These biomarkers could also be used as selection factors to determine which normal subjects, for example, have significant beta-amyloid loads in their brains and may be at higher risk of progression to MCI/AD in a clinical trial. Discussions about the feasibility and cost of such biomarker prevention trials are ongoing, but this is certainly an area of research that will be much more prominent in the near future.

Clinical Trials to Maintain or Improve Cognitive Function with Age

As the population ages, there is growing interest not only in preventing AD but in maintaining general good cognitive function and health throughout life. Although modest in comparison with AD, cognitive decline associated with normal aging significantly compromises quality of life and independent living. Terms like “use it or lose it” refer to mental fitness and perhaps how exercise or diet might keep cognitive decline at bay. NIA is testing a number of interventions to see if they might directly benefit cognitive health. As these tests move forward, NIH encourages the adoption of healthy lifestyle practices, as some, like exercise and social engagement, are known to reduce risk of other diseases or are otherwise important as people age.

Trial results

There is widespread popular belief that mental fitness can be increased with consistent brain exercise (e.g., crossword puzzles, Web-based games). To date, clinical trials have yielded little clear evidence to support this notion. This year, however, two clinical trials reported that different cognitive training protocols improved certain aspects of cognitive function in older adults. The Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study tested a computer-based training intervention designed to improve speed and accuracy of auditory information processing in a randomized trial with 487 cognitively normal older adults age 65 and older in San Francisco and Los Angeles, CA, and Rochester, MN.

Investigators found that training on one particular set of auditory tasks can improve a person’s performance...
on other auditory tasks and that participants who received training later showed improved performance on not only the specific exercises they had been trained with, but other auditory memory and attention exercises as well. (Smith et al., 2009)

In another study of 66 cognitively normal adults ages 65 to 75 at Wake Forest University in Winston-Salem, NC, supported by NIA, NINDS, and NCRR, researchers observed significant benefits of an intervention aimed at improving the brain’s ability to focus on one set of visual or auditory signals while resisting distraction by irrelevant ones (Mozolic et al., 2009). These trials showed training effects on highly related tasks, but leave the question unanswered as to what sort of brain exercise, or combination of exercises, could improve cognitive performance more broadly.

The Experience Corps study from Johns Hopkins University in Baltimore, MD, supports the concept that activities aimed at enriching life experience can lead to positive changes in specific brain circuits in older people. Employing an “immersion” intervention that combined physical, social, and cognitive activity simultaneously through participation in a volunteer program for young children in Baltimore City public schools, the researchers examined cognitive improvements and brain function in eight older female study participants who were already in the study compared to nine matched controls who were on the wait list to participate. The study revealed improved executive function—the ability to exercise control over cognitive function, such as switching quickly and accurately from task to task or carrying out a sequence of tasks appropriately—in the study participants that was correlated with increased activity in prefrontal cortex relative to controls (Carlson et al., 2009). The results indicate that an intervention designed to promote better cognitive function through everyday activity may enhance plasticity in relevant brain regions. Larger studies will be necessary to validate these findings.

**Additional advance in remediating age-related cognitive impairment:**

- Hertzog et al. (2009) Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced?

**Ongoing trials on age-related cognitive function**

NIA currently supports 27 active clinical trials, including pilot and large-scale trials as well as treatment studies, to better understand the mechanisms related to cognitive decline and to better target interventions (see Table 3). Approaches include cognitive training, exercise, nutritional supplementation, hormone therapy, combinations of these, and pharmacological intervention. In addition, interventions to control hypertension and to regulate kidney dialysis to improve cognitive function are underway. Even though the range of interventions is wide, the trials share the common focus of trying to remediate age-related cognitive decline.
# TABLE 3. Ongoing Age-Related Cognitive Decline Clinical Trials Funded by NIA

