ALZHEIMER'S DISEASE

Unraveling the Mystery

National Institute on Aging
National Institutes of Health

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Preface

Over the past few decades, Alzheimer's disease (AD) has emerged from obscurity. Once considered a rare disorder, it is now seen as a major public health problem that has a severe impact on millions of older Americans and their families. The National Institute on Aging (NIA) is the lead agency for AD research at the National Institutes of Health (NIH). NIA launched its AD program in 1978, and since then, the study of this disease has become one of NIA's top priorities. Several other NIH institutes also conduct and sponsor studies on AD.

Thanks to the work of NIH institutes, other research organizations around the world, and many private-sector research, education, and advocacy groups, the study of AD is moving ahead rapidly. This book explains what AD is, describes the main areas in which researchers are working, and highlights new approaches for helping families and friends care for people with AD.

TO GET THE MOST OUT OF THIS BOOK

Learn the Basics of the Healthy Brain

- The parts of the brain (pages 10-13)
- How neurons work (pages 14-16)
- The changing brain in healthy aging (pages 17-19)

Discover What Happens to the Brain in AD

- The hallmarks of AD (pages 21-26)
- The changing brain in AD (pages 27-33)

Explore Cutting-Edge AD Research

- Looking for causes (pages 36-47)
- Diagnosing AD (pages 48-53)
- Searching for treatments (pages 54-61)

Learn about Caregiver Support

- Who are AD caregivers? (page 63)
- Reducing the personal costs of caregiving (pages 64-67)
- Taking care of mom or dad from a distance (page 68)

TO LEARN EVEN MORE

Visit NIA's Alzheimer's Disease Education and Referral Center website at *www.nia.nih.gov/Alzheimers.* There, you will find resources to accompany this book, such as downloadable versions of the illustrations and an animation that shows what happens to the changing brain in AD. And while you are there, explore the ADEAR Center's many other offerings. These include free publications about AD and AD caregiving, clinical trials information, a list of NIA-funded Alzheimer's Disease Centers, and NIA's searchable AD Library database of thousands of materials about AD.

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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**

See the glossary on page 70 for definitions of **boldfaced** terms.

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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.

Visit the National Institute on Aging (NIA) Alzheimer's Disease Education and Referral (ADEAR) Center website at *www.nia.nih.gov/Alzheimers/ADvideo* to view an animation that helps this part of the book come alive.

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- **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

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.

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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.

D.

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

1990s

- The U.S. Food and Drug Administration (FDA) approves tacrine (Cognex®), 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 **transgenic** mouse model of AD is created.
- Additional diagnostic criteria are developed for AD.
- Characteristics of **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 **clinical trials**.

2000s

- The FDA approves other AD drugs, including rivastigmine (Exelon®), galantamine (Razadyne®), donepezil (Aricept®), and memantine (Namenda®) 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.

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PART 1

The Basics of the Healthy Brain

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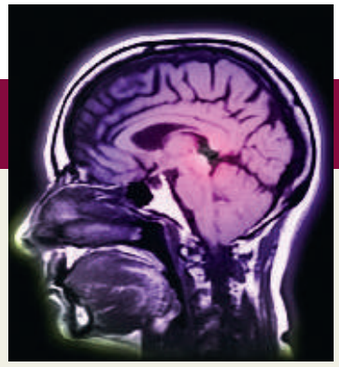
To understand AD, it is important to know a bit about the brain. This part of *Unraveling the Mystery* gives an inside view of the normal brain, how it works, and what happens during aging.

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 100,000,000,000,000 (100 trillion)

NUMBER OF CAPILLARIES
(tiny blood vessels)
about 400,000,000,000 (400 billion)

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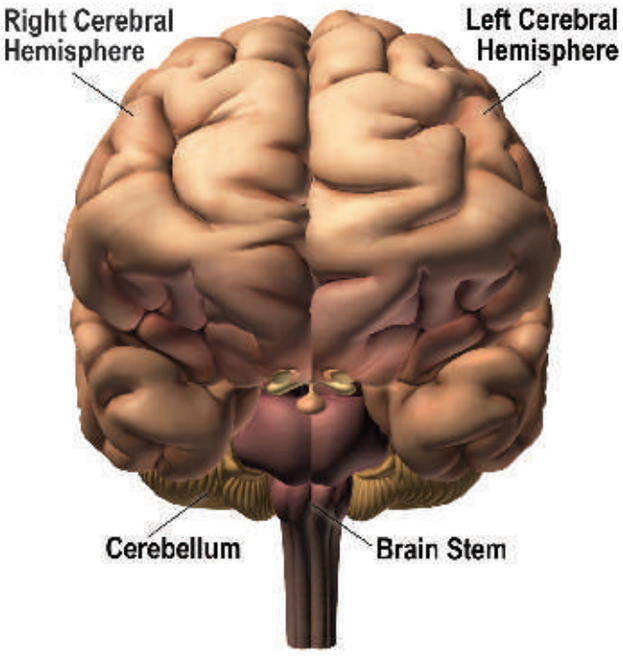
Inside *the* Human Brain

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

Front View of the Brain



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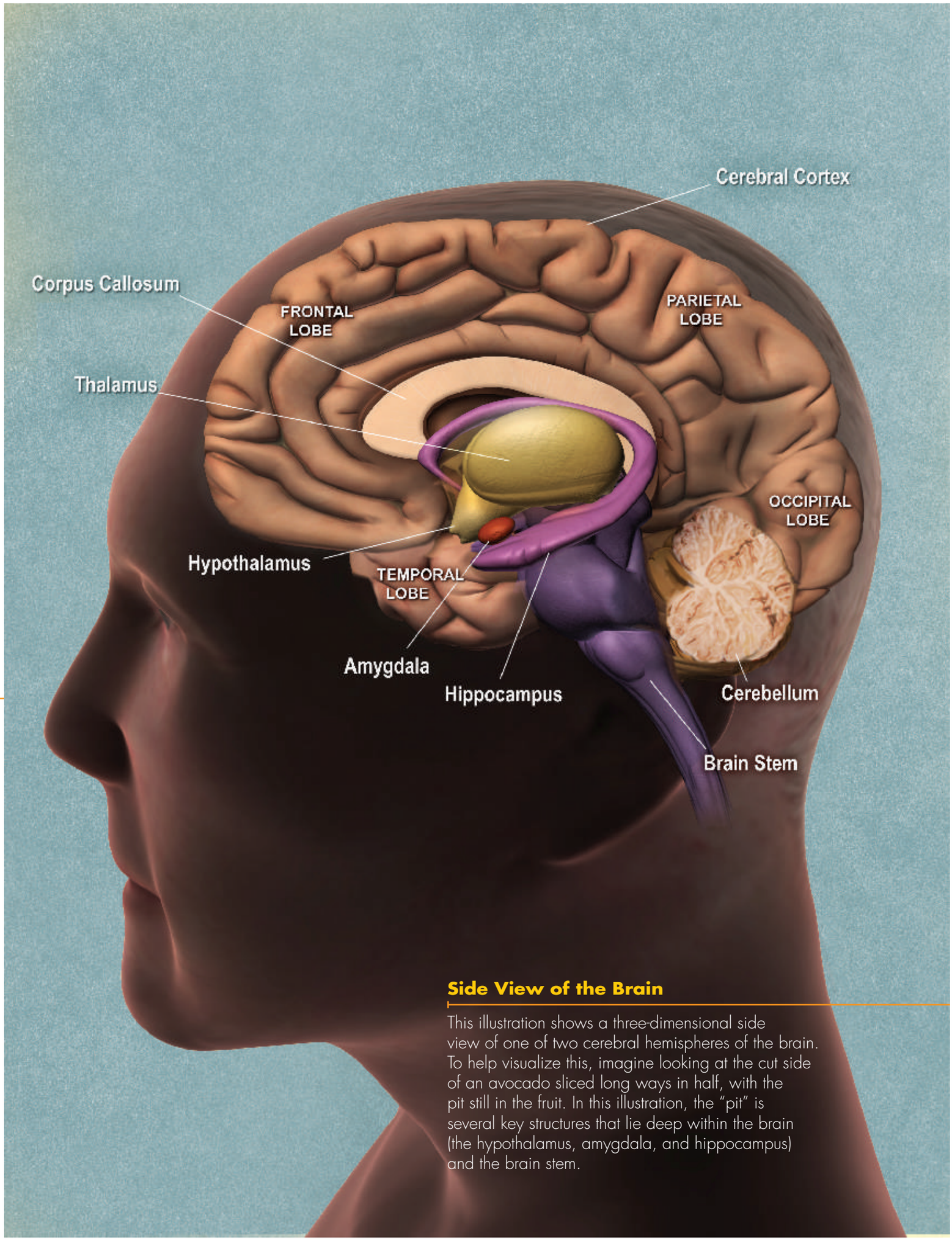

