National Institute on Aging
National Institutes of Health

ALZHEIMER'S DISEASE

Unraveling the Mystery

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UnravelingtheMystery

Preface

Over the past few decades, Alzheimer's disease 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. Research on Alzheimer's disease has grown accordingly. The small group of pioneers who conducted research on the disease in the 1970s has expanded to thousands of scientists in laboratories and institutions all over the world.

The lead agency for Alzheimer's research at the National Institutes of Health (NIH) is the National Institute on Aging (NIA), which launched its Alzheimer's disease program in 1978. 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 Alzheimer's disease, including the National Institute of Neurological Disorders and Stroke, the National Institute of Mental Health, and the National Institute of Nursing Research.

In the private sector, the Alzheimer's Association, other voluntary organizations, and private industry are also working to combat this disease. They fund research, contribute to public policy decisions, inform and educate the public, and provide critical services to people with Alzheimer's disease and their families. Their support for research is critical in the effort to understand and defeat this disorder.

Thanks to these many groups, the study of Alzheimer's disease is moving ahead rapidly. This booklet explains what Alzheimer's disease is, describes what we have learned to date, and provides a glimpse into future directions for research.

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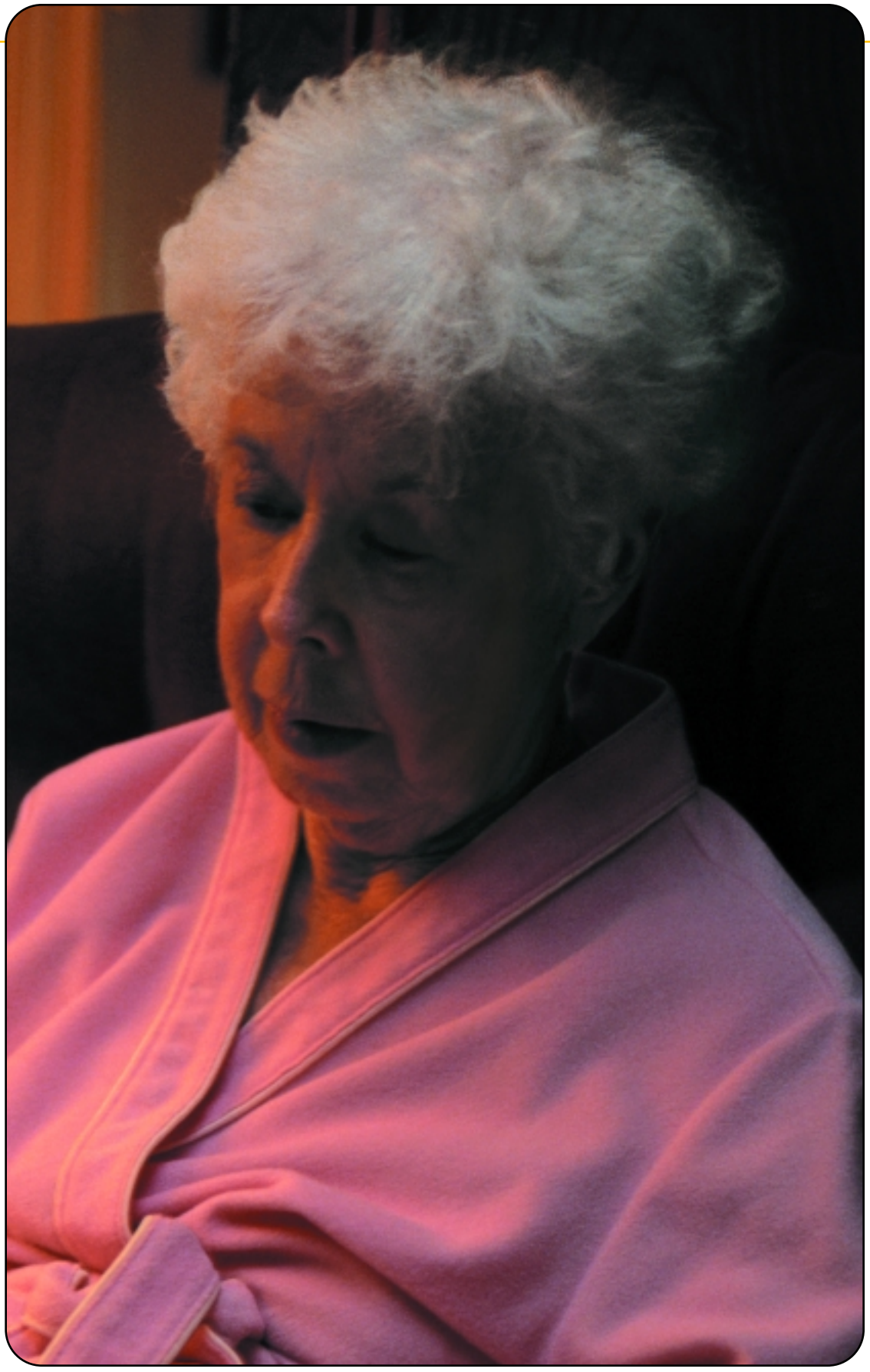
Introduction

Often, Mary was afraid, a nameless, shapeless fear. Her impaired mind could not put a name or an explanation to her fear. People came, memories came, and then they slipped away. She could not tell what was reality and what was memory of people past. The bathroom was not where it was yesterday. Dressing became an insurmountable ordeal....Mary gradually lost the ability to make sense out of what her eyes and ears told her....She worried about her things: a chair, and the china that had belonged to her mother. They said they had told her over and over, but she could not remember where her things had gone. Perhaps someone had stolen them. She had lost so much....

Mary was glad when her family came to visit. Sometimes she remembered their names; more often she did not. She never remembered that they had come last week, so she regularly scolded them for abandoning her....She was glad when they didn't try to remind her of what she had just said or that they had come last week, or ask her if she remembered this person or that one. She liked it best when they just held her and loved her.

This excerpt from *The 36-Hour Day*, a book for families and caregivers of people with Alzheimer's disease (AD) and other similar diseases, gives a glimpse into what an Alzheimer's patient might be thinking and feeling. The gradual slipping away of mind and memory is frightening and frustrating, both for the person with the disease and for family and friends. Not so long ago, we couldn't do much for Mary or others like her. Happily, that situation is changing. Thousands of scientists, voluntary organizations, health care professionals, and families are working hard to learn more about Alzheimer's. They are also finding ways to manage, treat, and eventually perhaps, prevent this terrible disease.

Alzheimer's is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks. Although the risk of developing AD increases with age – in most people with AD, symptoms first appear after age 60 – AD is not a part of normal aging. It is caused by a disease that affects the brain. In the absence of disease, the human brain often can function well into the tenth decade of life.



The Impact of Alzheimer's Disease

AD is the most common cause of **dementia** among people age 65 and older. Dementia is the loss of memory, reason, judgment, and language 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.

AD is a major public health problem for the United States because it has such a huge impact on individuals, families, the health care system, and society. Scientists estimate that up to 4 million people now have AD. For every 5-year age group beyond 65, the percentage of people with AD doubles.

More than 34 million people are now age 65 or older. This number is 13 percent of the total population of the U.S. The percentage of people over age 65 will increase rapidly over the next few years as the "baby boom" generation reaches 65. In addition, the group of people over 85 – the group with the highest risk of Alzheimer's disease – is the fastest growing segment of the population. By 2050, 14 million older Americans are expected to have Alzheimer's disease if the current numbers hold and no preventive treatments become available.

Slightly more than half of those with AD are cared for at home, while the rest are in different kinds of care facilities. A recent study estimated that the annual cost of caring for one person with AD in 1996 was between $18,400 and $36,100, depending on how advanced the disease was and whether or not the person was at home. The cost of care has been steadily rising since then. The national cost of caring for people with AD is now thought to be about $100 billion every year.

The cost of care is not only financial. Families, friends, and caregivers struggle with great emotional and physical stress as they cope with the physical and mental changes in their loved ones. Caregivers must juggle many responsibilities and adjust to new and changing roles. As the disease gets worse and caring at home becomes increasingly difficult, family members face difficult decisions about long-term care. The number of caregivers – and their needs – will steadily grow as our population ages and the number of people with AD increases.

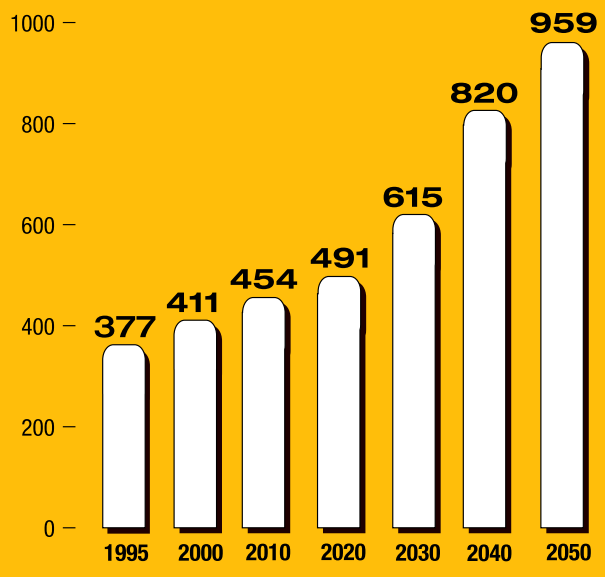
How Many **New Cases** of AD Were There in **1995?** How Many **New Cases** May Occur in the **Future?**

Researchers recently projected the number of new cases of AD that could occur every year over the next 50 years if current population trends continue and no preventive treatments emerge. They estimate that the number of new cases every year will double between 1995 and 2050 – from 377,000 to 959,000. Two factors will combine to cause this large increase:

- The fact that the risk of AD increases as people get older.
- The growing numbers of older people, especially those over 85.

The annual number of new cases will begin to climb sharply around the year 2040, when all the baby boomers will be over 65.

Estimated Number of New AD Cases, in Thousands



Source: Hebert et al. (2001). Alzheimer Dis Assoc Disord, 15(4), 169-173.

Unraveling the Mystery

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

Where Are People with **Alzheimer's Disease Cared For?**

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

Unraveling the Mystery has two sections. Part 1 gives readers the basics – it's a "walking tour" through the brain. Illustrations with text show what a healthy brain looks like and how it works, and what happens in a brain affected by AD. Part 2 talks about current research and the advances that are bringing us closer to ways of managing, and eventually defeating, AD. Throughout, terms in **bold** are defined in a glossary at the end of the booklet.

The end of the booklet also includes a list of publications and resources that family members and caregivers may find useful as they live day-to-day with the disease.

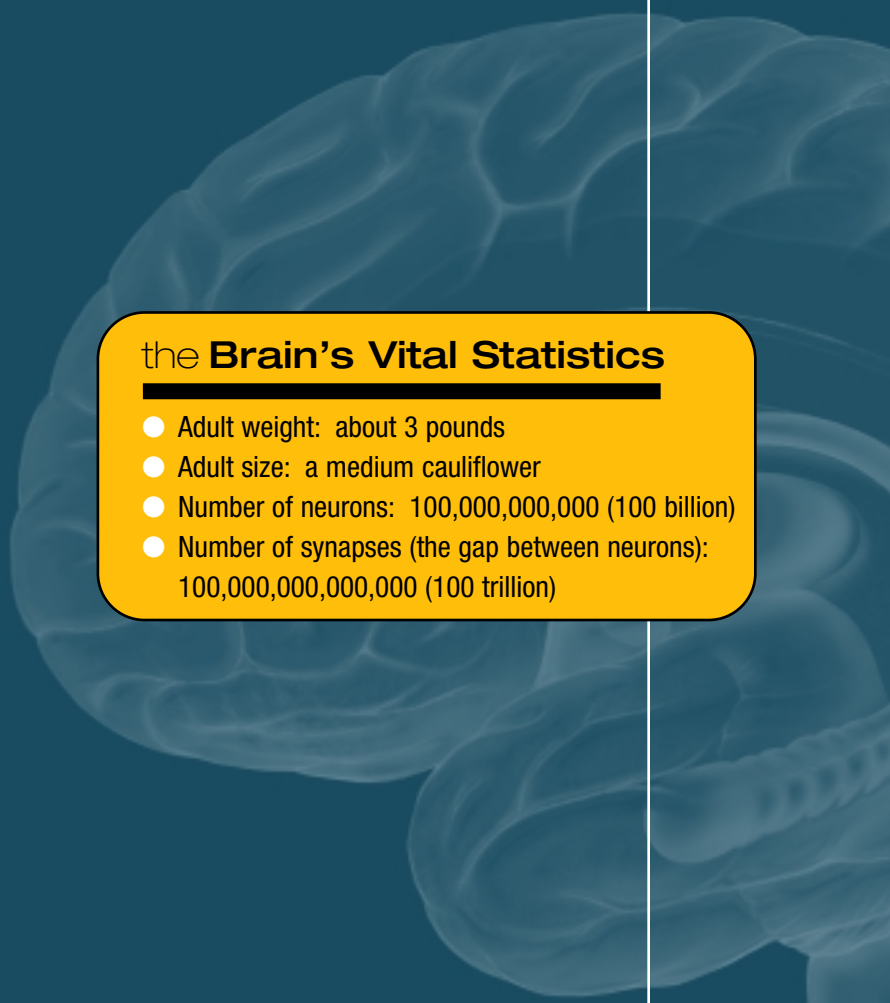
A booklet like this would not have been possible 25 years ago. Other than some basics, we knew very little about AD. We did not even know it was a distinct disease, different from normal aging. Today, we know much more about Alzheimer's disease – what it is, who gets it, how it develops, and what course it follows. We are better able to diagnose it early and accurately. We even have some promising leads on possible treatments. Recent studies are also beginning to focus on factors that might be used to reduce a person's risk of developing AD in the future. Research conducted over the last two decades 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.