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator/ Institution</th>
<th>Intervention</th>
<th>Population</th>
<th>Anticipated Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Training</strong></td>
<td></td>
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<tr>
<td>Active Interventions for the Aging Mind</td>
<td>Denise Park, Univ. of Texas, Dallas</td>
<td>Cognitive enrichment through training in digital photography or quilting</td>
<td>Healthy adults age 60+</td>
<td>2012</td>
</tr>
<tr>
<td>Brain-Based Approach to Enhancing Executive Control Functions in Healthy Aging</td>
<td>Mark D’Esposito, Univ. of California, Berkeley</td>
<td>Cognitive training</td>
<td>Healthy adults age 50+</td>
<td>2012</td>
</tr>
<tr>
<td>Expanding the Implementation of an Effective Cognitive Aging Intervention</td>
<td>Helga Noice, Elmhurst College</td>
<td>Cognitive enrichment through training in acting</td>
<td>Healthy adults age 65+</td>
<td>2010</td>
</tr>
<tr>
<td>Experience Corps Trial: Improving Health in Older Populations through Generativity</td>
<td>George Rebok, Johns Hopkins Univ.</td>
<td>Health promotion for older adults embedded within a social engagement program (volunteering in schools)</td>
<td>Healthy adults age 60+</td>
<td>2011</td>
</tr>
<tr>
<td>Senior Odyssey: A Test of the Engagement Hypothesis of Cognitive Aging</td>
<td>Elizabeth Stine-Morrow, Univ. of Illinois, Urbana-Champaign</td>
<td>Cognitive enhancement through participation in the Odyssey of the Mind program</td>
<td>Healthy adults age 60+</td>
<td>2012</td>
</tr>
<tr>
<td>Speed of Processing Modes to Prevent Cognitive Decline in Older Adults</td>
<td>Fredric D. Wolinsky, Univ. of Iowa</td>
<td>Comparison of standard versus enhanced visual processing training</td>
<td>Healthy adults age 50+</td>
<td>2011</td>
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<tr>
<td><strong>Omega-3 Fatty Acids and Antioxidants</strong></td>
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<tr>
<td>Omega-3 and Blueberry Supplementation in Age-Related Cognitive Decline</td>
<td>Robert Krikorian, Univ. of Cincinnati</td>
<td>Omega-3 and blueberry supplements</td>
<td>Healthy adults age 62-80</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
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<tr>
<td>Aging and the Renin-Angiotensin System in Elderly Hypertensive Individuals</td>
<td>Ihab Hajjar, Hebrew Rehabilitation Center for Aged</td>
<td>Angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, diuretic</td>
<td>Adults age 60+ with uncontrolled hypertension and cognitive impairment</td>
<td>2012</td>
</tr>
<tr>
<td>Trial Name</td>
<td>Principal Investigator/ Institution</td>
<td>Intervention</td>
<td>Population</td>
<td>Anticipated Completion Date</td>
</tr>
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<tr>
<td>Estrogen Effects on Cholinergic Function in Older Women</td>
<td>Paul Newhouse, Univ. of Vermont</td>
<td>Acute or chronic 17β-estradiol + muscarinic and nicotinic cholinergic antagonist</td>
<td>Healthy women age 50+</td>
<td>2014</td>
</tr>
<tr>
<td>Estrogen Use in Protection from Cognitive Decline</td>
<td>Natalie Rasgon, Stanford Univ.</td>
<td>Continuation of or removal from postmenopausal estrogen treatment</td>
<td>Healthy women age 50-65</td>
<td>2011</td>
</tr>
<tr>
<td>Hormones and Cognitive Processing in Early Postmenopausal Women</td>