Side View of the Brain

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.

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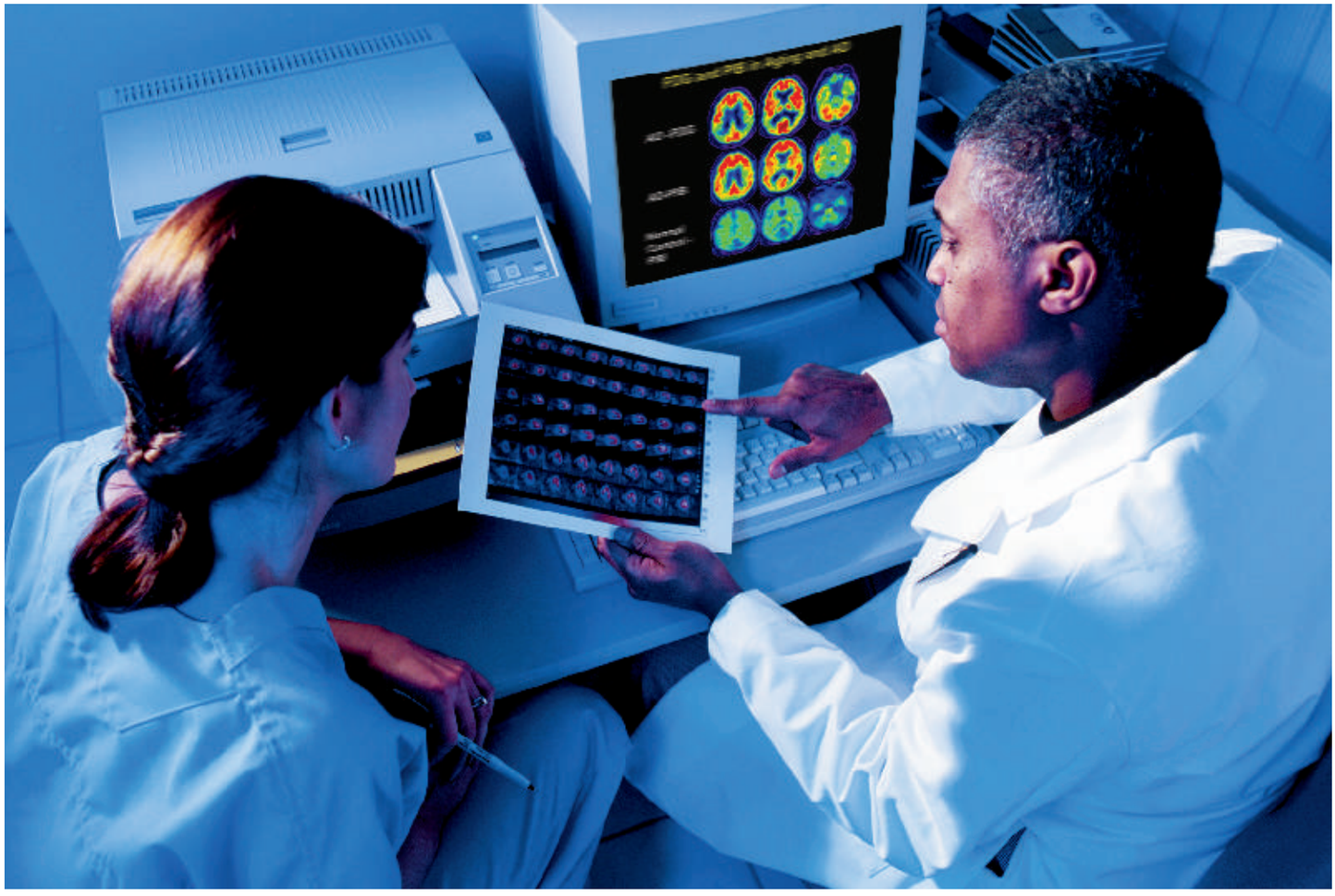

In essence, a PET scan produces a "map" of the active brain.

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 whilesleeping 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.

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Neurons *and Their* Jobs

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.

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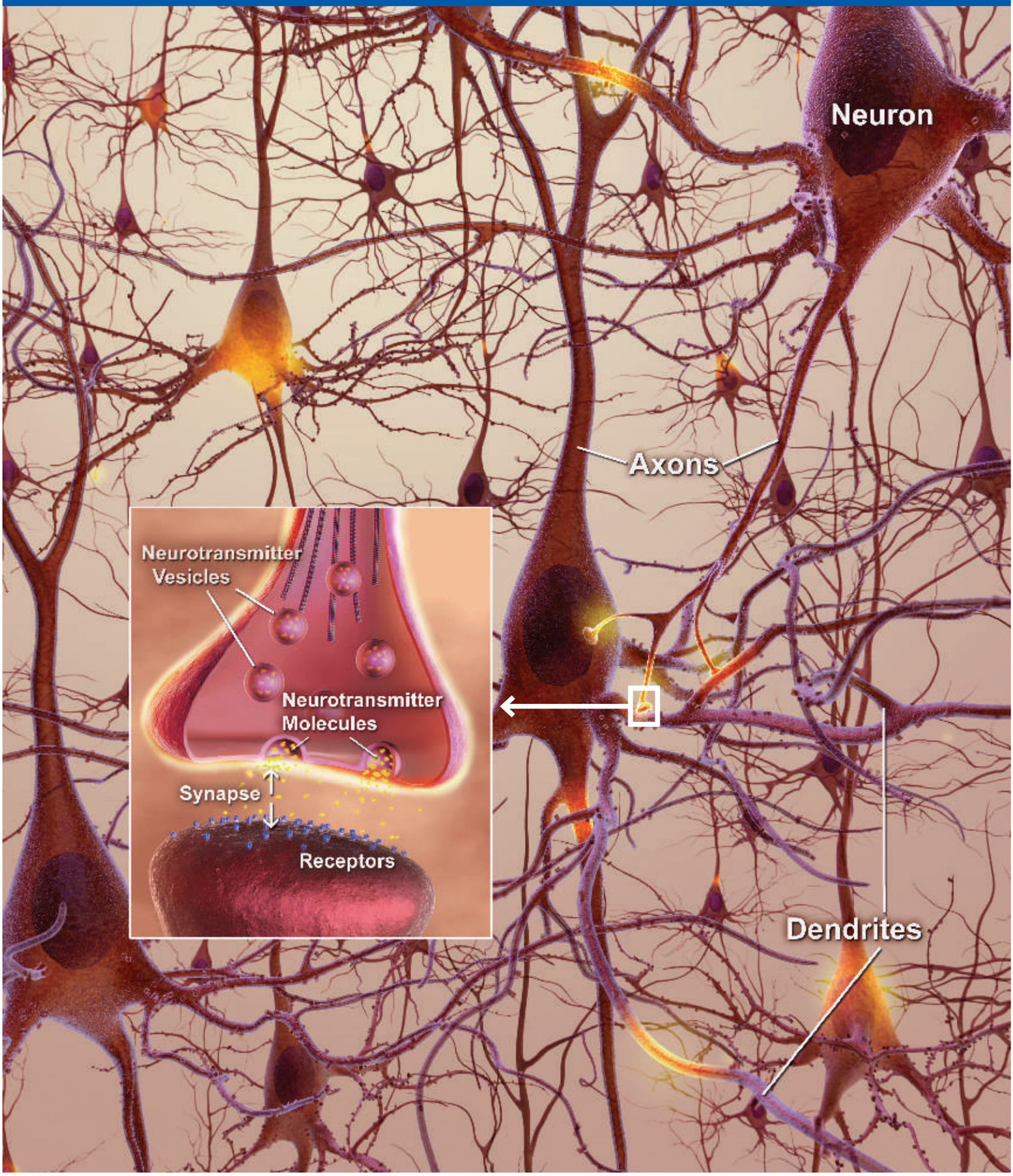
Neurons in the Brain