Part 1 A Walking Tour Through the Brain

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

Our brains are made of nerve cells and lots of other cell types. Nerve cells are also called **neurons**. The neurons of all animals function in basically the same way, even though animals can be very different from each other. What sets people apart from other animals is the huge number of nerve cells we have in the **cerebral cortex**, regions of which are proportionally much larger in humans than in any other animals. These regions are the parts of the brain where **cognitive functions**, like thinking, learning, speaking, remembering, and making decisions, take place. The many interconnections among the nerve cells in these regions also make us different from other animals.

To understand Alzheimer's disease, it's important to know a bit about the brain. Part 1 of *Unraveling the Mystery* first gives an inside view of the normal brain, how it works, and what happens during aging. Then, it shows what happens to the brain in Alzheimer's and how the disease slowly destroys a person's mental and physical capacities.



the Brain's Vital Statistics

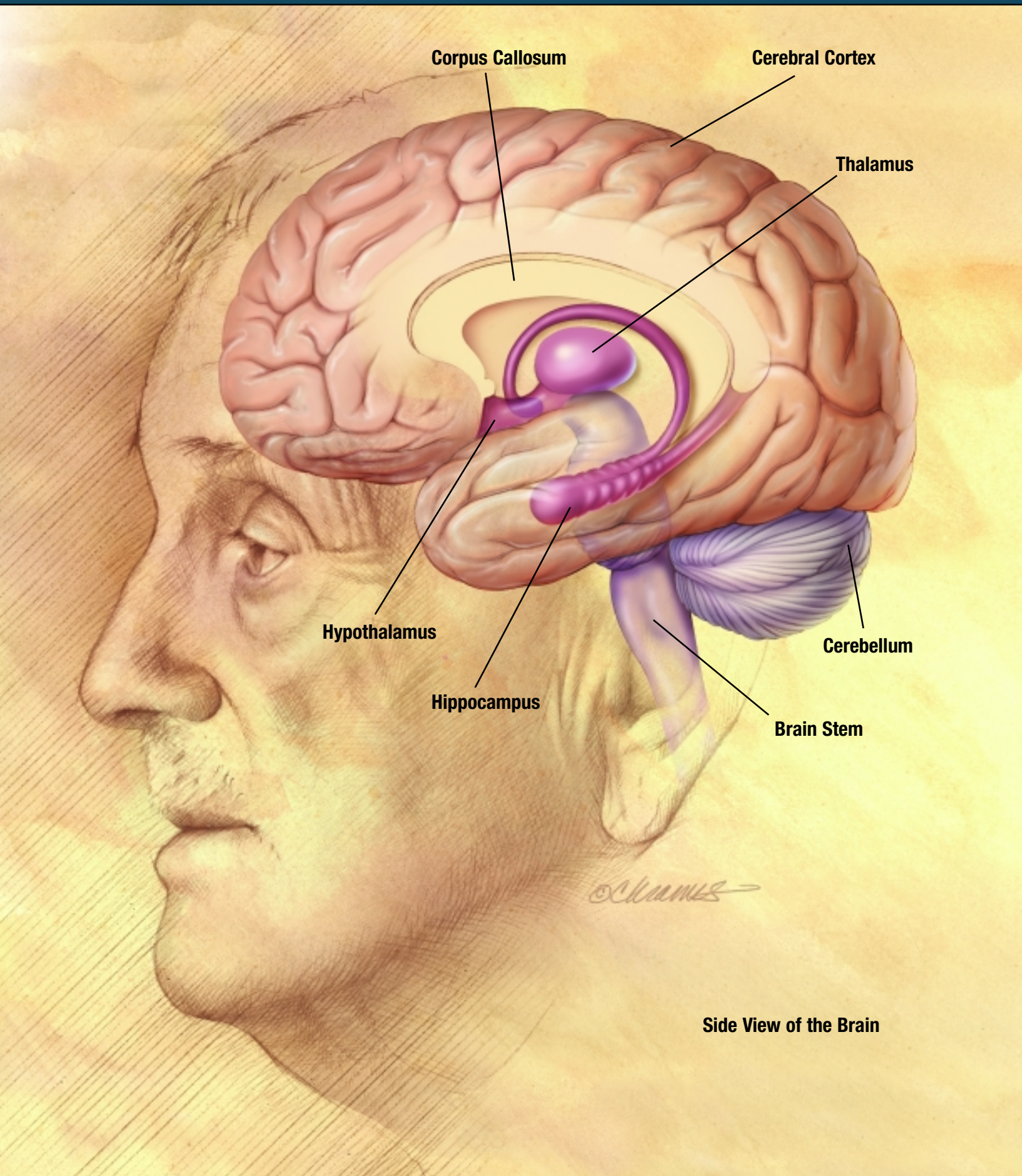
- Adult weight: about 3 pounds
- Adult size: a medium cauliflower
- Number of neurons: 100,000,000,000 (100 billion)
- Number of synapses (the gap between neurons): 100,000,000,000,000 (100 trillion)

InsidetheHumanBrain

The Three Main Players

- The **cerebral hemispheres** accounts for 85 percent of the brain's weight. The billions of neurons in the two hemispheres are connected by a thick bundle of nerves called the **corpus callosum**. Scientists now think that the two hemispheres differ not so much in *what* they focus on (the "logical versus artistic" notion), but *how* they process information. The left hemisphere appears to focus on the details (such as recognizing a particular face in a crowd). The right hemisphere focuses on the 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 conscious thought and mental activity.

- The **cerebellum** takes up a little more than 10 percent of the brain. It's in charge of balance and coordination. The cerebellum also has two hemispheres. They are always receiving information from the eyes, ears, and muscles and joints about the body's movements and position. Once the cerebellum processes the information, it works through the rest of the brain and spinal cord to send out instructions to the body. The cerebellum's work allows us to walk smoothly, maintain our balance, and turn around without even thinking about it.



Side View of the Brain

- The **brain stem** sits at the base of the brain. It connects the spinal cord with the rest of the brain. Even though it's 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:

- The **limbic system** links the brain stem with the higher reasoning elements of the cerebral cortex. It controls emotions and instinctive behavior. This is also where the sense of smell is located.

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

- The **thalamus** receives sensory and limbic information, processes it, and then sends it to the cerebral cortex.

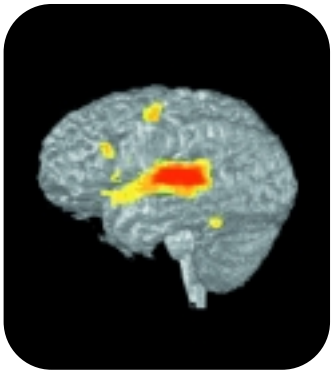
- The **hypothalamus** is a structure under the thalamus that monitors activities like body temperature and food intake. It issues instructions to correct any imbalances. The hypothalamus also controls the body's internal clock.

The Brain in Action

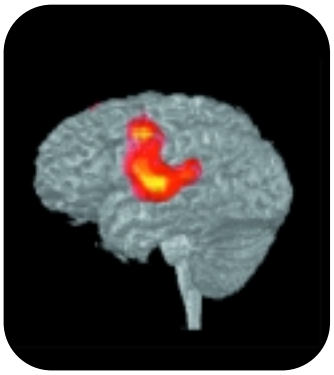
New imaging techniques allow scientists to monitor brain function in living people. This is opening up worlds of knowledge about normal brain function and how it changes with age or disease.

One of these techniques is called **positron emission tomography**, or PET scanning. PET scans measure blood flow and glucose **metabolism** throughout the brain. (For more on metabolism see ***Neurons and Their Jobs*** on p. 16.) When nerve cells in a region of the brain become active, blood flow and metabolism in that region increase. These increases are usually shown as red and yellow colors on a PET scan. Shades of blue and black indicate decreased or no activity within a brain region. In essence, a PET scan produces a "map" of the active brain.

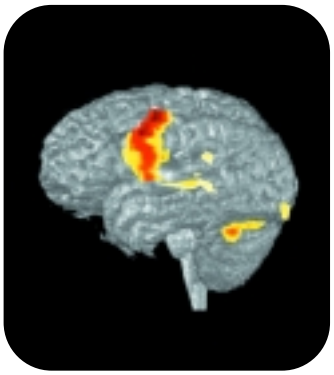
Scientists use PET scans to see what happens in the brain when a person is engaged in a physical or mental activity, at rest, or even sleeping or dreaming. Scientists can also inject chemicals tagged with a tracer that will "light up" on PET scans. These tracers can track the activity of brain chemicals, for example **neurotransmitters** such as dopamine and serotonin. Some of these neurotransmitters are altered with age, disease, and drug treatment.



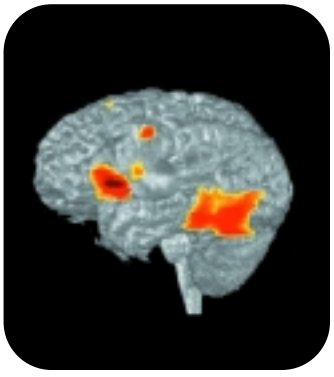
Hearing Words



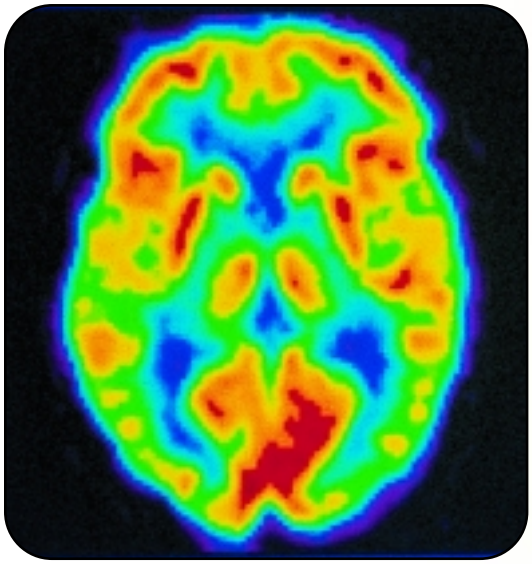
Speaking Words



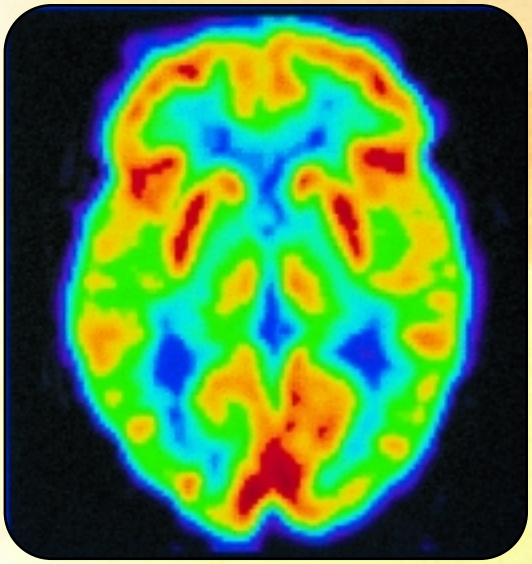
Seeing Words



Thinking about Words



PET Scan of 20-year-old Brain



PET Scan of 80-year-old Brain

The Aging Brain

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

- Some neurons shrink, especially large ones in areas important to learning, memory, planning, and other complex mental activities.
- Tangles and plaques develop in neurons and surrounding areas, though in much smaller amounts than in AD (see p. 20 for more on plaques and tangles).
- Damage by **free radicals** increases (free radicals are a kind of molecule that reacts easily with other molecules; see p. 36 for more on these molecules).

What is the impact of these changes? Healthy older 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. However, if given enough time to perform the task, the scores of healthy people in their 70s and 80s are often the same as those of young adults. As they age, adults also often improve their vocabulary and other forms of verbal knowledge.

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 all of the cell's activities, and several other structures that perform specific functions. The axon, which is much, much narrower than the width of a human hair, extends out from the cell body and transmits messages to other neurons. Sometimes, the messages have to travel over very long distances (even up to 5 feet!). Dendrites also branch out from the cell body. They receive messages from the axons of other nerve cells. Each nerve cell is connected to thousands of other nerve cells through its axon and dendrites. Neurons are surrounded by **glial cells**, which support, protect, and nourish them.

Groups of neurons in the brain have special jobs. For example, some are involved with thinking, learning, and memory. Others are responsible for receiving sensory information. Still others communicate with muscles, stimulating them into action.