<td>Yolanda Smith, Univ. of Michigan</td>
<td>Estradiol and prometrium (progesterone)</td>
<td>Healthy early postmenopausal women age 45-55</td>
<td>2011</td>
</tr>
<tr>
<td>KEEPS-CA (Kronos Early Estrogen Prevention Study–Cognitive and Affective Study)</td>
<td>Sanjay Asthana, Univ. of Wisconsin, Madison</td>
<td>Oral conjugated equine estrogen and transdermal 17β-estradiol</td>
<td>Healthy postmenopausal women age 42-58</td>
<td>2012</td>
</tr>
<tr>
<td>Sex Steroids and Cognition in Postmenopausal Women</td>
<td>Elliot Hirshman, George Washington Univ.</td>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>Healthy postmenopausal women age 55-65 and 70-80</td>
<td>2011</td>
</tr>
<tr>
<td>Testosterone Trial</td>
<td>Peter Snyder, Univ. of Pennsylvania</td>
<td>Testosterone gel</td>
<td>Older men</td>
<td>2015</td>
</tr>
<tr>
<td>Dose-Response Study of Exercise in Older Adults</td>
<td>Jeffrey Burns, Univ. of Kansas</td>
<td>Aerobic exercise</td>
<td>Healthy older adults</td>
<td>2012</td>
</tr>
<tr>
<td>Exercise, Age-Related Memory Decline, and Hippocampal Function</td>
<td>Scott Small &amp; Richard Sloan, Columbia Univ.</td>
<td>Exercise training or maintenance of sedentary lifestyle</td>
<td>Healthy adults age 20-65</td>
<td>2015</td>
</tr>
<tr>
<td>Exercise, Cognitive Training</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Brain and Cognitive Changes after Reasoning or Physical Training in Cognitively Normal Seniors</td>
<td>Sandra Chapman, Univ. of Texas, Dallas</td>
<td>Cognitive training, aerobic exercise</td>
<td>Adults age 60-75</td>
<td>2011</td>
</tr>
<tr>
<td>Trial Name</td>
<td>Principal Investigator/ Institution</td>
<td>Intervention</td>
<td>Population</td>
<td>Anticipated Completion Date</td>
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<tr>
<td>Combining Exercise and Cognitive Training to Improve Everyday Function</td>
<td>Ellen Binder &amp; Mark McDaniel, Washington Univ.</td>
<td>Aerobic exercise and cognitive training</td>
<td>Healthy adults age 55-75</td>
<td>2012</td>
</tr>
<tr>
<td>Impact of Exercise and Engagement on Cognition in Older Adults</td>
<td>Denise Park, Univ. of Texas, Dallas</td>
<td>Walking, exercise regimen (aerobic tasks); quilting, photography (cognitive tasks)</td>
<td>Healthy adults age 60-85</td>
<td>2011</td>
</tr>
<tr>
<td>Improvement of Visual Processing in Older Adults</td>
<td>Karlene Ball, Univ. of Alabama, Birmingham</td>
<td>Combination of visual processing training and exercise</td>
<td>Healthy adults age 65+</td>
<td>2011</td>
</tr>
<tr>
<td>Influence of Fitness and Cognitive Training on Brain and Cognition</td>
<td>Arthur Kramer, Univ. of Illinois, Urbana-Champaign</td>
<td>Aerobic training (walking), combined aerobic training/cognitive training (dancing)</td>
<td>Adults age 60-75</td>
<td>2015</td>
</tr>
<tr>
<td>Tai Chi and Guided Autobiography for Remediation of Age-Related Cognitive Decline</td>
<td>Victor Henderson, Stanford Univ.</td>
<td>Low-impact Tai Chi exercise and autobiographical writing</td>
<td>Healthy adults age 70+</td>
<td>2012</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Guanfacine Treatment for Prefrontal Cognitive Dysfunction in Elderly Subjects</td>
<td>Christopher Van Dyck, Yale Univ.</td>
<td>Guanfacine</td>
<td>Healthy adults age 75+</td>
<td>2011</td>
</tr>
</tbody>
</table>