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 (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,

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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.

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ACTIVE Study May Provide Clues to Help Older Adults Stay Mentally Sharp

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 recieved 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.

PART 2

What Happens to the Brain *in* AD

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The Hallmarks *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).

To view a video showing what happens to the brain in AD, go to *www.nia.nih.gov/Alzheimers/ADvideo.*

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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).

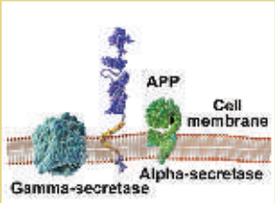

Figure 1

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).

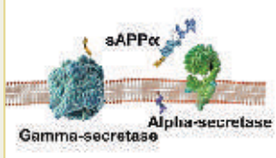

Figure 2

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.

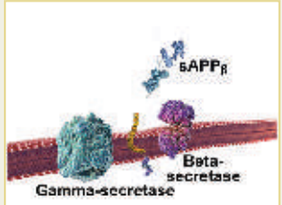

Figure 3

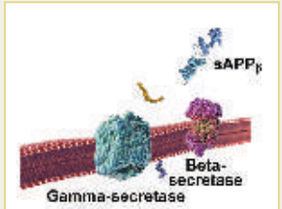

Figure 4

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.

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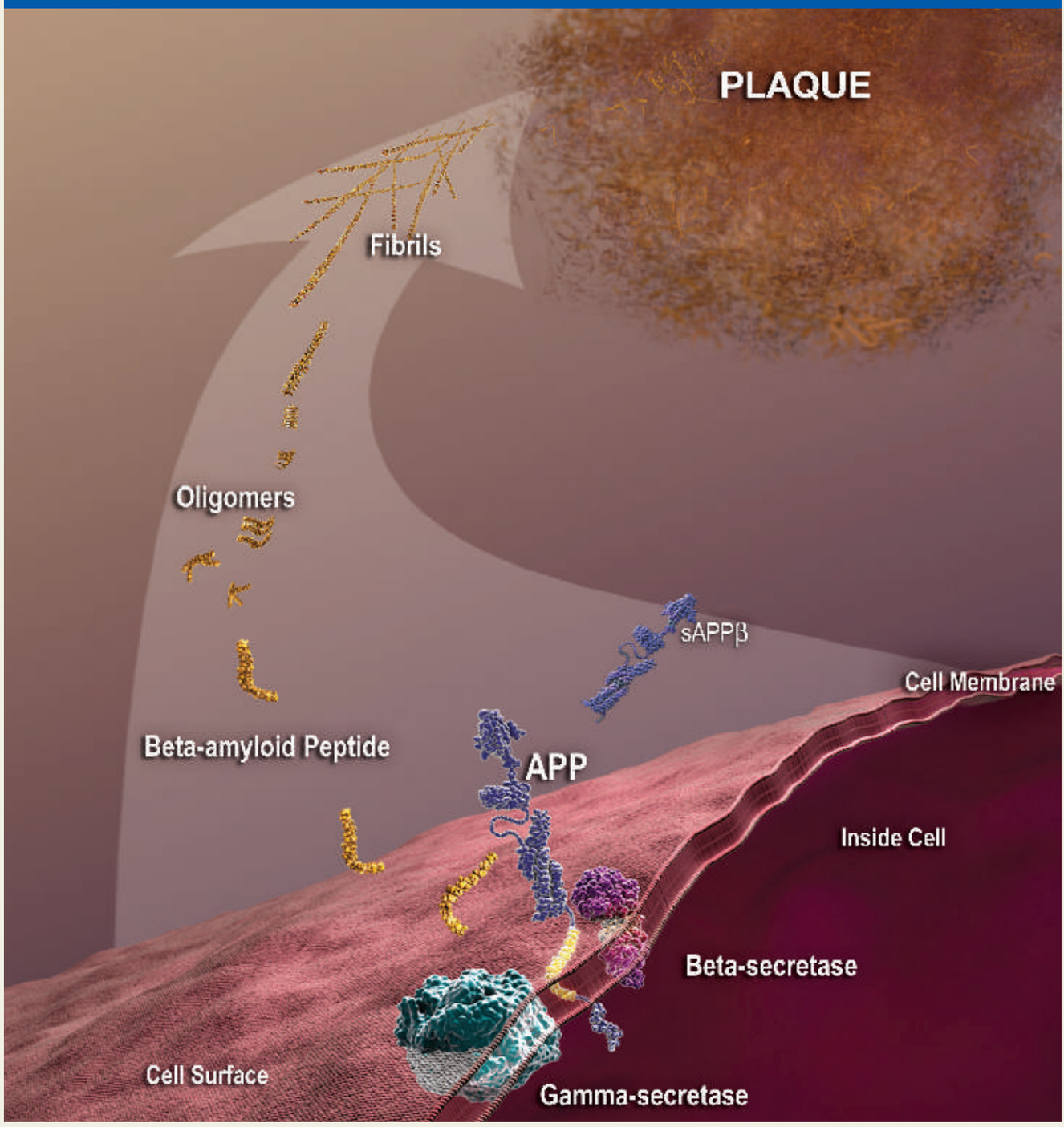
From APP to Beta-Amyloid Plaque