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

Communication: Sending Millions of Messages a Second

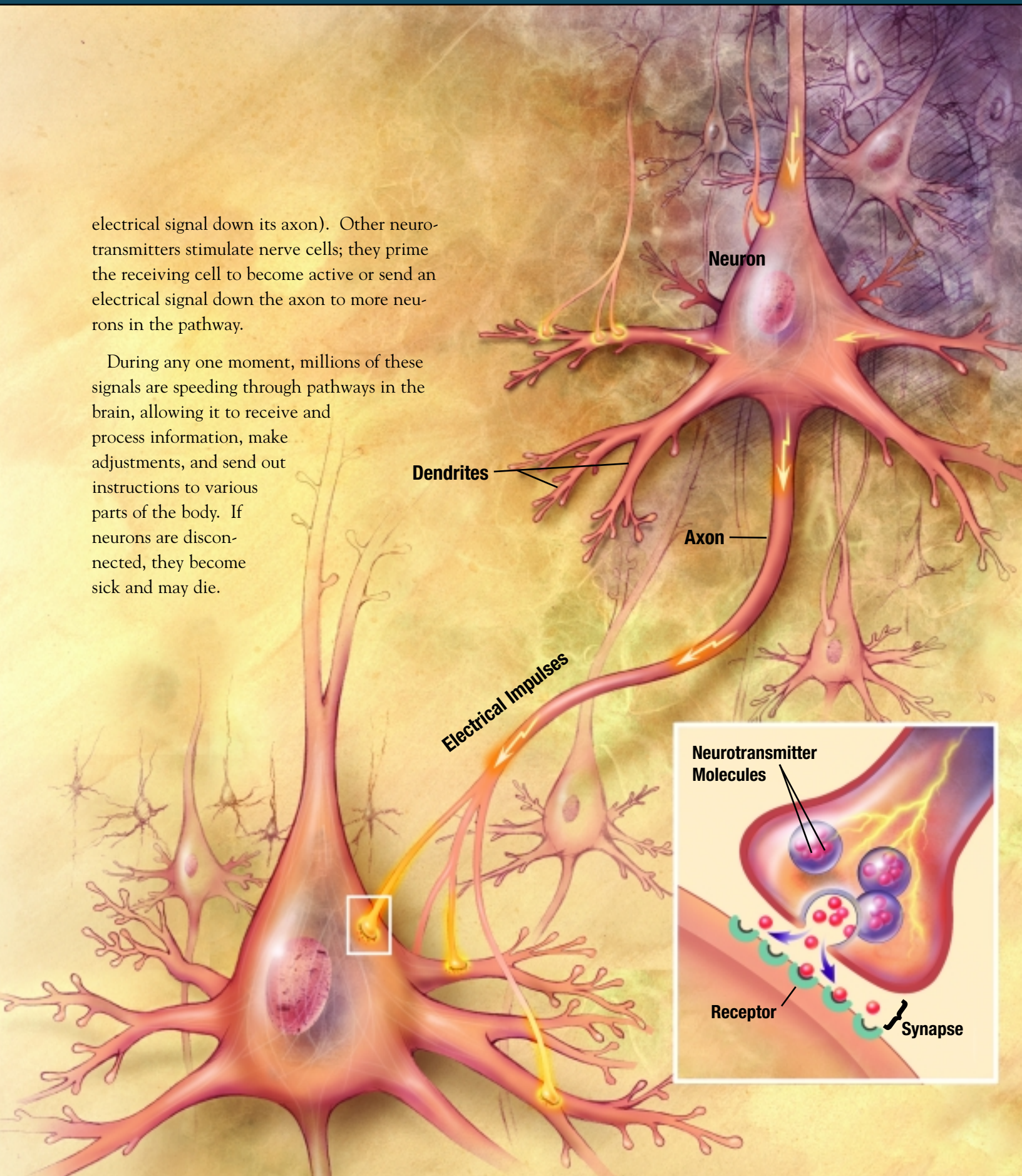
Imagine the telecommunication cables that run under our streets. All day and night, millions of telephone calls are flashing down fiber optic cables at incredible speeds, letting people strike deals, give instructions, share a laugh, or learn some news. Multiply that many-fold and that's the brain. Neurons are the great communicators, always in touch with their neighbors.

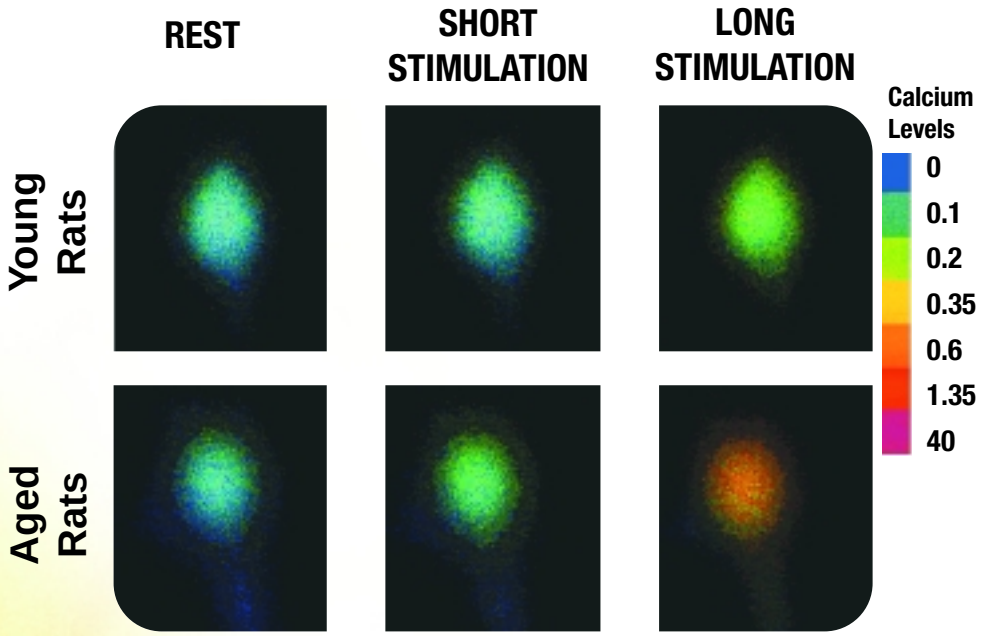
As a neuron receives messages from surrounding cells, an electrical charge, or nerve impulse, builds up. This charge travels down the axon until it reaches the end. Here, it triggers the release of chemical messengers called neurotransmitters, which move from the axon across a tiny gap to the dendrites or cell bodies of other neurons. The typical neuron has up to 15,000 of these tiny gaps, or **synapses**. After they move across the synapse, neurotransmitters bind to specific receptor sites on the receiving end of dendrites of the nearby neurons. They can also bind directly to cell bodies.

Once the 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; they prime the receiving cell to become active or send an electrical signal down the axon to more neurons in the pathway.

During any one moment, millions of these signals are speeding through pathways in the brain, allowing it to receive and process information, make adjustments, and send out instructions to various parts of the body. If neurons are disconnected, they become sick and may die.





This figure shows young and aged rat neurons at rest and with increasing duration of stimulation. When neurons are stimulated, metabolism increases. The stimulated neurons of young rats maintain calcium within normal levels. Older rats are unable to do this. High levels of calcium in old neurons may make them susceptible to dysfunction and death. The color scale is an index of cellular calcium with red indicating the highest levels.

Metabolism: Turning Chemicals and Nutrients Into Energy to Keep Neurons Working

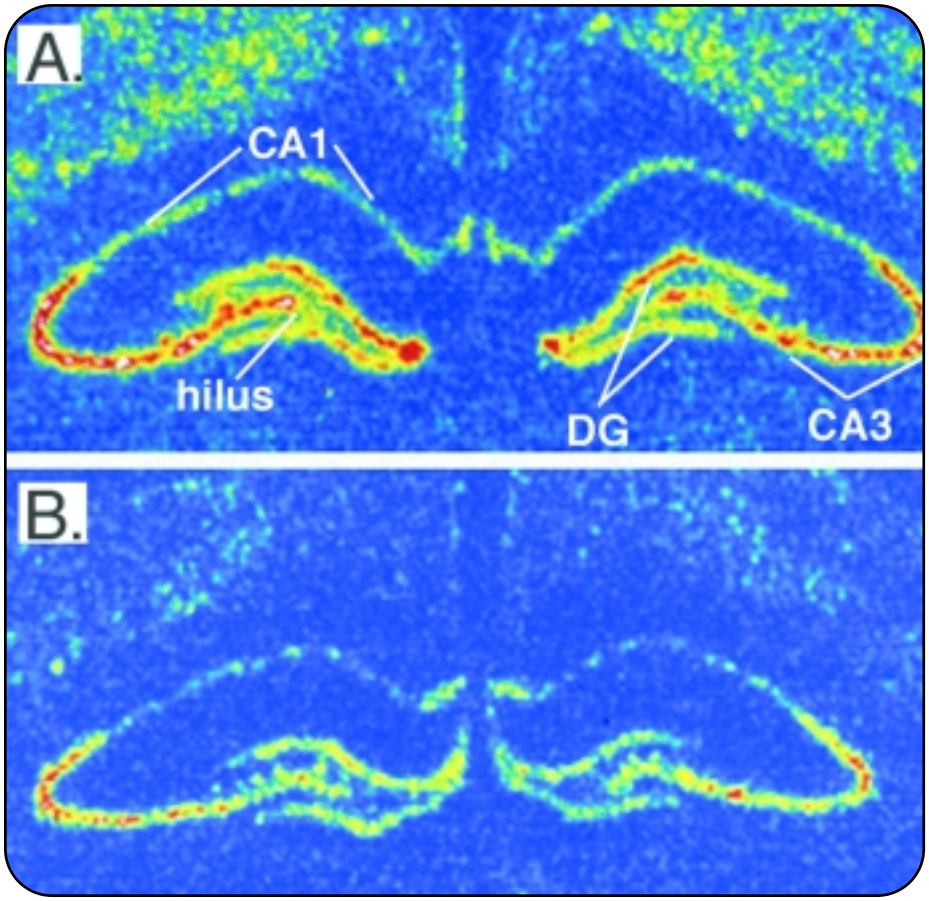
Metabolism is the process by which cells and molecules break down chemicals and nutrients to generate energy and form building blocks that make new cellular molecules like proteins.

Efficient metabolism needs enough blood circulating to supply the cells with oxygen and glucose, a type of sugar. Glucose is the only source of energy usually available to the brain. Without oxygen or glucose, neurons will die.

Repair: Keeping Long-lived Neurons in Good Working Order

Unlike most cells, which have a fairly short lifespan, nerve cells, which are generated in the fetus or a short time after birth, live a long time. Brain neurons can live for up to 100 years or longer. In an adult, when neurons die because of disease or injury, they are not usually replaced. Recent research, however, shows that in a few brain regions, new neurons can be born, even in the old brain.

To prevent their own death, living neurons must constantly maintain and remodel themselves. If cell cleanup and repair slows down or stops for any reason, the nerve cell cannot function well. Eventually, it dies.



This figure shows the effects of exercise on levels of brain-derived neurotrophic factor (BDNF) in the hippocampus of rats. Growth factors like BDNF help many neurons survive. Levels of the message that makes BDNF are much higher in exercising rats (A) than in sedentary animals (B). Exercise may promote healthy neurons in rats by causing their neurons to make more protective BDNF. Red and yellow denote the highest levels of BDNF, while green and blue denote the lowest.

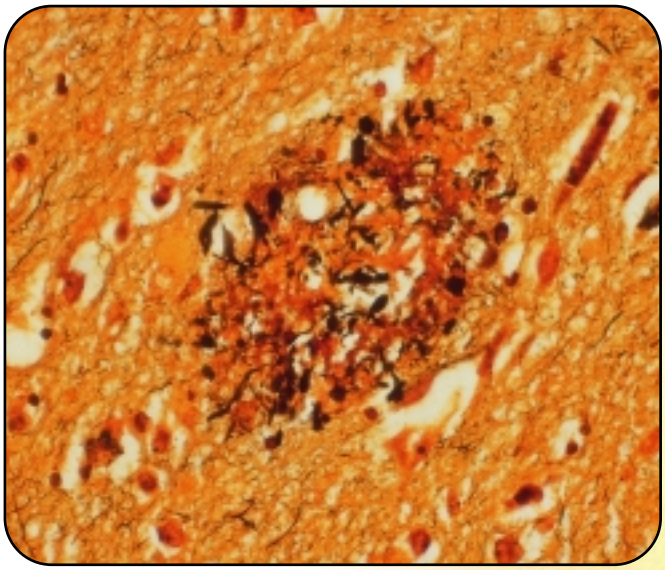
Plaques and Tangles: the Hallmarks of AD

Alzheimer's disease disrupts each of the three processes that keep neurons healthy: communication, metabolism, and repair. This disruption causes certain 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 AD patients have an abundance of two abnormal structures – **beta-amyloid plaques** and **neurofibrillary tangles**. This is especially true in certain regions of the brain that are important in memory. Plaques are dense, mostly insoluble (cannot be dissolved) deposits of protein and cellular material outside and around the neurons. Tangles are insoluble twisted fibers that build up inside the nerve cell. Though many older people develop some plaques and tangles, the brains of AD patients have them to a much greater extent. Scientists have known about plaques and tangles for many years, but recent research has shown much about what they are made of, how they form, and their possible roles in AD.

Amyloid Plaques

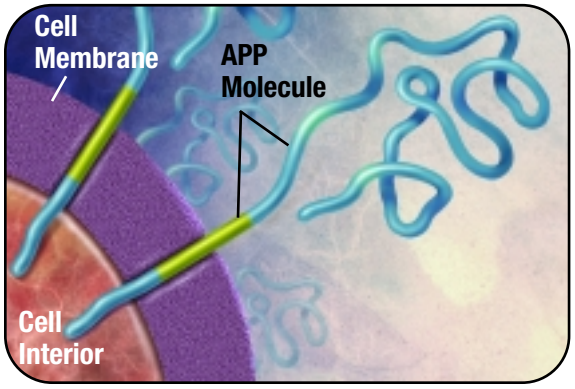
Plaques are made of **beta-amyloid**, a protein fragment snipped from a larger protein called **amyloid precursor protein (APP)**. These fragments clump together and are mixed with other molecules, neurons, and non-nerve cells. In AD, plaques develop in the hippocampus, a structure deep in the brain that helps to encode memories, and in other areas of the cerebral cortex that are used in thinking and making decisions. We still don't know whether beta-amyloid plaques themselves cause AD or whether they are a by-product of the AD process. We do know that changes in APP structure can cause a rare, inherited form of AD (see p. 33 for more on inherited AD).



