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 radioactive 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 postsynaptic, 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.
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 (see The Hallmarks of AD on page 21 for more information on plaques and tangles).
- Damage by free radicals increases (free radicals are a kind of molecule that reacts easily with other molecules; see The Aging Process on page 42 for more on these 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

_Vascular Disease_ on page 43 and _Lifestyle Factors_ on page 45 provide more information about these issues and how they may influence the risk of developing AD.
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.
What Happens to the Brain in 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).

To view a video showing what happens to the brain in AD, go to www.nia.nih.gov/alzheimers/alzheimers-disease-video.
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.
From APP to Beta-Amyloid Plaque

- APP
- Beta-secretase
- Gamma-secretase
- Beta-amyloid Peptide
- Oligomers
- Fibrils
- sAPPβ
- Cell Surface
- Inside Cell
- Cell Membrane
- PLAQUE
Healthy and Diseased Neurons

HEALTHY NEURON

DISEASED NEURON
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.
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.
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
Imagine 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.

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...
This chart shows current thinking about the evolution from healthy aging to AD. Researchers view it as a series of events that occur in the brain over many years. This gradual process, which results from the combination of biological, genetic, environmental, and lifestyle factors, eventually sets some people on a course to MCI and possibly AD. Other people, whose genetic makeup may be the same or different and who experience a different combination of factors over a lifetime, continue on a course of healthy cognitive aging.

Amnestic MCI: memory problems; other cognitive functions OK; brain compensates for changes

Total loss of independent function

Normal age-related memory loss

Healthy Aging

Amnestic MCI

Clinically Diagnosed AD

<table>
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<tr>
<th>Life Course</th>
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<td>Birth</td>
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AD brain changes start decades before symptoms show

Cognitive decline accelerates after AD diagnosis

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 transformative 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.

The Buddy Program pairs medical students and people with AD to spend time with—and learn from—each other.
AD RESEARCH: Better Questions, New Answers
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.
DNA, Chromosomes, and Genes: The Body’s Amazing Control Center

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 ε4, 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. ☀
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 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.

**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
- PD
- VaD
- ALS
- FTLD

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*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. 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 (see *Describing Scientific Findings: The Type of Study Makes an Important Difference* on page 47 for more information about epidemiologic studies). 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
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.

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
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.

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 (see Participating in a Clinical Trial on page 59 for more on this kind of research).