**Note:** For information on new and currently recruiting trials, visit: [www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials](http://www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials) or [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).
Supporting AD Caregivers

Family members often bear much of the burden of caring for people with AD. This includes the time and energy spent on caretaking, worry about the mental and physical decline of a loved one, and frustration in trying to communicate with and help them. While caregiving can be rewarding, it can also be incredibly stressful and contribute to physical and emotional health problems for the caregiver. Understanding caregivers’ needs and health risks and supporting them are critical for reducing the personal and public health burden of AD.

Starting in 1995, NIA and NINR funded two clinical trials, REACH I and REACH II, to develop and test strategies for helping dementia caregivers manage their stress and emotional burden. The interventions included education on dementia, training in specific caregiving skills, and encouragement and techniques for physical and emotional self-care. The REACH findings are now being put into practice through two Federal agencies, the Veterans Administration (VA) and the Administration on Aging (AoA).

The VA successfully used REACH strategies in a demonstration project with 19 of its home health care services and is now considering the use of REACH throughout the VA system. AoA’s REACH OUT Program is beginning to implement these strategies through local social service agencies. Researchers reported on one of the AoA-funded efforts, a partnership between the Alabama Department of Senior Services and the University of Alabama. An analysis of 236 caregivers showed significant improvement in caregivers’ sense of burden, social support, depression, and health, as well as care recipient behavior problems and mood (Burgio et al., 2009).

Efforts are underway to develop tests to gauge the emotional well-being of caregivers and identify areas where they may need support. One of these, the Risk Appraisal Measure (RAM), was tested on participants in the REACH II trial. The test probes six areas in which caregivers are at risk: depression, burden, self-care, health behavior, physical safety, and problem behaviors in the care recipients. RAM shows promise as a test to identify caregivers who might benefit from assistance in specific areas, for use in future research on supportive measures, and as a guide for clinicians and community health agencies (Czaja et al., 2009).

Occupational therapy

Participation in meaningful activity is known to promote well-being in older adults, and its potential to reduce symptoms of dementia is now receiving more attention. The Tailored Activity Program (TAP) is a home-based occupational therapy plan that assesses the interests and capabilities of individuals with dementia, provides a program of customized activities for each individual, and trains their families to use those activities as part of their daily care routines. A preliminary study of 57 people with dementia and their caregivers, conducted by researchers at Thomas Jefferson University in Philadelphia, PA, and funded by NIMH, found that the TAP program improved overall levels of pleasure and engagement in the demented individuals, as assessed by their caregivers. It also reduced the extent to which caregivers were upset by the behavioral symptoms of the individuals they were caring for, and improved their sense of skill and personal control in dealing with behavioral problems (Gitlin et al., 2009).

Additional advances in support for caregivers:

- Hilgeman et al. (2009) Testing a theoretical model of the stress process in Alzheimer’s caregivers with race as a moderator. University of Alabama, Tuscaloosa. Supported by NIA and NINR.

- Mitchell et al. (2009) The clinical course of advanced dementia. Hebrew SeniorLife Institute for Aging Research, Boston. Supported by NIA.

- Norton et al. (2009) Caregiver-recipient closeness and symptom progression in Alzheimer disease. Utah State University. Supported by NIA.

- Skarupski et al. (2009) Race differences in emotional adaptation of family caregivers. Rush University. Supported by NIA.

- Vitaliano et al. (2009) Depressed mood mediates decline in cognitive processing speed in caregivers. University of Washington. Supported by NIDDK, NCRR, and NIMH.
Advancing the Future of AD Research: RESOURCES AND COLLABORATION

Alzheimer’s researchers are gaining better understanding of AD pathology and using new insights to develop therapies more likely to be successful in clinical trials. The outpouring of AD-related applications in response to the 2009 American Recovery and Reinvestment Act (ARRA) initiative, many of which were successful in review, demonstrated the vitality of new ideas in the scientific community. Several of these ideas, now supported by ARRA and non-ARRA funds, resulted in large collaborative projects designed to address the multifaceted nature of aging and AD research. However, the profusion of good ideas combined with investment in more expensive collaborative grants has its downside, and that is that the overall success rate for grants is very low and may be difficult to improve in the current economic climate.

As planners and stewards of Federally funded science, NIA must both develop and sustain the research infrastructure necessary for productive research and at the same time phase out approaches that may have outlived their usefulness. In this endeavor, it is critical to maintain and encourage lines of research that hold promise for new therapies while reducing investment in research less crucial to the mission. The Institute keeps current and looks to the future in several ways—by convening and collaborating in forward-looking workshops in these new areas; by working within NIA to vigorously discuss new science and opportunities for new investments; and by partnering with other NIH Institutes and Federal agencies, not-for-profit groups, and industry.

Collaboration has been key for NIA’s coordinating mechanisms and initiatives. By pooling and sharing data widely, and efficiently using the well-established AD research infrastructure, NIA is advancing AD science even within the limits of existing resources.

Research Infrastructure

NIA Intramural Research Program (IRP). In addition to funding a broad portfolio of aging-related and AD research at institutions across the country, NIA supports its own laboratory and clinical research program based in Baltimore, MD. The NIA IRP focuses on understanding age-related changes in physiology and behavior, the ability to adapt to biological and environmental stresses, and developing insight about the pathophysiology of age-related diseases, including AD. Laboratory research ranges from basic science, such as neurogenetics and cellular and molecular neurosciences, to personality and cognition. The IRP also leads the Baltimore Longitudinal Study of Aging, America’s longest-running scientific study of human aging, begun in 1958, along with other clinical research studies.