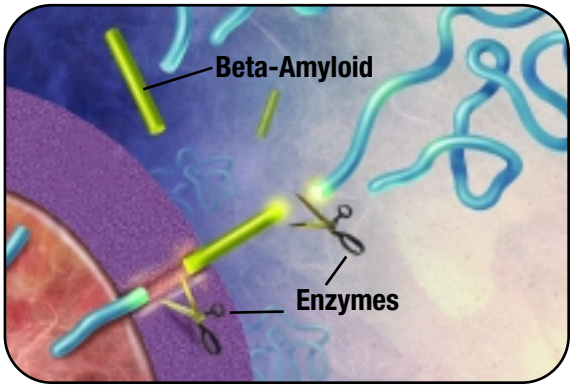
An AD Plaque

From APP to Beta-amyloid

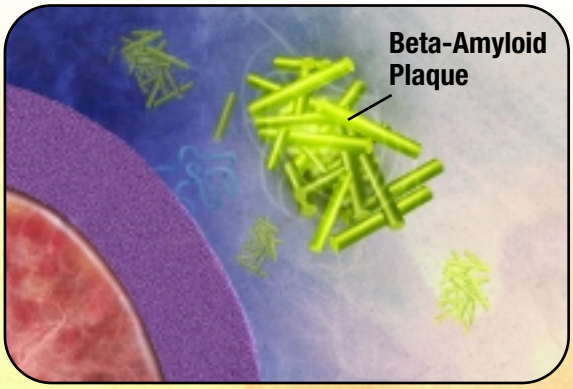
APP is a protein that appears to be important in helping neurons grow and survive. APP may help damaged neurons repair themselves and may help parts of neurons grow after brain injury. In AD, something causes APP to be snipped into fragments, one of which is called beta-amyloid; the beta-amyloid fragments eventually clump together into plaques.



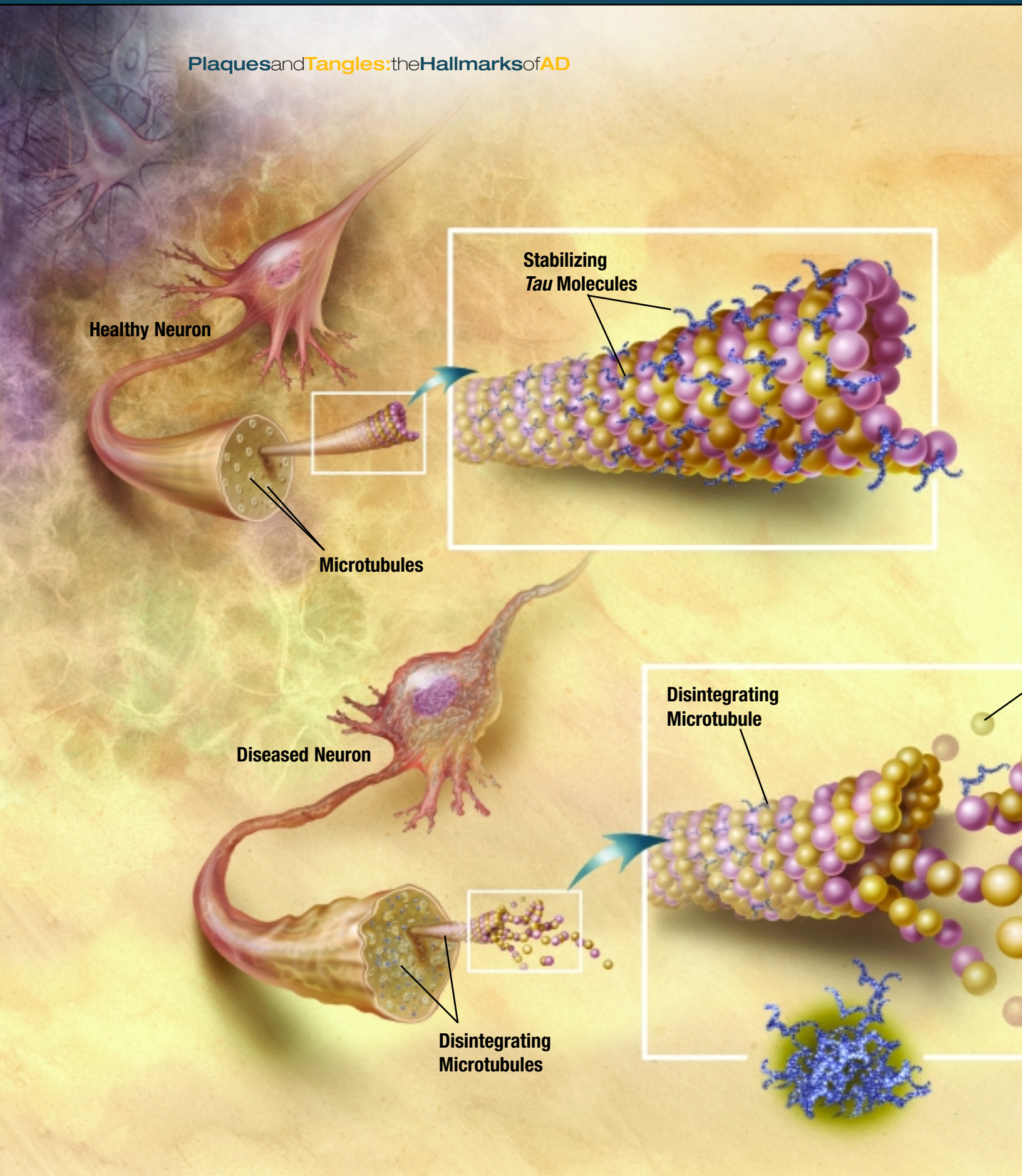
APP is associated with the cell membrane, the thin barrier that encloses the cell. After it is made, APP sticks through the neuron's membrane, partly inside and partly outside the cell.



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

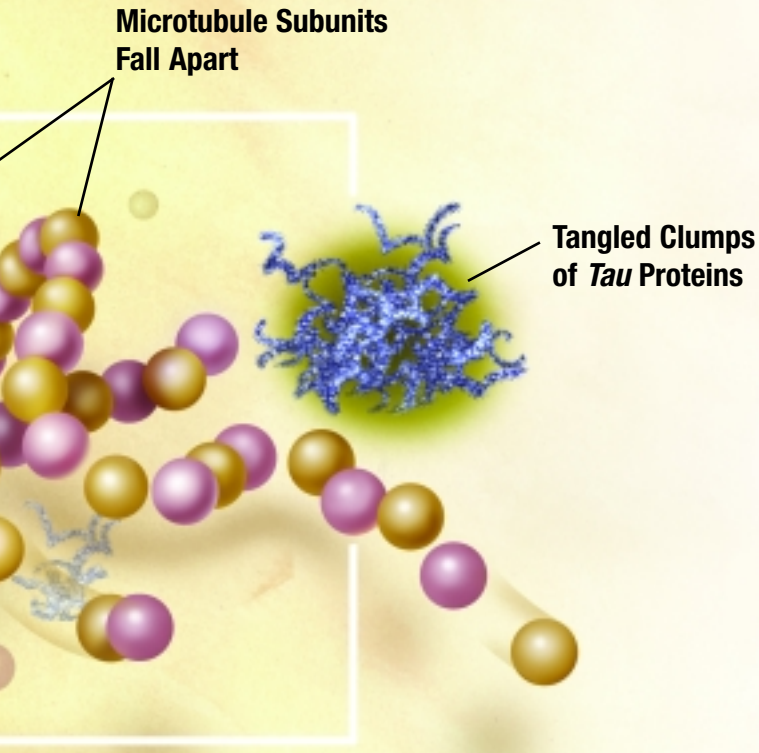


The beta-amyloid fragments begin coming together into clumps outside the cell, then join other molecules and non-nerve cells to form insoluble plaques.


Healthy Neuron
Stabilizing
Tau Molecules
Microtubules
Diseased Neuron
Disintegrating
Microtubule
Disintegrating
Microtubules

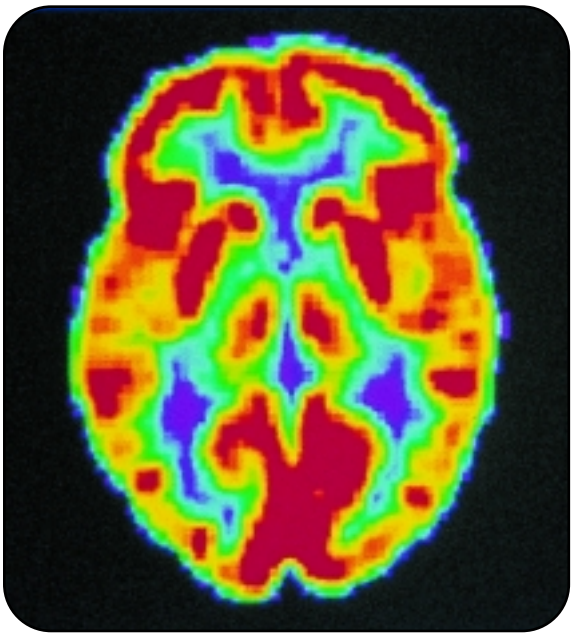
Neurofibrillary Tangles

Healthy neurons have an internal support structure partly made up of structures called **microtubules**. These microtubules act like tracks, guiding nutrients and molecules from the body of the cell down to the ends of the axon and back. A special kind of protein, ***tau***, makes the microtubules stable. In AD, *tau* is changed chemically. It begins to pair with other threads of *tau* and they become tangled up together. When this happens, the microtubules disintegrate, collapsing the neuron's transport system. This may result first in malfunctions in communication between neurons and later in the death of the cells.

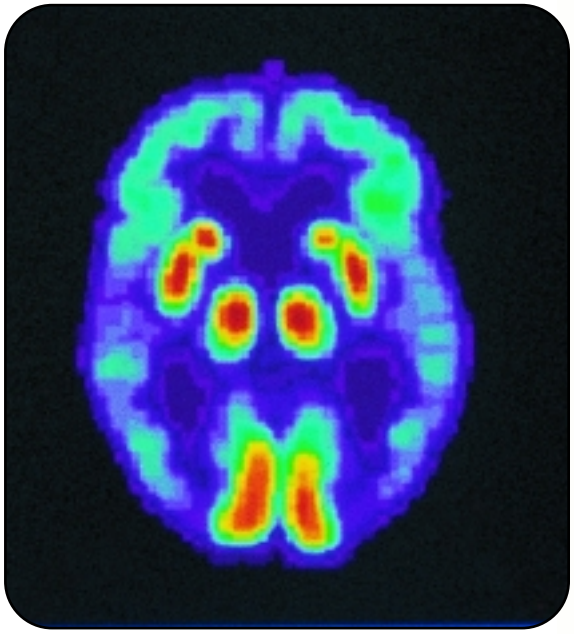


the Changing Brain in Alzheimer's Disease

No one knows exactly what causes the Alzheimer's disease process to begin or why some of the normal changes associated with aging become so much more extreme and destructive in patients with the disease. We do 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 years if the patient is over 80 when diagnosed, as long as 10 or more years if the patient is younger. Although the course of AD is not the same in every patient, symptoms seem to develop over the same general stages.