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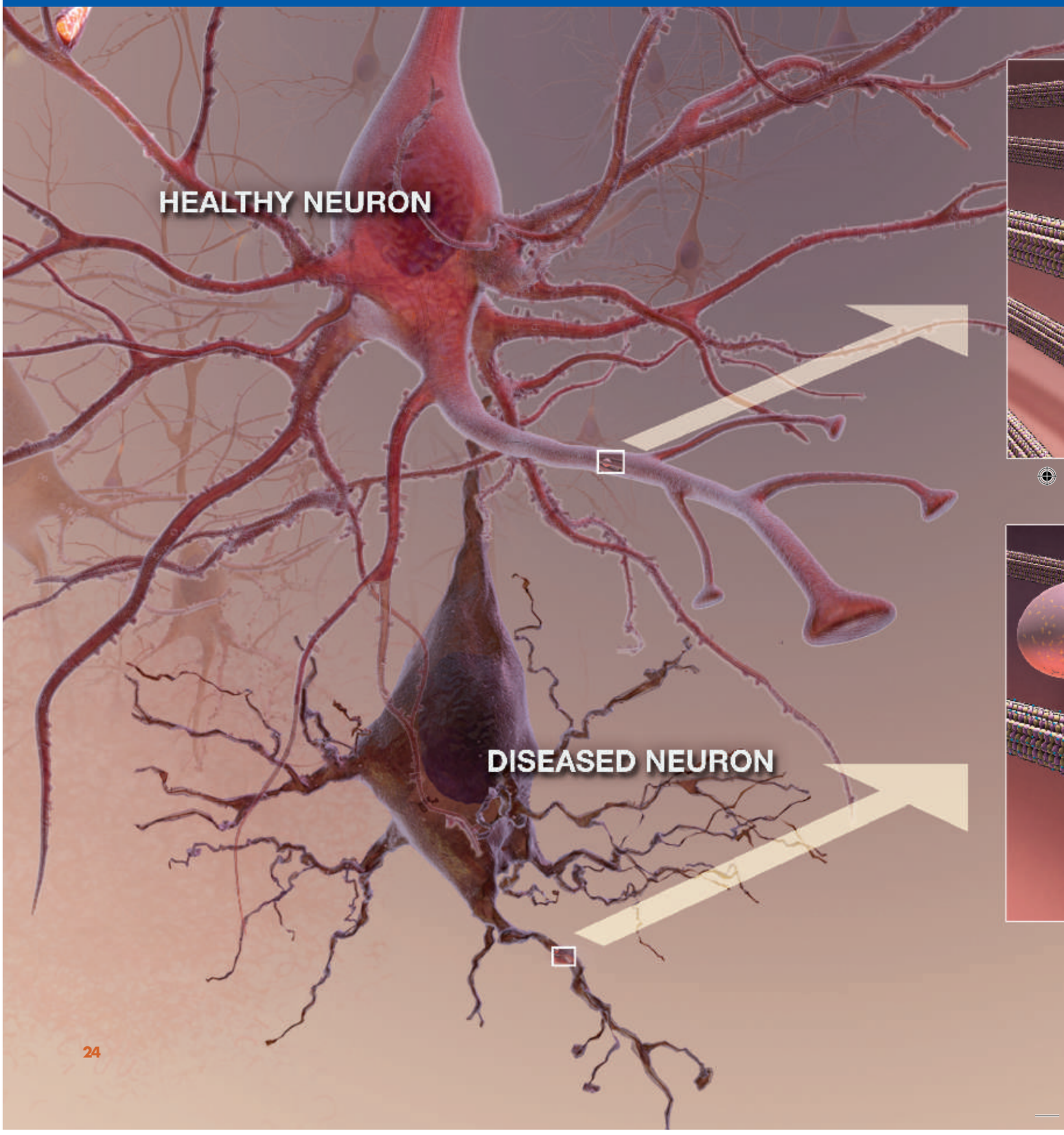
Healthy and Diseased Neurons



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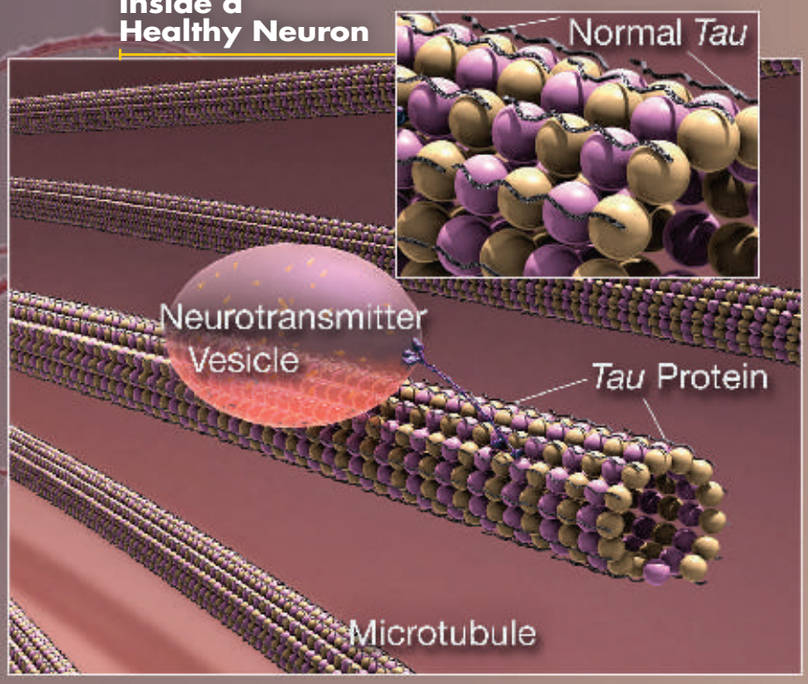
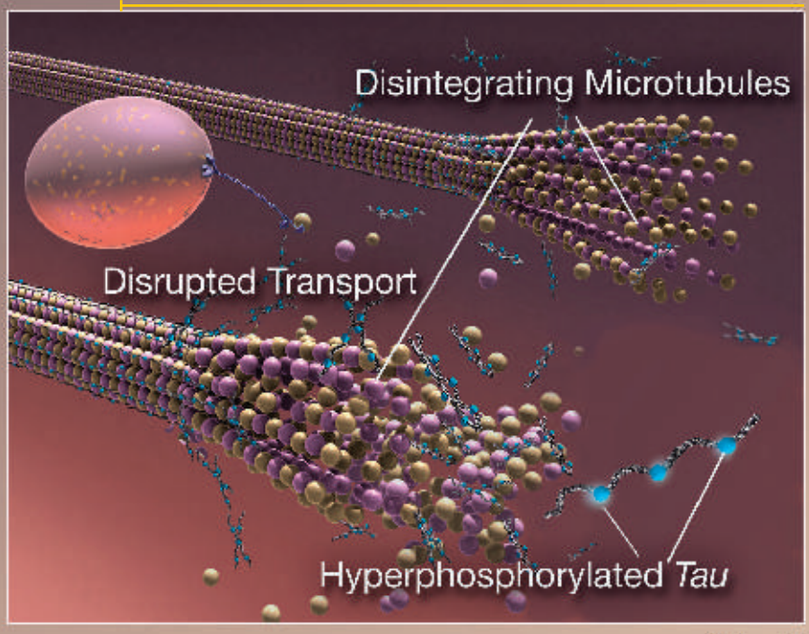
Inside a Healthy Neuron



Inside a Diseased Neuron



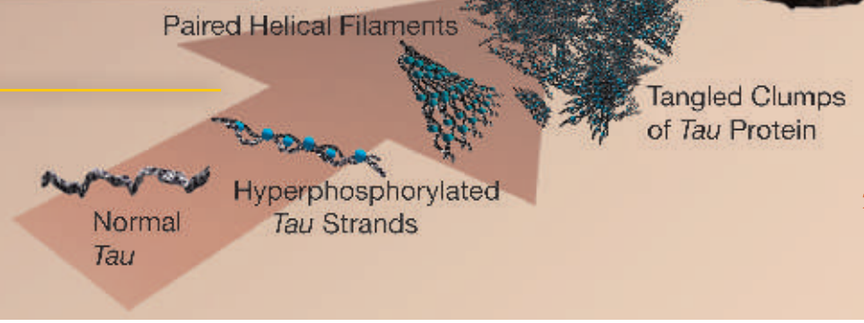
NEUROFIBRILLARY TANGLES

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.