Alzheimer’s Disease Centers. NIA’s Alzheimer’s Disease Centers (ADCs) form the backbone of the national AD research effort. These multidisciplinary centers, located
at 30 institutions nationwide, promote research, training and education, and technology transfer. With participation by the community, the Centers conduct longitudinal multicenter and collaborative studies of AD diagnosis and treatment, age-related neurodegenerative diseases, and predictors of future change in people without dementia that may indicate the initial stages of development of AD. Complementary studies, such as imaging studies and autopsy evaluations, also are conducted at ADCs. All people enrolled in the Centers receive a standard annual evaluation. Data from those evaluations are collected and stored by the National Alzheimer’s Coordinating Center (NACC, see below) as the Uniform Data Set.

The ADCs serve as sites for other major studies, such as the ADCS and ADNI (see descriptions below). Recently, DNA from 10,000 individuals enrolled in the ADCs was collected for use by the Alzheimer’s Disease Genetics Consortium (ADGC) for whole genome analysis.

**National Alzheimer’s Coordinating Center (NACC).** NIA established NACC in 1999 with the goal of pooling and sharing data on participants in ADC studies. The longitudinal clinical data from living subjects and the brain material and pathological data collected at autopsy give scientists opportunities to conduct clinical-pathological studies with much larger patient samples collected from multiple centers than they could working independently. NACC helps coordinate these studies and, in some cases, provides limited funding.

By 2009, NACC had collected information on more than 90,000 ADC study participants and neuropathologic data on more than 10,000 brains from autopsied participants. Much of these data and autopsy materials are available to qualified AD researchers worldwide. Since 2000, there have been over 60 publications by external researchers using NACC data, 51 publications by NACC personnel, and 95 publications from NACC-funded collaborative ADC projects.

One such study quantitatively assessed pathological plaques and neurofibrillary tangles at autopsy in 97 nondemented participants age 60 years or older (average age 84 years) who had been enrolled in one of seven different ADCs. While all of the research subjects had been determined not to have dementia before death, some did have mild cognitive impairment. The researchers concluded that it is likely that neuropathological processes related to AD in persons without dementia are associated with this mild cognitive decline. By age 80-85 years, many nondemented older adults had substantial AD pathology. (Price et al., 2009)

The NACC data are helping to reveal different symptom patterns in different subsets of AD patients—patterns that would not have become apparent without analyzing a dataset of this size. NACC has also been involved in coordinating other NIA efforts, such as the identification and selection of appropriate postmortem material from the individual ADCs to send to the National Cell Repository for Alzheimer’s Disease for use in the ADGC GWAS studies.

**Alzheimer’s Disease Cooperative Study (ADCS).** NIA launched the ADCS in 1991 to develop and test new interventions and treatments for AD that might not otherwise be developed by industry. Operated under a cooperative agreement with the University of California, San Diego, the large clinical trials consortium, a significant component of NIA’s AD Prevention Initiative, comprises more than 75 sites throughout the United States and Canada. The ADCS focuses on testing agents that lack patent protection, patented drugs
that are marketed for other indications, and novel compounds developed by individuals, academic institutions, and small biotech companies. It also develops new evaluation instruments for clinical trials and innovative approaches to clinical trial design. The group also provides infrastructure support to other Federally funded clinical efforts, including ADNI and the Dominantly Inherited Alzheimer Network (DIAN, a study of familial AD). (See Alzheimer’s Disease Cooperative Study, page 40, for a summary of current trials and studies conducted by the ADCS.)

**The National Cell Repository for Alzheimer’s Disease (NCRAD).** This NIA-funded repository, located at Indiana University Medical Center in Indianapolis, provides resources that help researchers identify the genes that contribute to AD and other types of dementia. NCRAD collects and maintains biological specimens and associated data on almost 43,000 people from a variety of sources, including genetically informative, phenotypically well-characterized families with multiple individuals affected by AD, as well as people enrolled in ADNI, ADGC, and the Ginkgo Evaluation of Memory Study. Qualified research scientists may apply to NCRAD for samples and data to conduct genetic research. Since it was funded, more than 52,000 DNA samples have been requested and sent to investigators across the U.S., resulting in 204 publications.