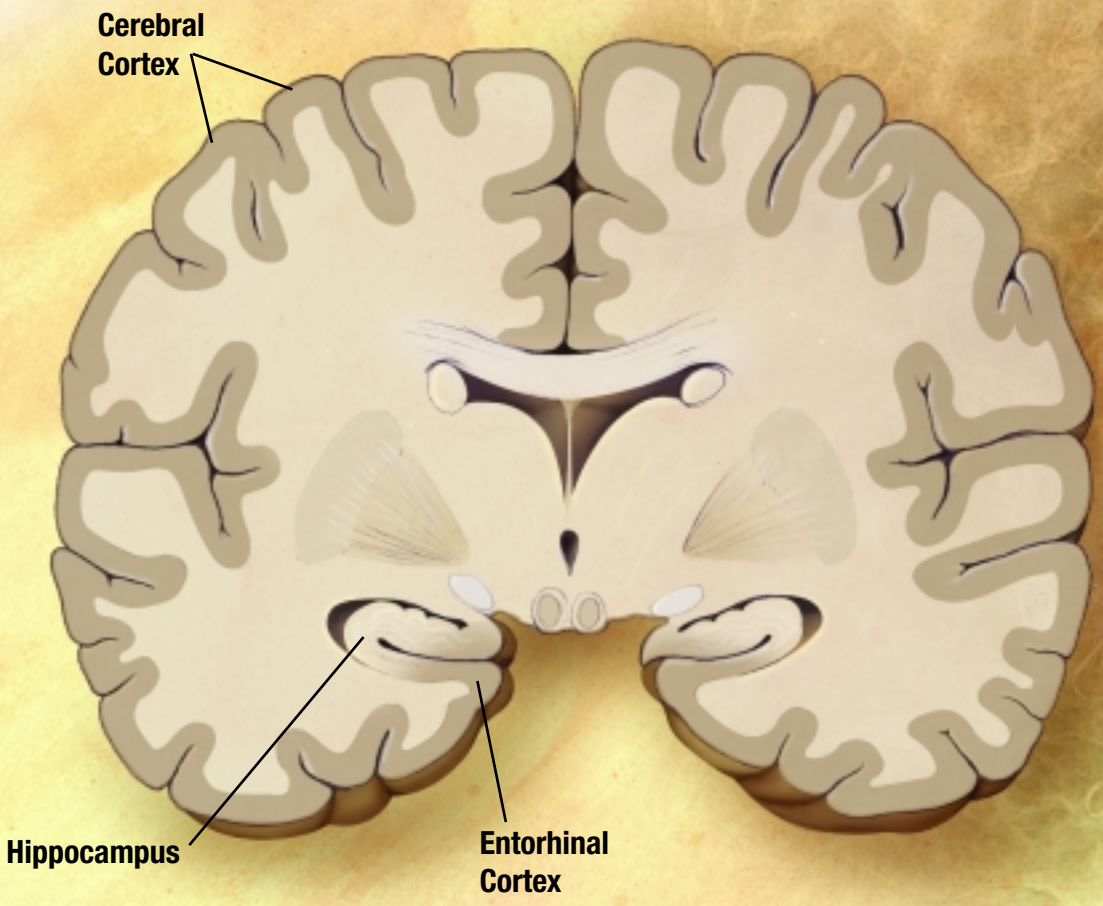
PET Scan of Normal Brain



PET Scan of Alzheimer's Disease Brain

Preclinical AD

AD begins in the **entorhinal cortex**, which is near the hippocampus and has direct connections to it. It then proceeds to the hippocampus, the structure that is essential to the formation of short-term and long-term memories. Affected regions begin to atrophy (shrink). These brain changes probably start 10 to 20 years before any visible signs and symptoms appear. Memory loss, the first visible sign, is the main feature of mild cognitive impairment (MCI) (see p. 41 for more on MCI). Many scientists think MCI is often an initial, transitional phase between normal brain aging and AD.

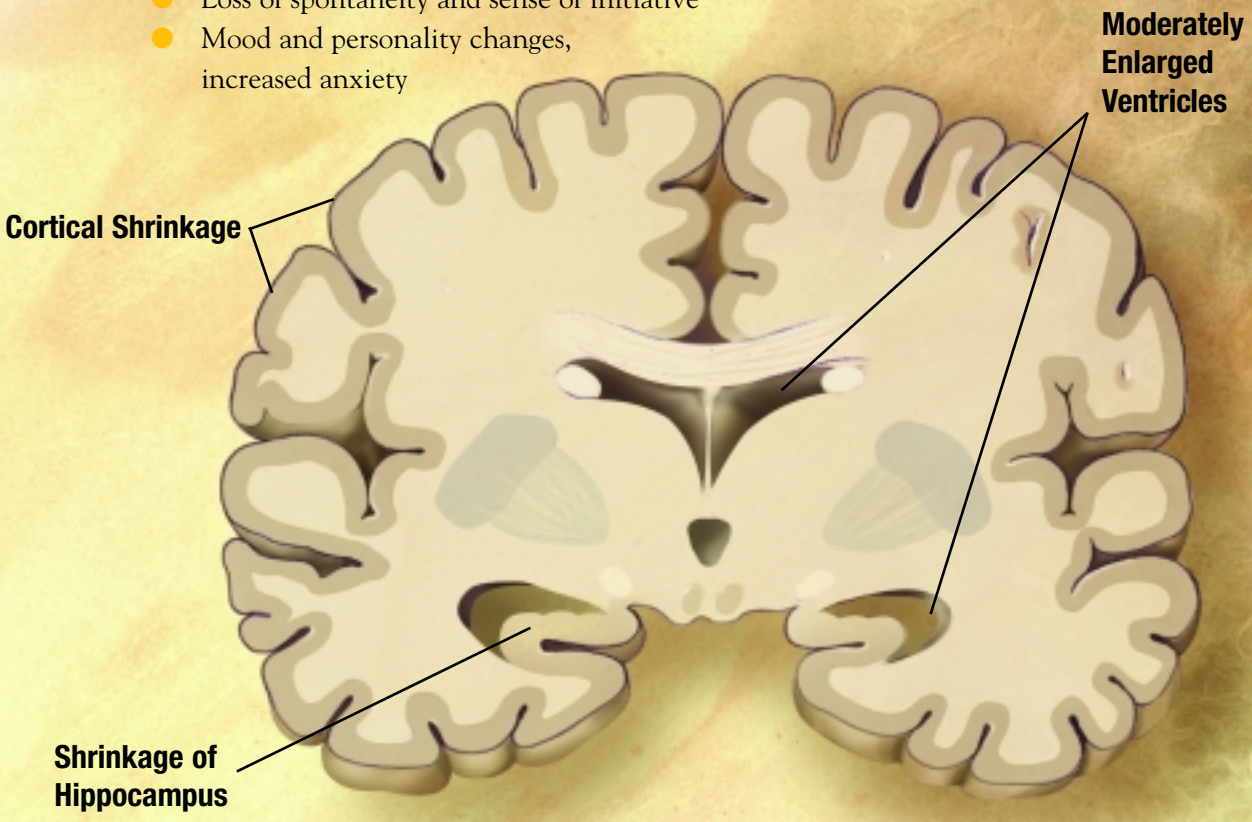


Mild AD

As the disease begins to affect the cerebral cortex, memory loss continues and changes in other cognitive abilities 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 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

The growing number of plaques and tangles first damage areas of brain that control memory, language, and reasoning. It is not until later in the disease that physical abilities decline. This leads to a situation in mild AD in which a person seems 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 because the early signs can be confused with changes that can happen normally with aging. Accepting these signs and deciding to go for diagnostic tests can be a big hurdle for patients and families to cross.



Moderate AD

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

- Increasing memory loss and confusion
- Shortened attention span
- Problems recognizing friends and family members
- Difficulty with language; problems with reading, writing, 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 sloppy table manners, undressing at inappropriate times or places, or vulgar language)
- Perceptual-motor problems (such as trouble getting out of a chair or setting the table)

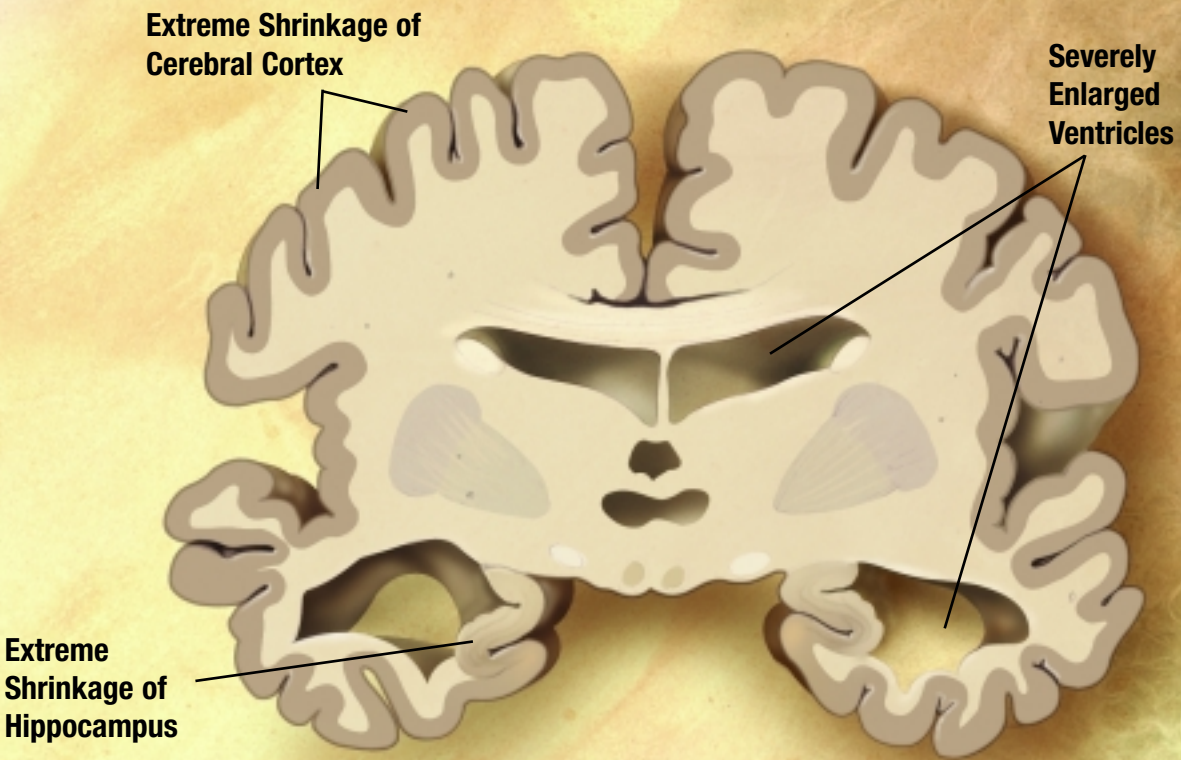
Behavior is the result of complex brain processes, all of which take place in a fraction of a second in the healthy brain. In AD, many of these processes are disturbed, and this is the basis for many distressing or inappropriate behaviors. For example, a person may angrily refuse to take a bath or get 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 is 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 around her can be strange and frightening. Sticking close to a trusted and familiar caregiver may be the only thing that makes sense and provides security. Taking off clothes may seem reasonable to a person with AD who feels hot and doesn't understand or remember that undressing in public is not acceptable.

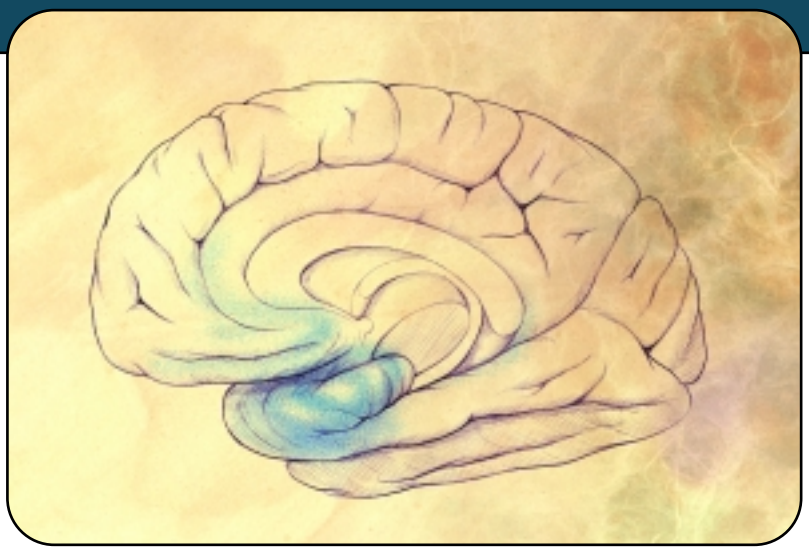
Severe AD

In the last stage of AD, plaques and tangles are widespread throughout the brain, and areas of the brain have atrophied further. Patients cannot recognize family and loved ones or communicate in any way. They are completely dependent on others for care. All sense of self seems to vanish. Other symptoms can include:

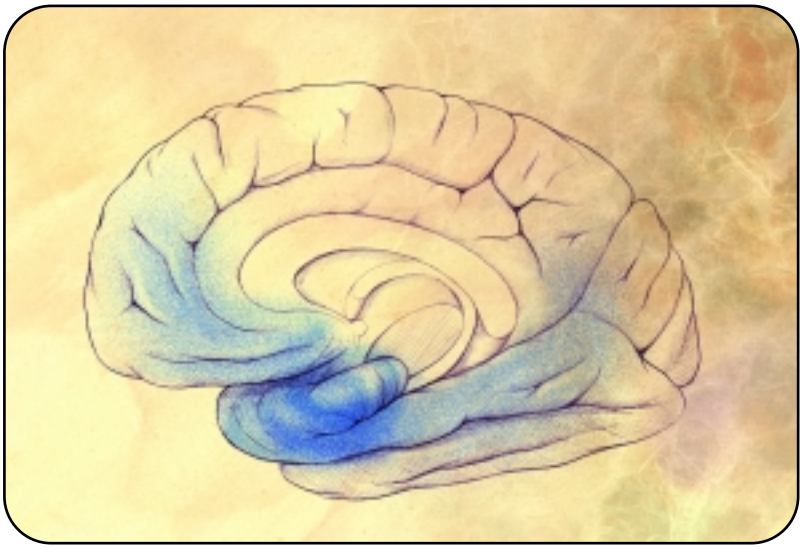
- Weight loss
- Seizures, skin infections, difficulty swallowing
- Groaning, moaning, or grunting
- Increased sleeping
- Lack of bladder and bowel control

At the end, patients may be in bed much or all of the time. Most people with AD die from other illnesses, frequently aspiration pneumonia. This type of pneumonia happens when a person is not able to swallow properly and breathes food or liquids into the lungs.