Formation of *Tau* Tangles



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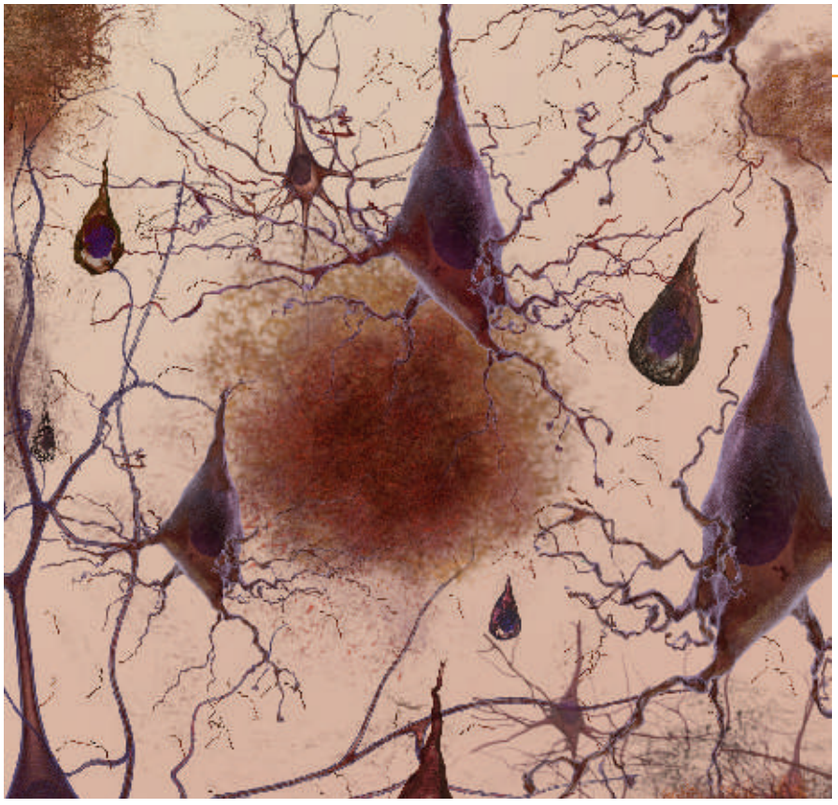
LOSS OF CONNECTION BETWEEN CELLS AND CELL DEATH

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.



Loss of Connection Between Cells

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

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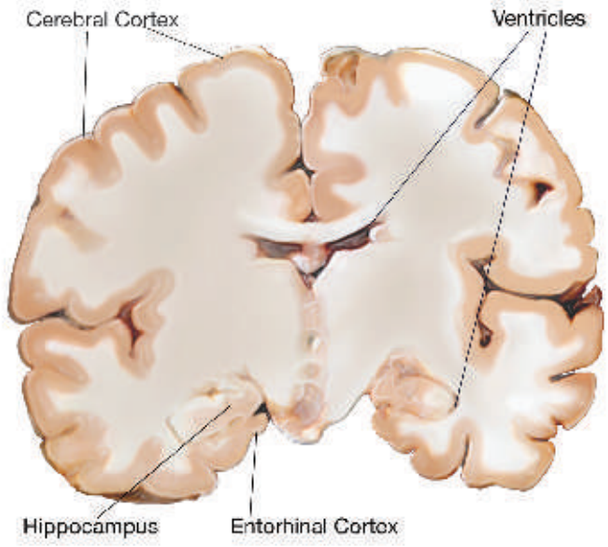
The Changing Brain *in* AD

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



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

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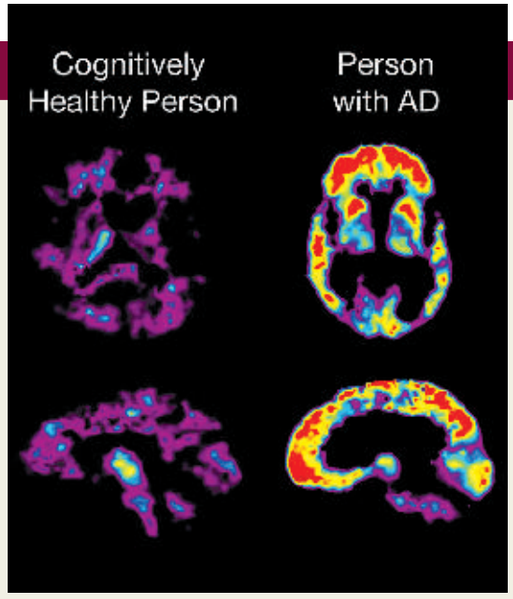
PiB and PET

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.



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

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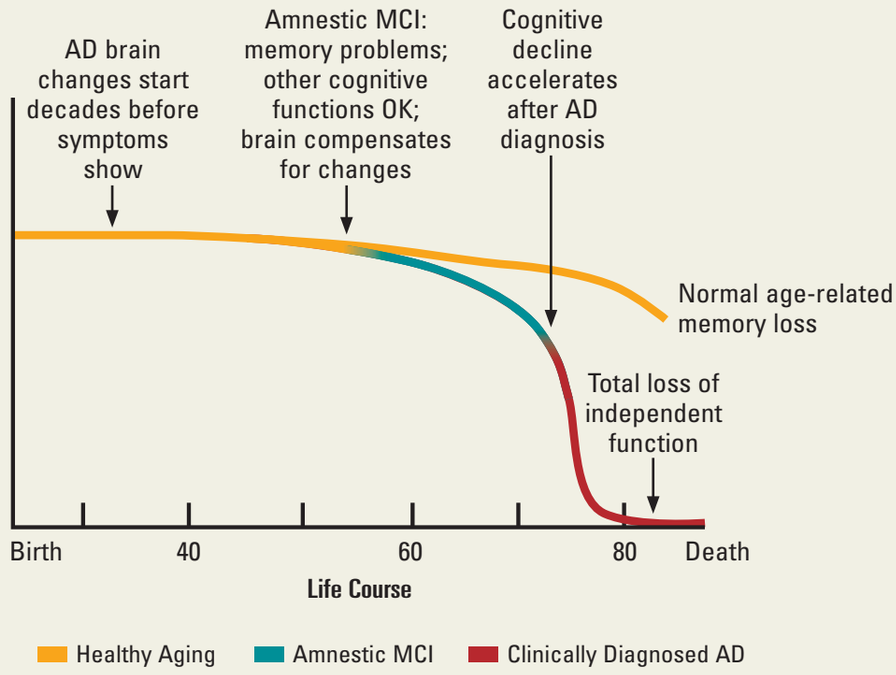
Charting the Course from Healthy Aging to AD

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.



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

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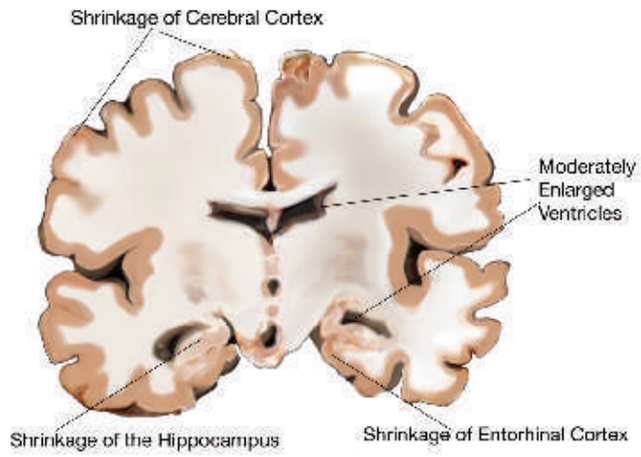
explored whether changes in older adults' ability to move about and use their bodies might be a sign of early AD. The researchers found that participants with MCI had more movement difficulties than the cognitively healthy participants but less than those with AD. Moreover, those with MCI who had lots 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 to Moderate 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.