**NIA Genetics of Alzheimer’s Disease Data Storage Site (NIAGADS).** Located at the University of Pennsylvania, NIAGADS is a Web-based data warehouse for AD genetic data. All genetic data derived from NIA-funded studies on the genetics of late-onset AD are deposited at NIAGADS, another NIA-approved site, or both. Data from GWAS that are stored at NIAGADS are also made available through the database of Genotype and Phenotype (dbGaP) at the National Library of Medicine’s National Center for Biotechnology Information, which was developed to archive and distribute the results of large-scale GWAS analyses. Through dbGaP, data sets from multiple GWAS done on different platforms can be merged, and data from thousands of study participants can be analyzed together, increasing the probability of gene discovery.

**Initiatives**

**Alzheimer’s Disease Neuroimaging Initiative (ADNI).** In 2004, NIA launched this groundbreaking initiative, the largest public-private partnership to date in AD research. The goal was to find neuroimaging and other biological markers that could be used to detect AD progression and measure the effectiveness of potential therapies. The study recruited 800 participants, a mix of cognitively healthy people and those with AD or MCI. To speed the pace of analysis and findings, ADNI investigators agreed to make their collected data widely available. MRI and PET scan brain images as well as clinical, genetic, and fluid biomarker data are available to qualified researchers worldwide through a Web-based database.

The first phase of ADNI has already borne remarkable fruit: more than 170 papers using ADNI data have been published from investigators around the world, and many more will come as further data are collected and analyzed. These early findings have generated excitement about using brain and fluid markers to identify people who may be at risk for developing AD or for cataloguing their pace of deterioration. Accomplishments include new findings about how changes in the structure of the hippocampus may help detect disease progression and effectiveness of potential treatments, and the establishment of biomarker and imaging measures that predict risk for cognitive decline and conversion to dementia in this clinical cohort. (See Biomarkers and ADNI, page 33, for descriptions of several published studies.) The success of ADNI has inspired similar efforts in Europe, Japan, and Australia. A follow-on effort, ADNI-GO, was launched with ARRA funds in 2009, and ADNI 2 was launched in fall 2010. ADNI 2 will enroll a new cohort.
of participants with very early MCI and continue to follow participants in the other ADNI cohorts, with the goal of identifying and tracking early changes in the brain before the onset of AD symptoms.

Alzheimer’s Disease Genetics Initiative (ADGI) and Alzheimer’s Disease Genetics Consortium (ADGC). The study of AD genetics is complicated by the likelihood that the risk of late-onset AD is influenced by many genes, each of which confers a relatively small risk. Identifying these genes requires analyzing the genomes of large numbers of people. ADGI was launched in 2003 to identify at least 1,000 families containing both members who have late-onset AD and members who do not. The ADGC was funded in 2009 to support the use of large-scale, high-throughput genetics technologies by researchers studying late-onset AD.

The ADGC confirmed the likely role of three newly discovered genes in contributing to the risk of LOAD (see Discovering New Genetic Mechanisms, page 21) and is now working to confirm additional genes in collaboration with research groups in Europe. In addition to providing additional insight into AD pathogenesis and suggesting therapeutic targets, these new gene discoveries may also one day help predict who is at risk for AD.

Revising AD Diagnostic Criteria. NIA and the Alzheimer’s Association organized two meetings in spring 2009 to discuss new data and technologies for improving the clinical diagnosis of AD and a research agenda for diagnosis at earlier stages of the disease. The current system of AD classification has deficiencies that limit its utility for drug development, research, and practice. Existing standards for diagnosis of the dementia stage of AD, the NINCDS-ADRDA clinical criteria, are more than 25 years old and do not address very early and presymptomatic AD. They were developed without the knowledge available from more recent studies on the epidemiology of AD, clinical-pathologic correlations, and diagnostic imaging and fluid biomarkers.