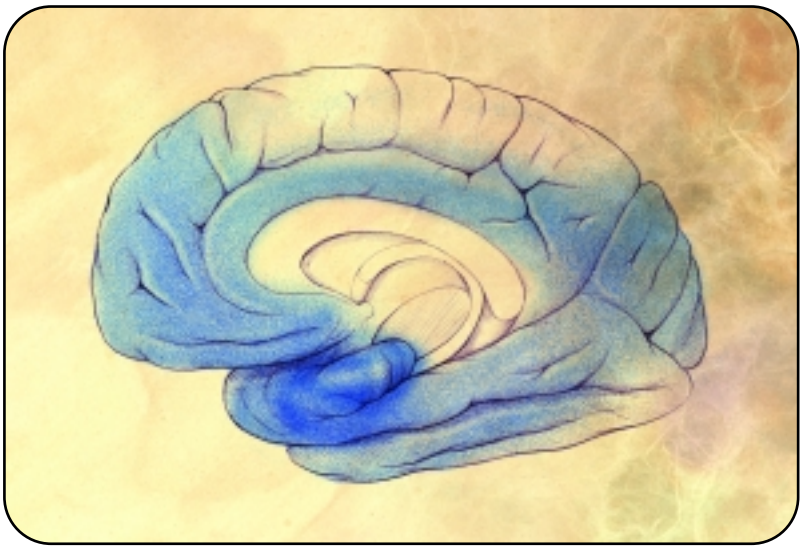




Preclinical AD



Mild to Moderate AD



Severe AD

Blue indicates areas affected at various stages of AD.

Part 2 AD Research: Finding New Answers and Asking Better Questions

In the past 25 years, scientists have studied Alzheimer's disease from many angles. They've looked at populations to see how many cases of AD occur and whether there might be links between the disease and lifestyles or genetic backgrounds. They've conducted clinical studies with healthy older people and those at various stages of AD. They've examined individual nerve cells to see how beta-amyloid and other molecules affect the ability of cells to function normally.

These studies have led to better 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 ask better questions about the issues that are still unclear.

Part 2 of *Unraveling the Mystery* describes what we're learning from our search for:

- The causes of AD
- New techniques to help in diagnosis
- New treatments
- Ways to improve support for families and other caregivers

Results from this research will bring us closer to the day when we will be able to prevent or even cure the devastating disease that robs our older relatives and friends of their most precious possession – their minds.

Then and Now: the Fast Pace of Developments in AD Research

What We Didn't Know Then	*What We Know Now (2002)*
15 Years Ago	
● We didn't know any of the genes that could cause AD.	● We know the 3 major genes for early-onset AD and 1 of the major risk factor genes for late-onset AD.
● We had no idea of the biological pathways that were involved in the development of damage to the brain in AD.	● We know a lot about the pathways that lead to the development of beta-amyloid plaques in the brain – one of the main features of AD.
10 Years Ago	
● We couldn't model the disease in animals.	● Scientists have developed special kinds of mice that produce beta-amyloid plaques.
5 Years Ago	
● NIH did not fund any prevention clinical trials.	● NIH is funding clinical trials that are looking at possible ways to prevent AD.
● We had no way to identify people at high risk of developing AD.	● We can identify individuals at high risk through imaging, neuropsychological tests, and structured interviews.
1 Year Ago	
● We didn't understand anything about how plaques and tangles relate to each other.	● By developing another kind of mice that have both plaques and tangles, we now know that plaques can influence the development of tangles.

theSearchforCauses

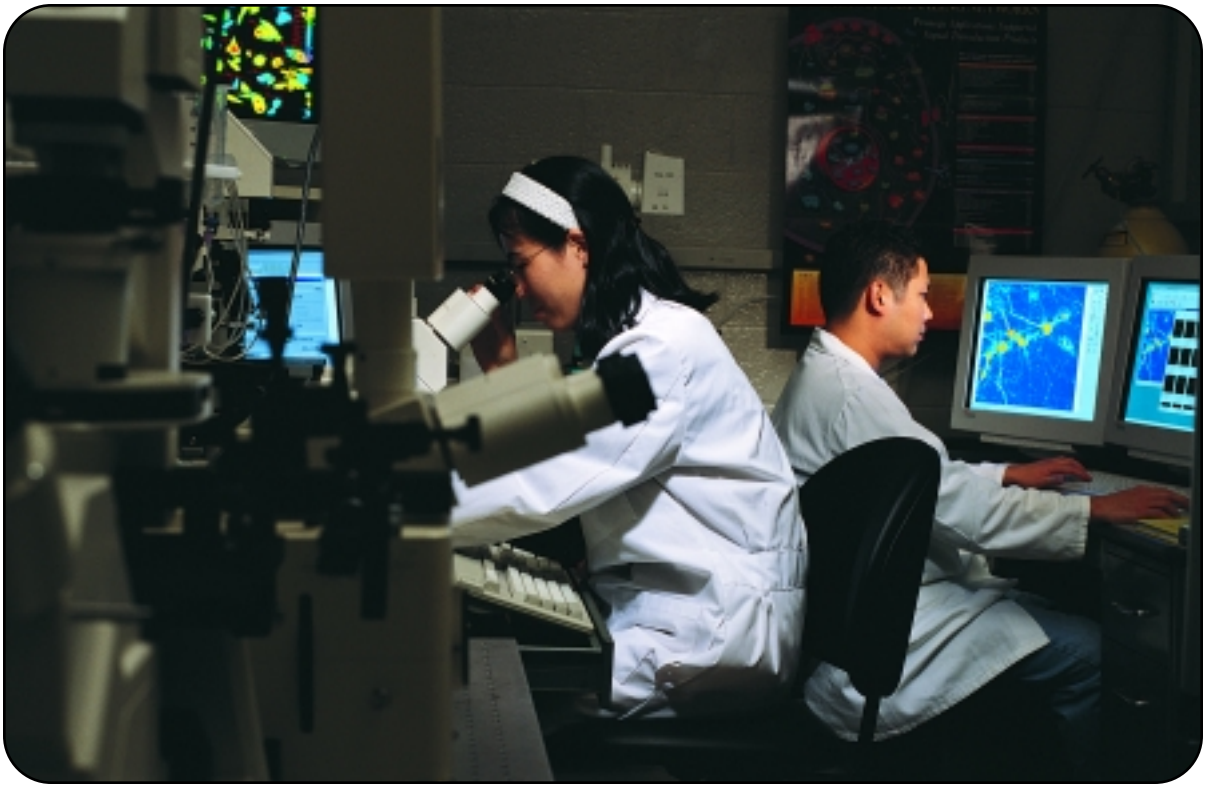
One of the most important parts of unraveling the AD mystery is finding out what causes the disease. What makes the disease process begin in the first place? What makes it worse over time? Why does the number of people with the disease increase with age? Why does one person develop it and another remain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

Some diseases, like 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 cause a disease process to start. The importance of each one of these factors may be different for each individual.

AD fits into this second group of diseases. We don't yet fully understand what causes AD, but we know 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

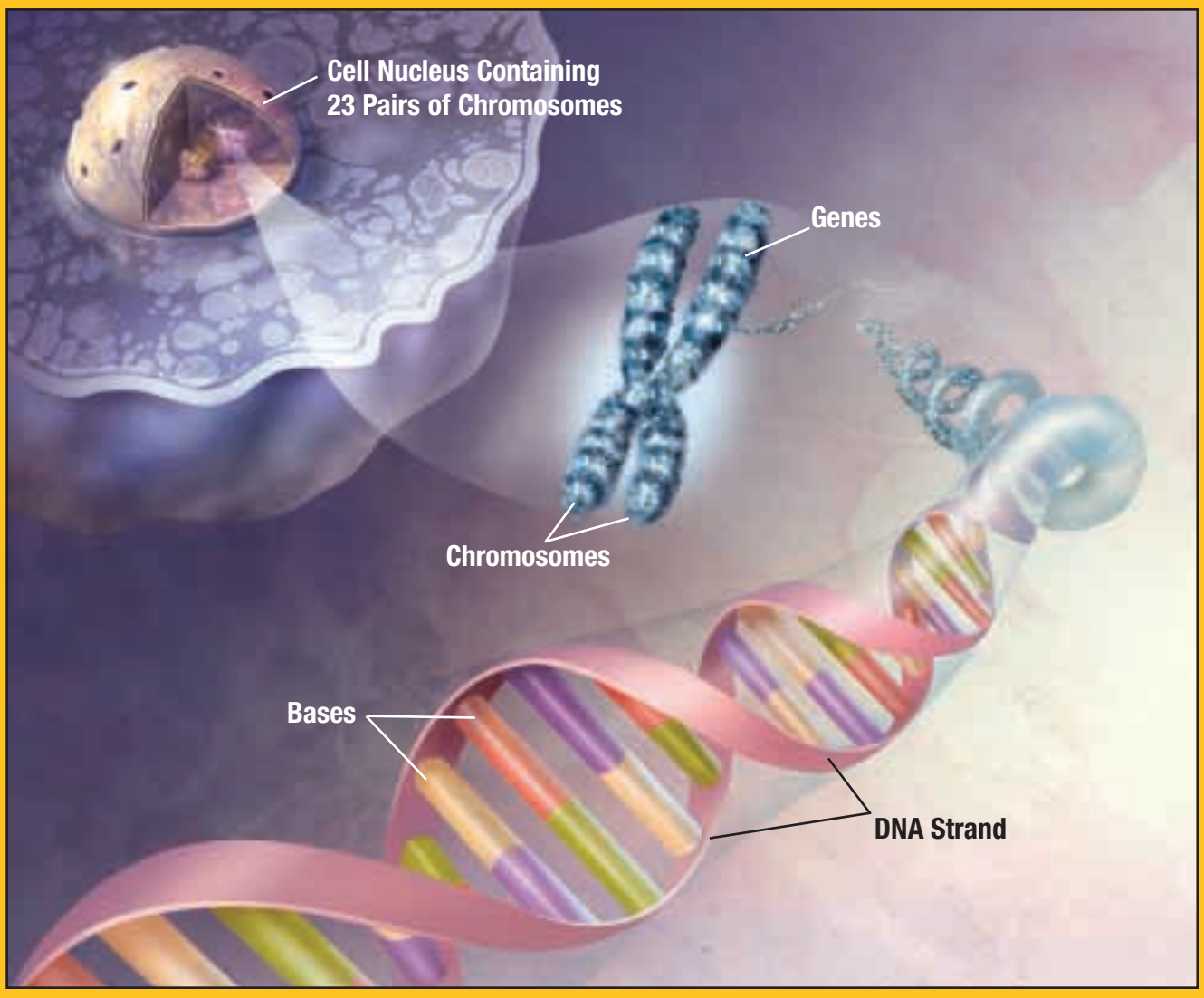
In the last few years, painstaking detective work by scientists has paid off in discoveries of genetic links to the two main types of AD. One type is the more rare, **early-onset Alzheimer's disease**. It usually affects people aged 30 to 60. Some cases of early-onset disease are inherited and are called familial AD (FAD). The other is **late-onset Alzheimer's disease**. It is the most common form and occurs in those 65 and older.



DNA, Chromosomes, and **Genes:**
the Body's Amazing Control Center

The nucleus of almost every human cell contains a vast chemical information database. This database carries all the instructions the cell needs to do its job. This database is **DNA**. DNA exists as two long, intertwined, thread-like strands packaged in units called **chromosomes**. Each cell has 46 chromosomes in 23 pairs. Chromosomes are made up of four chemicals, or bases, arranged in various sequence patterns. People inherit material in each chromosome from each parent.

Each chromosome has many thousands of segments, called **genes**. The sequence of bases in a gene tells the cell how to make specific proteins. Proteins determine the physical characteristics of living organisms. They also direct almost every aspect of the organism's construction, operation, and repair. Even slight alterations in a gene can produce an abnormal protein, which, in turn, can lead to cell malfunction, and eventually, to disease. Any rare change in a gene's DNA that causes a disease is called a **mutation**. Other more common (or frequent) changes in a gene's DNA don't automatically cause disease, but they can increase the chances that a person will develop a particular disease. When this happens, the changed gene is called a **genetic risk factor**.



Genes and Early-onset Alzheimer's Disease

Over the past several decades, researchers working on AD realized that some cases, particularly of early-onset AD, ran in families. This led them to examine DNA samples from such 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 (APP) to be produced. On chromosome 14, the mutation causes an abnormal protein called presenilin 1 to be produced. On chromosome 1, the mutation causes yet another abnormal protein to be produced. This protein, called presenilin 2, is very similar to presenilin 1. Even if only one of these genes 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.

Even though early-onset AD is very rare and mutations in these three genes do not play a role in the more common late-onset AD, these findings were crucial because they showed that genetics was indeed a factor in AD, and they helped to identify some key players in the AD disease process. Importantly, they showed that mutations in APP can cause AD, highlighting the key role of beta-amyloid in the disease. Many scientists believe that mutations in each of these genes cause an increased amount of the damaging beta-amyloid to be made in the brain.

The findings also laid the foundation for many other studies that have pushed back the boundaries of our knowledge and created new possibilities for future treatment. For example, in the last several years, a series of highly sophisticated experiments have shown that presenilin may actually be one of the **enzymes** (substances that cause or speed up a chemical reaction) that clips APP to form beta-amyloid (the protein fragment that is the main component of AD plaques). This discovery has helped clarify how presenilins might be involved in the early stages of AD. It has also given scientists crucial new targets for drug therapy and has spurred many new studies in the test tube, in animals, and even in people.