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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

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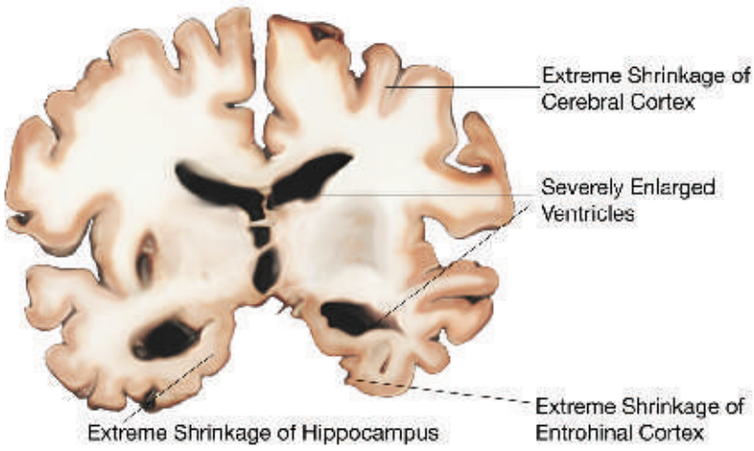
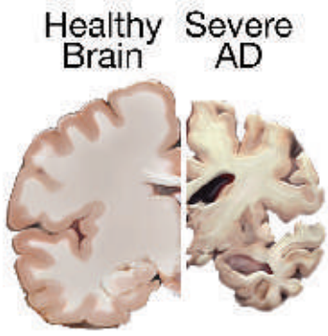
- Groaning, moaning, or grunting
- Increased sleeping
- Lack of bladder and bowel control

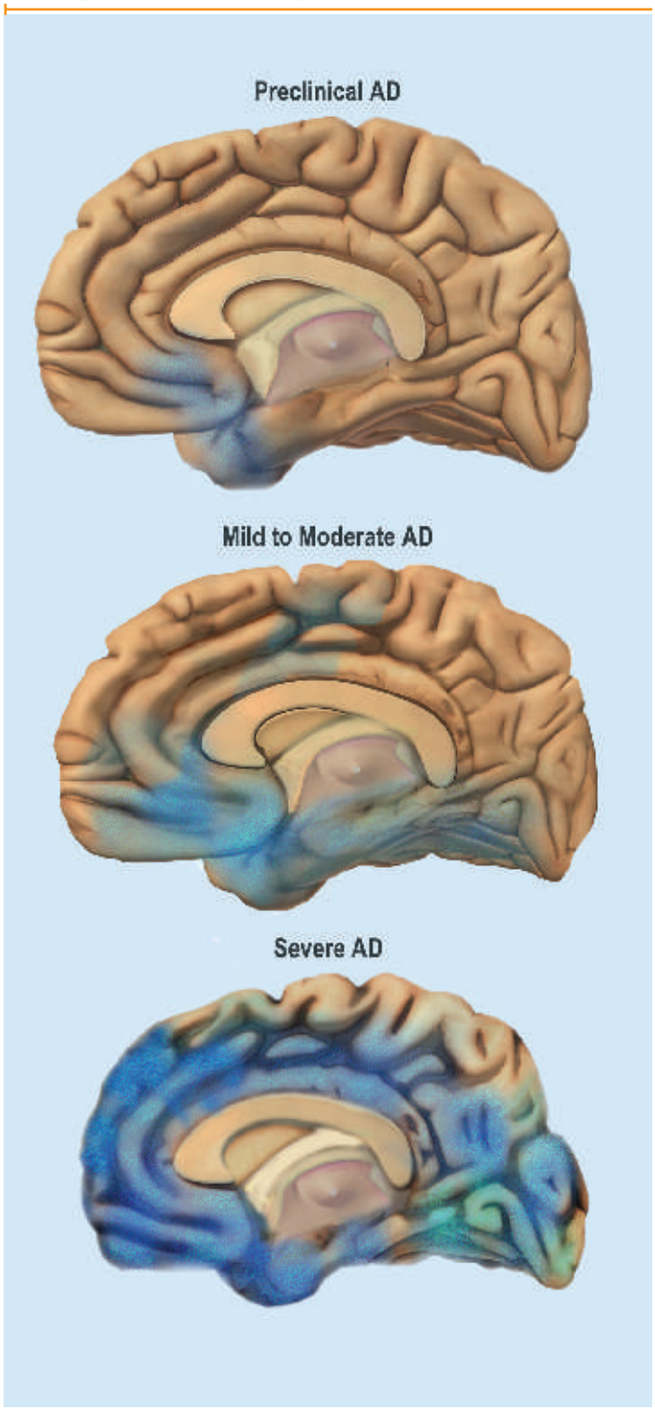
Near the end, the person may be in bed much or all of the time. The most frequent cause of death for people with AD is aspiration pneumonia. This type of pneumonia develops when a person is not able to swallow properly and takes food or liquids into the lungs instead of air.

Severe AD





AD Spreads Through the Brain



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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.

The Buddy Program pairs medical students and people with AD to spend time together to learn from each other.

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.

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PART 3

AD RESEARCH: Better Questions, New Answers

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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.

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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

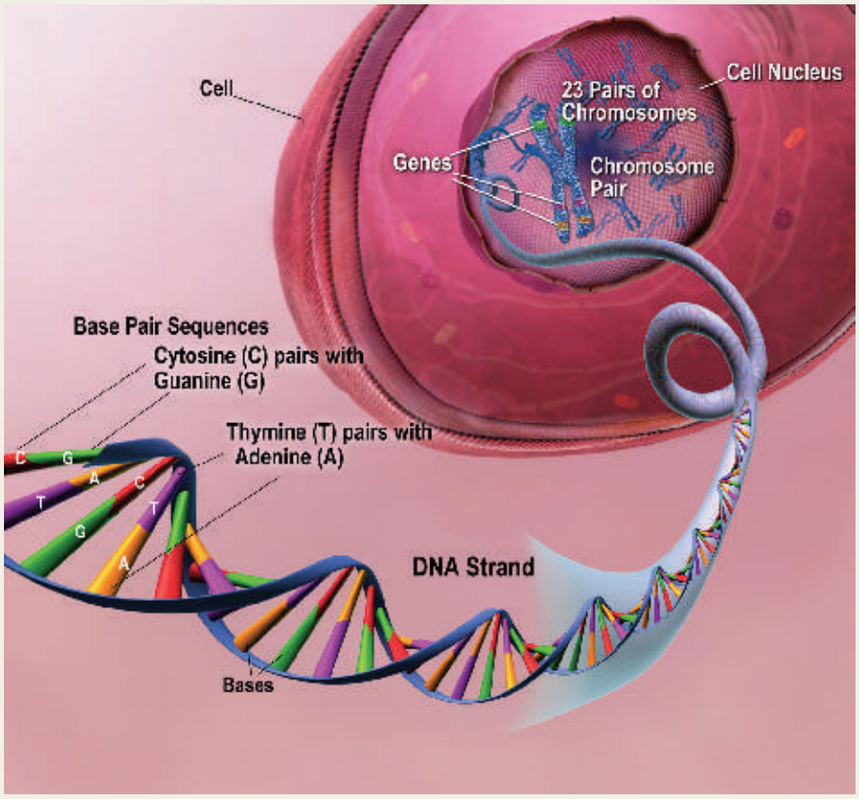
Genetic studies of complex neurodegenerative diseases such as AD focus on two main issues—whether a gene might influence a person's overall risk of developing a disease and whether a gene might influence some particular aspect of a person's risk, such as the age at which the disease begins. Slow and 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**.

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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.

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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.