Following discussion at the meetings, three working groups were set up, one to revise the NINCDS-ADRDA criteria for Alzheimer’s dementia; a second to better define the stage(s) between normal and Alzheimer’s dementia, often termed MCI; and a third to examine factors in older individuals with no symptoms or very minor symptoms that may predict MCI and Alzheimer’s dementia.

The overall goals of this project are to better define the natural history of AD, from its asymptomatic stages to clinically diagnosed dementia, and to attempt to relate clinical symptoms as they emerge to underlying pathophysiology. An overarching goal is to stimulate research on how imaging and fluid biomarkers can contribute to the identification of people at risk for cognitive dysfunction and to better diagnose them after symptoms appear.

The groups presented their preliminary proposals at the International Conference on Alzheimer’s Disease (ICAD) in July 2010. The three committees are reviewing public comments and will publish proposed guidelines in a scientific journal in 2011. The guidelines, primarily for use in research studies, will likely be revisited and revised periodically as new data emerge from imaging and biomarker research studies.

AD Translational Initiative. Launched in 2004, the AD Translational Initiative supports early drug discovery and drug development research by academic scientists and small biotechnology companies, with the goal of
finding ways to treat and prevent AD, MCI, and age-related cognitive decline. This effort is broadening the range of potential treatments and therapeutic targets by supporting critical steps of translational research that are traditionally not supported by the pharmaceutical industry. In 2009, the NIA committed $5 million to continue two funding initiatives for early drug discovery and preclinical drug development through 2012. (See more about translational research, page 35.)

**AD Pilot Clinical Trials Initiative.** This initiative, begun in 1999, is aimed at increasing the number and quality of preliminary clinical evaluation of interventions for AD, MCI, and age-associated cognitive decline. The goal is not to duplicate or compete with pharmaceutical companies but to encourage, complement, and accelerate the process of testing new, innovative, and effective treatments. Initially focused on drug interventions, the program has been broadened to nonpharmacologic as well as pharmacologic interventions. NCCAM and NINR also participate in this initiative. (See **AD Clinical Trials**, page 38, for summaries of pilot clinical trials.)

**Research Partnership on Cognitive Aging.** Through the Foundation for NIH, NIA and the McKnight Brain Research Foundation convened a Cognitive Aging Summit in 2007 focused on healthy brain aging and function. This summit helped galvanize the field and served as a catalyst for two subsequent research initiatives. The first, “Remediation of Age-Related Cognitive Decline,” is funding research on pilot interventions to reverse age-related decline or maintain successful function. The second, “Neural and Behavioral Profiles of Cognitive Aging,” is funding studies to understand neural and behavioral mechanisms involved the maintenance of cognitive health and to identify characteristics that distinguish normal age-related change from pathological decline. A second Summit, held in October 2010, shared progress from funded studies and identified future research directions.

**NIH Toolbox for Assessment of Neurological and Behavioral Function.** Awarded in 2006, this contract is supported by the NIH Blueprint for Neuroscience Research and the NIH Opportunity Network for Basic Behavioral and Social Science Research. The goal is to develop a set of brief tests to assess cognitive, sensory, motor, and emotional function, particularly in studies with many people (such as epidemiological studies and clinical trials). The tests will be available in English and Spanish and applicable for use in individuals age 3 to 85, enabling direct comparison of cognitive and other abilities at different ages across the lifespan.

**NIH Blueprint for Neuroscience Research Initiative on the Human Connectome Project.** The Human Connectome Project was started in 2010 to develop and share knowledge about the structural and functional connectivity of the healthy human brain. This collaborative effort will use state-of-the-art imaging instruments, analysis tools, and informatics technologies to map the neural pathways underlying human brain function. The project will map the connectomes in 1,200 healthy adults—twin pairs and their siblings—and will study anatomical and functional connections between regions of the brain, which will be related to behavioral test data. The goal is to reveal the contributions of genes and environment in shaping brain circuitry and the variability in such connectivity. The human connectome map of the healthy adult brain will serve as a foundation to further understand how brain networks change with age and neurological diseases like Alzheimer’s.


“This course was developed from the public domain document: Alzheimer’s Disease: Unraveling the Mystery and the Progress Report on Alzheimer’s Disease Translating New Knowledge – U.S. Department of Health and Human Services.”