A Different Genetic Story in Late-onset Alzheimer's Disease

While some scientists were focused on 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, these investigators had narrowed their search to a region of chromosome 19. At the same time, other colleagues were looking for proteins that bind to beta-amyloid. They were hoping to clarify some of the steps in the very early stages of the disease process. They found that one form of a protein called **apolipoprotein E (ApoE)** did bind quickly and tightly to beta-amyloid. They also found that the gene that produces ApoE was located in the same region of chromosome 19 pinpointed by the geneticists. This finding led them to suggest that one form of this gene was a risk factor for late-onset Alzheimer's disease.

Other studies since then have shown that the gene that produces 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. 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 AD patients who develop the disease in later life. It is not limited to people whose families have a history of AD, though. AD patients with no known family history of the disease are also more likely to have an APOE ε4 allele than people who do not have AD. Dozens of studies have confirmed that the APOE ε4 allele increases the risk of developing AD. These studies have also helped to explain some of the variation in the age at which AD develops. However, inheriting an APOE ε4 allele doesn't 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.

Although we still don't exactly know how APOE ε4 increases AD risk, one theory is that when its protein product binds quickly and tightly to beta-amyloid, the normally soluble amyloid becomes insoluble. This may mean that it is more likely to be deposited in plaques.

While scientists are working to understand more fully the APOE gene and its role in AD, they have also identified regions on other chromosomes that might contain genetic risk factors. For example, in 2000, three teams of scientists, using three different strategies, published studies showing that chromosome 10 has a region that may contain several genes that might increase a person's risk of AD. Identifying these genes is one important step in the research process that will lead to new understanding about the ways in which changes in protein structures cause the disease process to begin and the sequence of events that occurs as the disease develops. Once they understand these processes, scientists can search for new ways to diagnose, treat, or even prevent AD.

Other Factors at Work in AD

Even if genetics explains some of what might cause AD, it doesn't explain everything. So, researchers have looked at other possibilities that may reveal how the Alzheimer's disease process starts and develops.

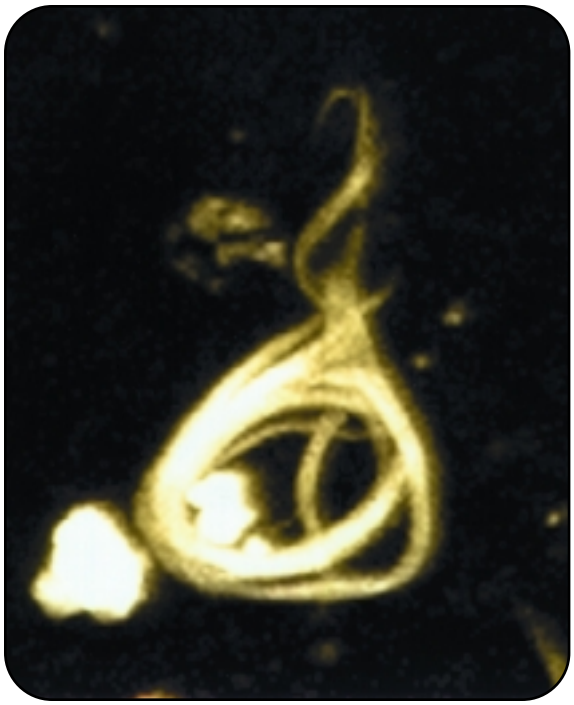
Beta-Amyloid

We still don't know whether beta-amyloid plaques cause AD or whether they are a by-product of the disease process. We do know, however, that forming beta-amyloid from APP is a key process in AD. That's why finding out more about beta-amyloid is an important avenue of ongoing AD research. Investigators are studying:

- The nature of beta-amyloid
- Ways in which it is toxic to neurons
- Ways in which plaques form and are deposited
- Ways in which beta-amyloid and plaques might be reduced in the brain

Tau

In the last few years, scientists have been giving an increasing amount of attention to *tau*, the other hallmark of Alzheimer's disease.

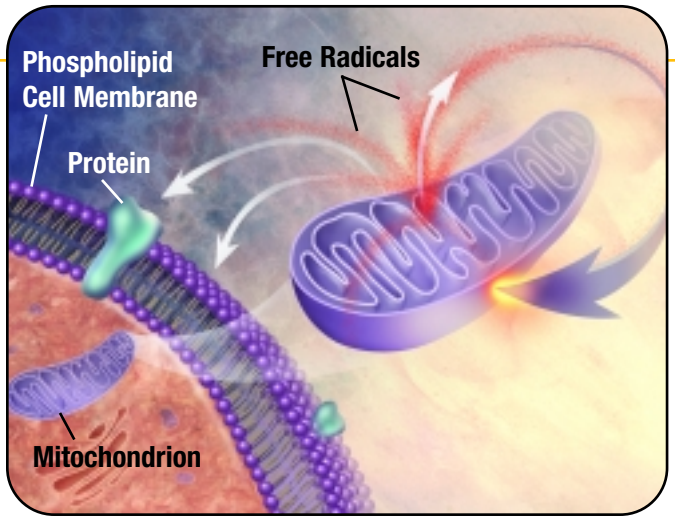


An AD Tangle

This protein is commonly found in nerve cells throughout the brain. In AD, *tau* undergoes changes that cause it to gather together abnormally in tangled filaments in neurons (for more on this, see p. 23 in ***A Walking Tour Through the Brain***). In studying *tau* and what can go wrong, investigators have found that *tau* abnormalities are also central to other rare neurodegenerative diseases. These diseases, called *tau*opathies, include frontotemporal dementia, Pick's disease, supranuclear palsy, and corticobasal degeneration. They share a number of characteristics, but also each have distinct features that set them apart from each other and from AD. Characteristic signs and symptoms include changes in personality, social behavior, and language ability; difficulties in thinking and making decisions; poor coordination and balance; psychiatric symptoms; and dementia. Recent advances, include the discovery of mutations in the *tau* gene that cause one *tau*opathy called frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). The development of several mouse models that produce *tau* tangles will allow researchers to address the many questions that remain about these diseases. The development of a "double transgenic" mouse that has both *tau* tangles and beta-amyloid plaques will also lead to further insights about AD.

Cardiovascular Risk Factors

Several recent studies in populations have found a possible link between factors related to cardiovascular disease and AD. One of these studies found that elevated levels of an amino acid called homocysteine, a risk factor for heart disease, are associated with an increased risk of developing AD. The relationship between AD and homocysteine is particularly interesting because blood levels of homocysteine can be reduced by increasing intake of folic acid and vitamins B6 and B12. In fact, in other studies, scientists have shown that folic acid may protect against nerve cell loss in brain regions affected by AD. Investigators have also found that the use of statins, the most common type of cholesterol-lowering drugs, is associated with a lower risk of developing AD.



Oxidative Damage From Free Radicals

Another promising area of investigation relates to a longstanding theory of aging. This theory suggests that over time, damage from a kind of molecule called a free radical can build up in neurons, causing a loss in function. Free radicals can help cells in certain ways, such as fighting infection. However, too many can injure cells because they are very active and can readily change other nearby molecules, such as those in the neuron's cell membrane or in DNA. The resulting molecules can set off a chain reaction, releasing even more free radicals that can further damage neurons. This kind of damage is called oxidative damage. It may contribute to AD by upsetting the delicate machinery that controls the flow of substances in and out of the cell. 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. Some epidemiological and laboratory studies suggest that anti-oxidants from dietary supplements or food may provide some protection against developing AD. Other studies suggest that low-calorie diets may protect against the development of AD by slowing down metabolic rates.

Inflammation

Another set of hints about the causes of AD points to inflammation in the brain. This process is part of the immune system and helps the body react to injury or disease. Fever, swelling, pain, or redness in other parts of the body are often signs of inflammation. Because cells and compounds that are known to be involved in inflammation are found in AD plaques, some researchers think it may play a role in AD.

They disagree, though, on whether inflammation is a good or a bad thing. Some think it is harmful – that it sets off a vicious cycle of events that ultimately causes neurons to die. Evidence from many studies supports this idea.

Other scientists believe that some aspects of the inflammatory process may be helpful – that they are part of a healing process in the brain. For example, certain inflammatory processes may play a role in combating the accumulation of plaques. Many studies are now underway to examine the different parts of the inflammatory process more fully and their effects on AD.

Brain Infarction

We've all heard the sensible advice about ways to live a long and healthy life: eat right, exercise, don't smoke, wear a seat belt. All of these habits can help prevent heart attacks, stroke, and injuries. This advice may even have some relevance for AD as well. Results from one long-term study of aging and AD show that participants who had evidence of stroke in certain brain regions had more symptoms of dementia than could be explained by the number of plaques and tangles in their brain tissue. These findings suggest that damage to blood vessels in the brain may not be enough to cause AD, but that it could make AD clinical symptoms worse.

New Techniques Help in Diagnosing AD

A healthy man in his early 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 a couple of miles from his house. He has no idea how he got there.

Not so long ago, this man's condition would have been swept into a broad catch-all category called "senile dementia" or "senility." Today, the picture is very different. We now know that Alzheimer's and other illnesses with dementia are distinct diseases. Armed with this knowledge, we have rapidly improved our ability to accurately diagnose AD. We are still some distance from the ultimate goal – a reliable, valid, inexpensive, and early diagnostic marker – but experienced physicians now can diagnose AD with up to 90 percent accuracy.

Early diagnosis has several advantages. For example, many conditions cause symptoms that mimic those of Alzheimer's disease. Finding out early that the problem *isn't* AD but *is* something else can spur people into

the Human Side of AD Research

The Religious Orders Study and the Nun Study: Lives of Service Continue Even After Death

One way that scientists have tried to unravel the mystery of AD and other complex diseases, like heart disease or cancer, is to compare the characteristics, lifestyles, and disease rates of different groups of people. This approach has often provided clues as to why some people get a disease and others don't.

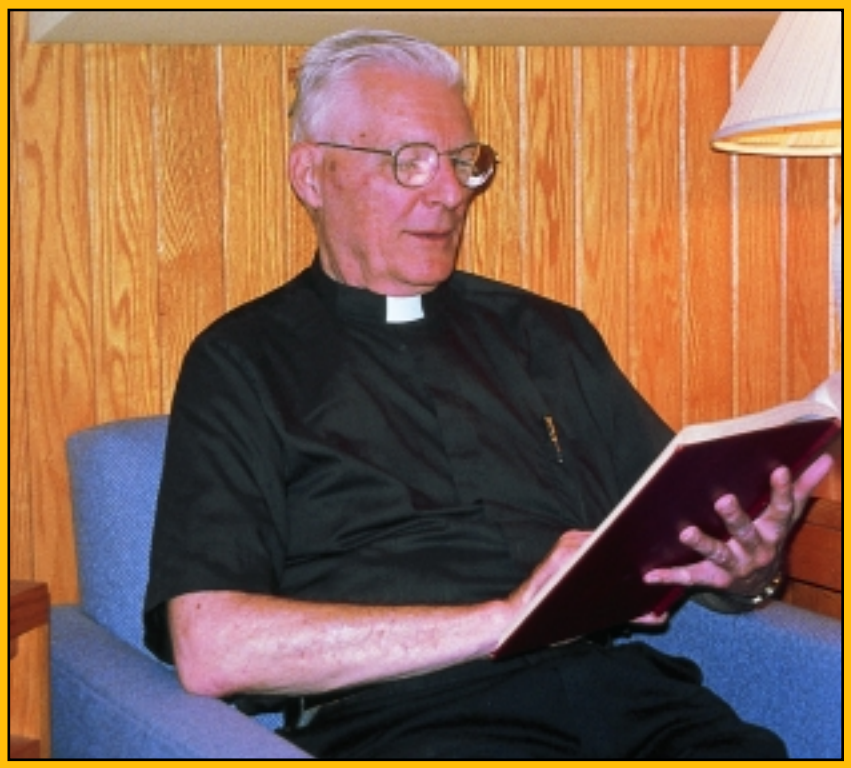
Another way is to study one group of people over time. The notion here is that data gathered over a period of years will reveal important clues about the origins of the disease under investigation. The knowledge gained also may lay the foundation for future treatment or prevention strategies. The Framingham Heart Study is one famous example of this kind of study. It has followed two generations of Massachusetts residents for 50 years, and its findings have revolutionized the way we think about, treat, and prevent heart disease.

(Continued on next page)

The National Institute on Aging is funding two Alzheimer's disease studies that are using this approach – but with a unique twist. These studies involve members of religious communities.

Since 1990, scientists have been working with more than 650 nuns of the School Sisters of Notre Dame, who are located in various parts of the U.S. The Nun Study is an expansion of a pilot project begun in 1986 with a School Sisters of Notre Dame convent in Mankato, Minnesota.

Since 1993, scientists have also been investigating the mental and physical capacities of older nuns, priests, and brothers in the Religious Orders Study. More than 30 religious communities in a dozen States are participating in this study.



All of the participants in both studies agree to have detailed physical and mental function exams every year. Volunteers may spend decades in the study, repeating the tests each year. These exams help researchers better understand the effects on the brain of aging, AD, and other disorders. Participants also agree to donate their brains to the study when they die. This allows the investigators to match many years' worth of clinical and psychological information with the results of examinations of after-death brain tissue. These volunteers consider participating in these studies a wonderful chance to continue their lives of service to others. As one participant in the Nun Study put it, "[They] can have my brain. What good is it going to do me when I'm six feet under?"

The large numbers enrolled in the study ensure that some volunteers will still have normal brain function at the time of death. Others will have developed the clinical signs of AD. Still others will have other neurological disorders, such as Parkinson's disease. The yearly examinations enable researchers to detect signs of AD among participants and to track, year by year, the progress and treatment of the disease among those who develop it.