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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,

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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

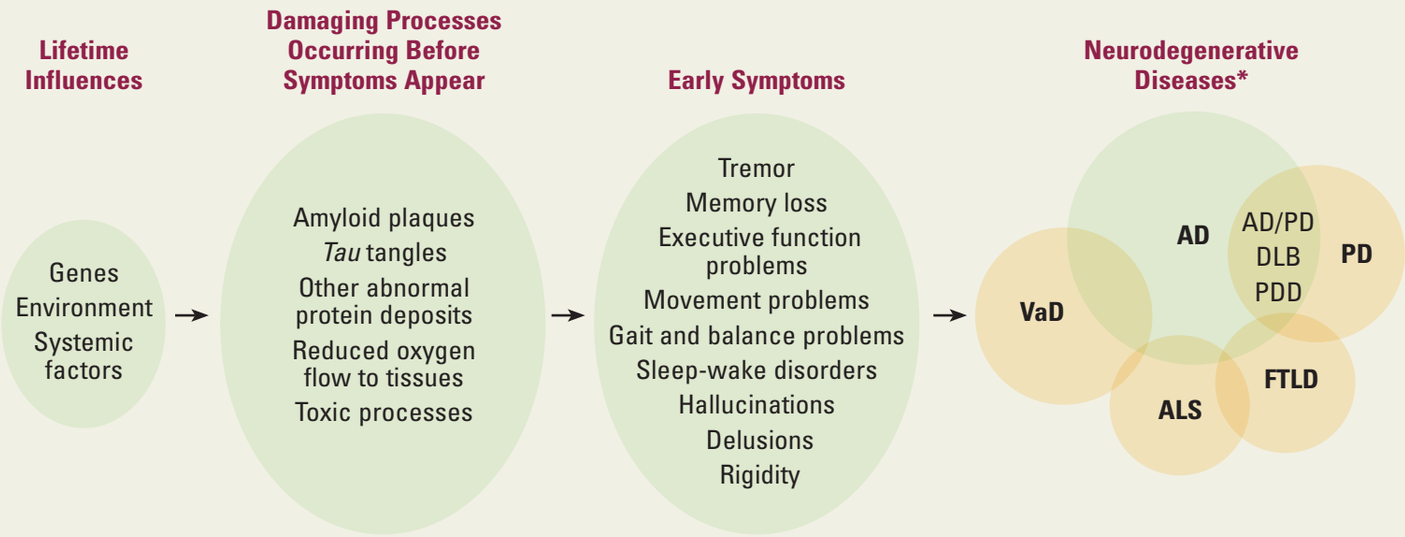
Researchers have found that a number of devastating neurodegenerative diseases (for example, AD, Parkinson's disease, dementia with Lewy bodies, frontotemporal lobar degeneration, Huntington's disease, and prion diseases) share a key characteristic—protein misfolding.

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

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.



*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

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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.

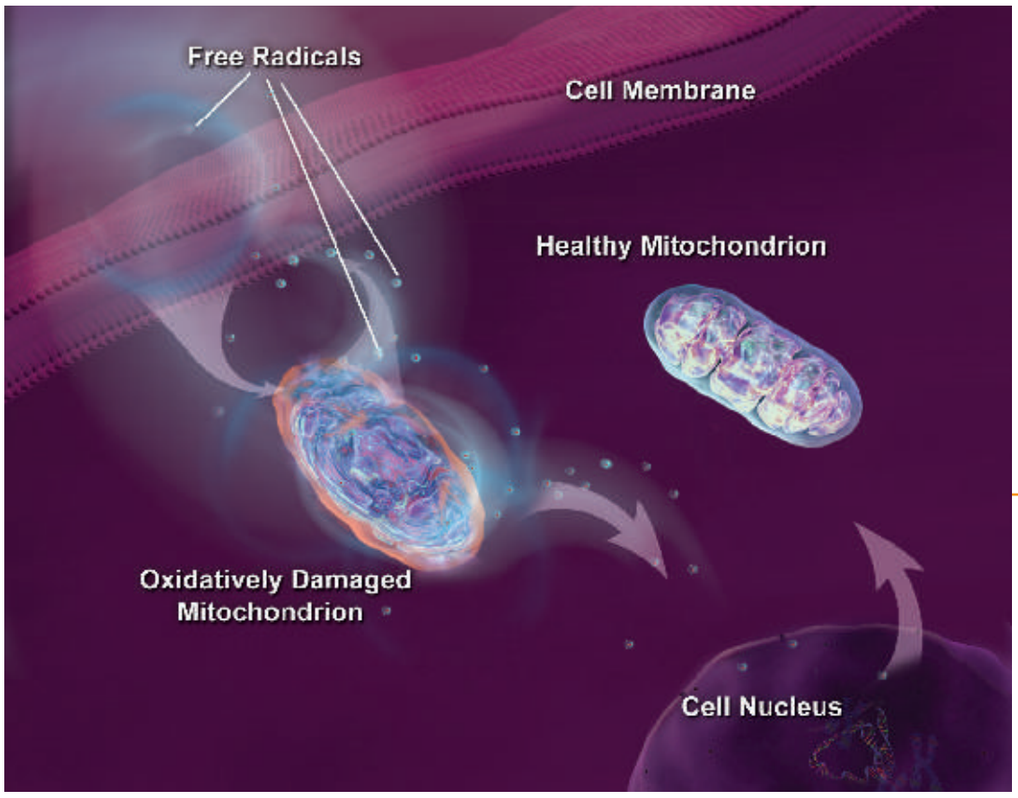
Scientists do not know exactly why or how these processes occur, but research into the unique characteristics and actions of various misfolded proteins is helping investigators learn more about the similarities and differences across age-related neurodegenerative diseases. This knowledge may someday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



Mitochondria and Free Radicals

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.

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The Brain's Vascular System

This image shows the complexity of the human brain's vascular system, particularly large and small arteries that carry oxygen from the lungs to the brain. Although many blood vessels are visible here, this image shows fewer than half of the total number in the brain.

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

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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.

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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.

If you want to know more about the benefits of exercise and physical activity and learn ways to be active every day, NIA has free information just for you!

Call 1-800-222-2225 or visit *www.nia.nih.gov/Exercise*.

- 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

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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

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

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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 the underlying course of the disease (see **Helping People with AD Maintain their Mental Functioning** on page 55 for more about these drugs).

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

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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.

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Causes of Dementia

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 B_{12} 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 (see **Very Early Signs and Symptoms** on page 28 for more on this work).

One of the most exciting areas of ongoing research in this area is neuroimaging. Over the past decade, scientists have developed several

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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.

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New Technologies Help People Participate in AD Research at Home

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.

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

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.

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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

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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.

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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.

Coping with Behavioral Symptoms

For more information on how to deal with behavioral issues and symptoms, visit the caregiving section of NIA's Alzheimer's Disease Education and Referral (ADEAR) Center website at: *www.nia.nih.gov/Alzheimers/Caregiving/HomeAndFamily*.

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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

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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 damage (see **The Aging Process** on page 42 for more on oxidative damage). About 6,000 of the more than 30,000 men enrolled in SELECT are participating in PREADVISE.

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Participating in a Clinical Trial

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

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Participating in a Clinical Trial *(Continued)*

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.

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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 (ADEAR) 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)*.

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PART 4

Improving Support *for* Families *and Other* Caregivers

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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.

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Research Findings *Benefit* Caregivers

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

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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

Where Are People with Alzheimer's Disease Cared For?

- Home
- Assisted living facilities (those in the early stages)
- Adult day care centers
- Nursing homes
- Special care units

For Information About AD Support Groups

To find out whether an AD support group is operating in your area, contact:

- NIA's Alzheimer's Disease Education and Referral (ADEAR) Center at 800-438-4380 or visit *www.nia.nih.gov/Alzheimers/ResearchInformation/ResearchCenters*
- Alzheimer's Association at 800-272-3900 or visit *www.alz.org*

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resources, involving other family members and friends, and balancing the needs of the person with their own needs.

■ **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

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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.

What Happens Next?

It is a question many people and their families ask when AD is first diagnosed. Members of an early-stage support group at the Northwestern University Alzheimer's Disease Center in Chicago wrote *What Happens Next?* to help people with early-stage dementia cope with their feelings and the practical aspects of everyday life.

To view or download a free copy, visit *www.nia.nih.gov/Alzheimers/Publications/WhatHappensNext.htm*.

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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.

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

"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.

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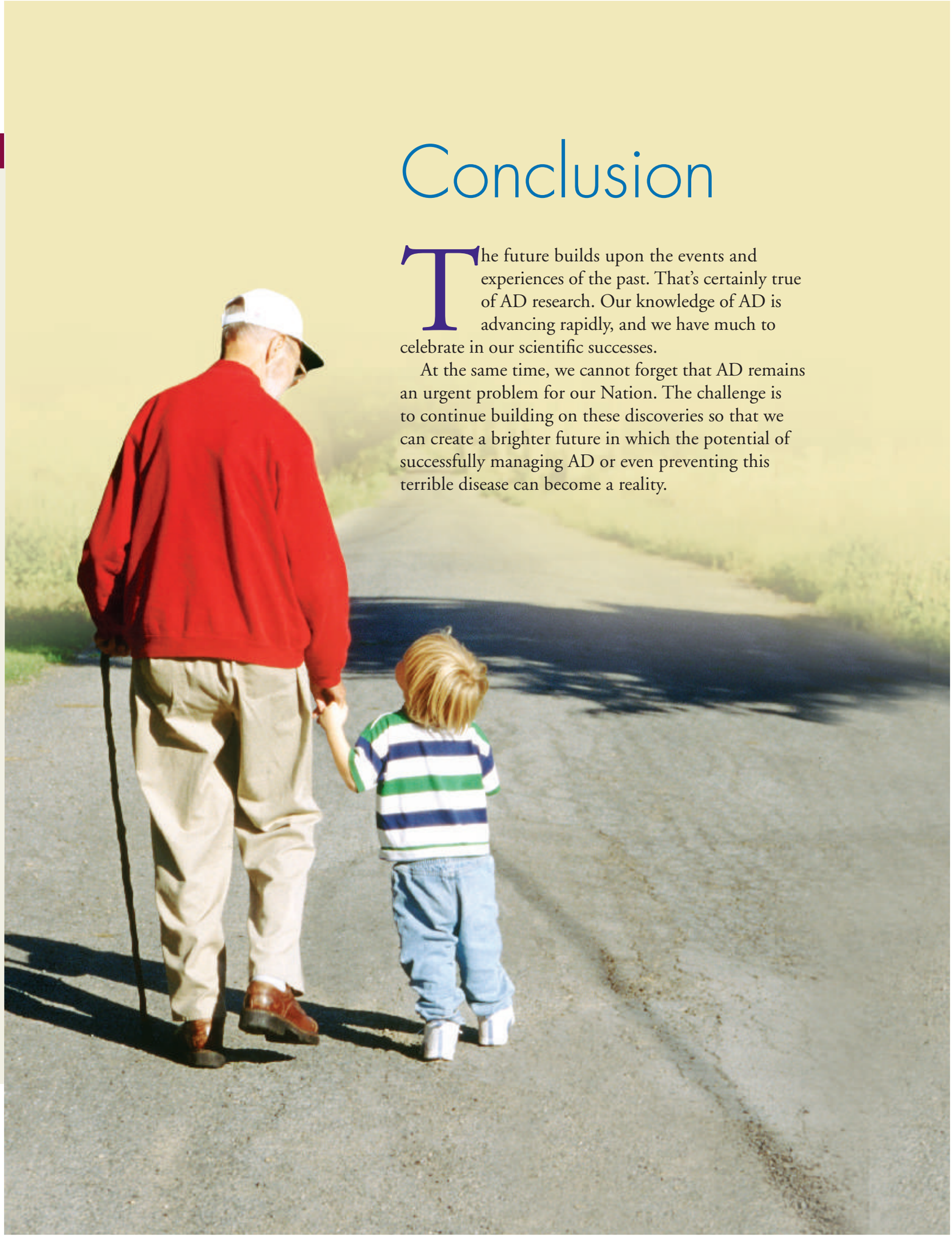
Conclusion

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.



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Glossary

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.

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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.

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Glossary

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.

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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.

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For *More* Information

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.

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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 900
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

1731 King Street, Suite 100
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.

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RESEARCH AND CLINICAL TRIALS

Alzheimer's Disease Cooperative Study

University of California, San Diego
9500 Gilman Drive
La Jolla, CA 92093-0949
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.

Dash, P., & Villemarette-Pittman, N. ***Alzheimer's Disease.*** New York: American Academy of Neurology, 2005.

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

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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.

Doraiswamy, P.M., & Gwyther, L., with Adler, T. ***The Alzheimer's Action Plan: The Experts' Guide to the Best Diagnosis and Treatment for Memory Problems.*** New York: St. Martin's Press, 2008.

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.

Kuhn, D., & Bennett, D.A. ***Alzheimer's Early Stages: First Steps for Family, Friends and Caregivers***, 2nd ed. Alameda, CA: Hunter House Publishers, 2003.

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.

Mace, N.L., & Rabins, P.V. ***The 36-Hour Day: A Family Guide to Caring for People With Alzheimer's Disease, Other Dementias, and Memory Loss in Later Life***, 4th ed. Baltimore: Johns Hopkins University Press, 2006.

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.

Messer, M. ***Pressure Points: Alzheimer's and Anger.*** Durham, NC: Duke Family Support Program, 2000. Available for $12.50 from the ADEAR Center, P.O. Box 8250, Silver Spring, MD 20907-8250; 800-438-4380; *www.nia.nih.gov/Alzheimers.*

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,

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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 ADEAR 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).

Perry, G., ed., ***Alzheimer's Disease: A Century of Scientific and Clinical Research***. *Journal of Alzheimer's Disease*, book edition, Fairfax, VA: IOS Press, Inc., 2006.

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.

Petersen, R., ed. ***Mayo Clinic Guide to Alzheimer's Disease: The Essential Resource for Treatment, Coping and Caregiving***. Rochester, MN: Mayo Clinic Health Solutions, 2006.

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.

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Restak, R. ***The Secret Life of the Brain***. Washington, DC: Joseph Henry Press, 2001.

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.

Shenk, D. ***The Forgetting. Alzheimer's: Portrait of an Epidemic***. New York: Random House, Inc., 2003.

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.

Snowdon, D. ***Aging With Grace: What the Nun Study Teaches Us About Leading Longer, Healthier, and More Meaningful Lives***. New York: Random House, Inc., 2002.

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.

Tanzi, R.E., & Sisodia, S.S. ***Alzheimer's Disease: Advances in Genetics***, Molecular and Cellular Biology. New York: Springer Publishing Company, 2006.

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.

Uetz, D., & Lindsay, A. ***Into the Mist: When Someone You Love Has Alzheimer's***. Philadelphia: Xlibris Corporation, 2005.

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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Credits

Writer
Anne Brown Rodgers

Medical Illustrator
Stacy Jannis
Jannis Productions

3D Modeling
Bill Dempsey
Rebekah Fredenburg

Graphic Design
Fatima Ameen and Jeffrey Dever
Dever Designs

Project Coordinator
Susan R. Farrer
JBS International, Inc.

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For additional copies of this report or further information about Alzheimer's disease, please contact:

Alzheimer's Disease Education and Referral (ADEAR) Center
P.O. Box 8250
Silver Spring, MD 20907-8250

Phone:
800-438-4380

Email:
adear@nia.nih.gov

Website:
www.nia.nih.gov/Alzheimers

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