But why work with religious orders? What's special about them? One reason why members of religious orders are good study participants is that they often live together and have similar lifestyles, educational levels, daily routines, and activities. This cuts down on the variations among participants that make it difficult for scientists to interpret research results. It also makes it easy for study staff to keep track of volunteers over time and to maintain complete information on them.

Working with these participants has allowed the research teams to explore several exciting ideas. For example, the Religious Orders Study team recently worked with their participants to examine a "use-it-or-lose-it" brainpower hypothesis. At an initial evaluation, the researchers asked more than 700 priests and nuns about the amount of time they spent in seven

common activities that involve significant information processing – watching television; listening to the radio; reading newspapers or magazines; reading books; playing cards, checkers, and puzzle games; and going to museums. After tracking the participants for 4 1/2 years, the researchers found that, on average, the risk of developing AD was 47 percent lower in those who did these activities most frequently than in those who did them least frequently. The reasons for this finding aren't entirely clear yet, but it may be that mentally stimulating activities protect the brain in some way. Or, perhaps some other mechanism may be at work that strengthens information processing skills to compensate for age-related declines in other cognitive areas.

The Nun Study has one particularly rich treasure trove to work with – the autobiographies written by the nuns when they entered the order. These personal records provide basic information on the nuns' early lives and families and are an objective measure of each woman's ability to think, remember, and present ideas in writing. Study investigators have found a fascinating link between their early writing skills and later cognitive abilities. The researchers performed an analysis of the autobiographies to determine the grammatical complexity and the "density" of ideas in each. They then examined brain tissue from nuns who had died. The investigators found that most of the nuns whose brain tissue showed significant signs of AD had written autobiographies with low grammatical complexity and idea density. Though the reasons for this link aren't fully understood, a higher linguistic ability early in life may provide some protection against the influences that lead to AD.

getting treatment for the real condition. For the small percentage of dementias that are treatable or even reversible, early diagnosis increases the chances of successful treatment.

Even when the cause of the dementia turns out to be Alzheimer's disease, it's good to find out sooner rather than later. One benefit is medical. The drugs now available to treat AD can help some people maintain their mental abilities for months to years, though they do not change the underlying course of the disease (see p. 42 for more on these drugs).

Other benefits are practical. The sooner the person with AD and family know, the more time they have to make future living arrangements, handle financial matters, establish a durable power of attorney, deal with other legal issues, create a support network, or even make plans to join a research study. Being able to participate for as long as possible in making decisions about the present and future is important to many people with AD.

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

Scientists are now exploring ways to help physicians diagnose AD earlier and more accurately. For example, some studies are focusing on changes in personality and 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 also help pinpoint changes in function.

A PET Scan in Progress

Researchers are working hard to improve these standardized tests so that they can better track the changes that might point to early AD or predict which individuals are at higher risk of developing AD in the future.

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 treatable or curable; others are less responsive to treatment.

Treatable Causes of Dementia

- medication side effects
- depression
- vitamin B12 deficiency
- chronic alcoholism
- certain tumors or infections of the brain
- blood clots pressing on the brain
- metabolic imbalances, including thyroid, kidney, or liver disorders

Other Causes of Dementia

- Alzheimer's disease
- vascular dementia
- frontotemporal dementia, including:
  - frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)
  - Pick's disease
  - supranuclear palsy
  - corticobasal degeneration

Other studies are examining the relationship between early damage to brain tissue and outward clinical signs. Still others are looking for changes in blood chemistry that might indicate the progression of Alzheimer's disease.

One of the most exciting areas of ongoing research in this area is neuroimaging. Over the last decade, scientists have developed several highly sophisticated imaging systems that have been used in many areas of medicine, including Alzheimer's disease. Positron emission tomography (PET), **single photon emission computed tomography** (SPECT), and **magnetic resonance imaging** (MRI) are all examples. These "windows" on the living brain can help scientists measure the earliest changes in brain function or structure in order to identify those people who are at the very first stages of the disease – even before they develop signs and symptoms.

These types of scans are still primarily research tools, but one day, neuroimaging might be used more commonly to help physicians diagnose AD early. These tools may even be used someday to monitor the progress of the disease and assess patient responses to drug treatment.

Current Tools for Diagnosing AD

A definitive diagnosis of Alzheimer's disease is still only possible after death, during an autopsy, when the plaques and tangles can actually be seen. But with the tools now available, experienced physicians can be pretty confident about making an accurate diagnosis in a living person. Here's how they do it.

They take a detailed patient history, including:

- A description of how and when symptoms developed
- A description of the patient's and his or her family's overall medical condition and history
- An assessment of the patient's emotional state and living environment

They get information from family members or close friends:

- People close to the patient 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 do a computerized tomography (CT) scan or a magnetic resonance imaging (MRI) test:

- Brain scans like these can detect strokes or tumors or can reveal changes in the brain's structure and function that indicate early AD.

They conduct neuropsychological testing:

- Q&A tests or other tasks that measure memory, language skills, ability to do arithmetic, and other abilities related to brain functioning help indicate what kind of cognitive changes are occurring.

Criteria for "Probable" Alzheimer's Disease

Because no simple and reliable biological test for AD is available, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Association together established criteria to help physicians diagnose AD. These criteria also help physicians distinguish between AD and other forms of dementia. "Probable" Alzheimer's disease is determined when a person has:

- Dementia confirmed by clinical and neuropsychological examination
- Problems in at least two areas of mental functioning
- Progressive worsening of memory and other mental functioning
- No disturbances of consciousness (no "blacking out")
- Symptoms beginning between ages 40 and 90
- No other disorders that might account for the dementia

As they get older, some people develop a memory deficit greater than that expected for their age. However, other aspects of cognition are not affected, so these people do not meet all the accepted criteria for AD. Thus, they are said to have "mild cognitive impairment" (MCI). About 40 percent of these individuals will develop AD within 3 years. Others, however, do not seem to progress to AD, at least in the time frame studied thus far (up to approximately 6 years). Understanding more about the characteristics and development of MCI is essential in helping clinicians diagnose early stages of AD.

the Search for New Treatments

Research over the last two decades has revealed many pieces of the Alzheimer's disease puzzle. Using recent advances in genetics and molecular biology, scientists have begun to put these pieces into place. In doing so, they've vastly increased our understanding of AD and opened many avenues that could lead to effective treatments.

It has become clear that there probably isn't a "magic bullet" that will, by itself, prevent or cure AD. However, scientists may be able to identify a number of interventions that can be used to reduce risk and treat the disease. Today, it is estimated that the National Institute on Aging, other NIH Institutes, and private industry are conducting **clinical trials** (studies involving humans that rigorously test how well an intervention works) on around 30 compounds that may be active against AD. These studies focus on three main areas:

- Helping people with AD maintain their mental functioning
- Slowing the progress of AD, delaying its onset, or preventing it
- Managing symptoms

Helping People with AD Maintain their Mental Functioning

In the mid-1970s, scientists discovered that levels of a neurotransmitter called **acetylcholine** fell sharply in people with Alzheimer's disease (see p. 16 in ***A Walking Tour Through the Brain*** for more on neurotransmitters). This discovery was one of the first that linked AD with biochemical changes in the brain.

Scientists have 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.

By late 2003, the Food and Drug Administration (FDA) had approved five medications to treat AD symptoms. Of these, four are known as cholinesterase inhibitors and are prescribed to treat mild to moderate AD symptoms. The first, tacrine (Cognex), has been replaced by three newer drugs – donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl). They act by stopping or slowing the action of acetylcholinesterase, an enzyme that normally breaks down acetylcholine. These drugs improve some patients' abilities to carry out activities of daily living, may improve certain thinking, memory, or speaking skills, and can help with certain behavioral symptoms. However, these medications will not stop or reverse AD and appear to help patients only for months to a few years.

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

Helping people with AD carry out their daily lives and maintain their mental abilities is one of the most important goals of AD treatment research. Many investigators are working to develop new and better drugs that can preserve these critical functions for as long as possible.

Slowing, Delaying, or Preventing Alzheimer's Disease

Understanding how AD develops—from beginning to end—is vital for finding drugs or other factors that may slow, delay, or even prevent the disease.

Investigators are looking at a number of possibilities for drug treatments. For example, inflammation of tissue in the brain and overproduction of free radicals are two processes that are thought to be a feature of AD. Clinical trials in both of these areas are looking at whether specific anti-inflammatory agents and agents that protect against oxidative damage can slow or prevent the development of AD.

Scientists are also conducting clinical trials to see if substances already used to reduce cardiovascular risk factors also help lower AD risk or delay progression of the disease. These trials are testing whether supplementation with folic acid and vitamins B6 and B12 can slow the rate of cognitive decline in cognitively normal men and women, women at increased risk of developing dementia, and people diagnosed with AD. A study of statins, the most common type of cholesterol-lowering drug, is also underway to see whether these drugs can slow the rate of disease progression in AD patients.

Estrogen is a hormone produced by a woman's ovaries during her childbearing years. Over the past 25 years, laboratory and animal studies, as

Science on the Cutting Edge

Immunizing Against AD: Just a Neat Idea or a Real Possibility?

Getting vaccinated against measles, tetanus, polio, and other diseases is common practice these days. A person is injected with a weakened form of a disease-causing bacterium or virus. His or her immune system mobilizes to fight against it, and this protects the person against getting the disease. One scientist wondered whether this approach could work for Alzheimer's disease as well.

Researchers have developed special kinds of mice (called **transgenic mice**) that gradually develop AD beta-amyloid plaques in the brain. These mice are invaluable tools to test how plaques can be stopped from forming. Over the course of several studies, scientists tested the effects of injections of a vaccine composed of beta-amyloid and a substance known to stimulate the immune system. They found that long-term immunization resulted in much less beta-amyloid being deposited in the brains of the mice. Similar transgenic mice that had been immunized also performed far better on memory tests than did a group of these mice that had not been immunized.

These exciting developments led to preliminary studies in humans to test the safety and effectiveness of the vaccine. Based on positive results, a further study was designed to measure the immune response in participants with AD who received immunizations with the beta-amyloid vaccine. In this study, which began in the fall of 2001, inflammation unexpectedly developed in the brains of some of the participants. As a result of this complication, the pharmaceutical companies that were conducting the research stopped the trial and are continuing to closely monitor the health of the participants.

Despite their disappointment with this development, the scientists and funders involved in this research emphasize that a tremendous amount of valuable information has been gained from this work so far. It is not unusual for such a revolutionary concept to have setbacks, and they are moving forward with other possible strategies.

well as observational studies in women, have suggested that estrogen has some positive effects on brain activity. These findings have created scientific interest in the relationship among estrogen, memory, and cognitive function.

Studies of estrogen in postmenopausal women with mild to moderate AD did not find estrogen beneficial. But, even if estrogen does not slow the progression of the disease in women already affected with AD, scientists thought perhaps menopausal hormone therapy might in some way affect age-related cognitive decline or protect a woman from developing AD. Two types of such therapies have been investigated—the use of estrogen alone in women who have had a hysterectomy and the use of estrogen plus progestin, which reduces the risk of thickening of the lining of the uterus and endometrial cancer, in other women.

In 2002 a large clinical trial showed that combined estrogen/progestin therapy taken daily for just over 5 years increased the risk of heart disease and breast cancer in some women. More recently, a substudy of that trial showed that this same therapy taken daily by women over age 65 actually increased their chance of developing dementia.

Scientists are continuing to evaluate estrogen alone to prevent dementia. This includes an NIA clinical trial of estrogen alone to prevent or delay development of AD in cognitively normal older women with a family history of dementia.

Questions remain. Scientists do not know whether estrogen or progestin causes the increased risk of disease. Would giving a different estrogen or progestational agent change the result? Would starting therapy around the age of 50, rather than 65, be more beneficial or more harmful? More research is needed on this complex matter.

Another area of work involves **nerve growth factor** (NGF). NGF is one of several growth factors in the body that maintain the health of neurons. NGF also promotes the growth of axons and dendrites, the neuron branches that connect with other neurons and that are essential in nerve cells' ability to communicate (see p. 16 in ***A Walking Tour Through the Brain*** for more on the structure and function of neurons). Studies have turned up a number of clues that link NGF to the neurons that use acetylcholine as a neurotransmitter, so researchers have been eager to see what happens when NGF is added to aging brain tissue. In animal studies, researchers have been able to reverse most of the age-related neuronal shrinkage and loss of ability to make acetylcholine. This success has led to a small-scale, privately-funded gene therapy trial that is testing whether this procedure can be done safely in humans and whether it might lessen symptoms of AD.

Finally, a number of clinical trials are focusing on the earliest stages of the disease process. For example, scientists are developing drugs that prevent enzymes from clipping beta-amyloid out from APP. Others are working on ways to stop beta-amyloid from clumping together into plaques. Teams of investigators are also studying certain enzymes that seem to be able to break beta-amyloid into pieces after it is released from cells but before it has a chance to form into plaques. Still other scientists are exploring the role of neurotransmitter systems other than acetylcholine, such as glutamate. One especially active area of research involves the possibility that a vaccine might be able to stimulate the immune system into getting rid of plaques once they have formed, stopping beta-amyloid and plaque buildup, or even getting rid of plaques once they have formed.

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 Gran in the nursing home. We had a great time. Then yesterday, I went to see her again. When I walked in her room, she started screaming and calling for help. I didn't know what to do."

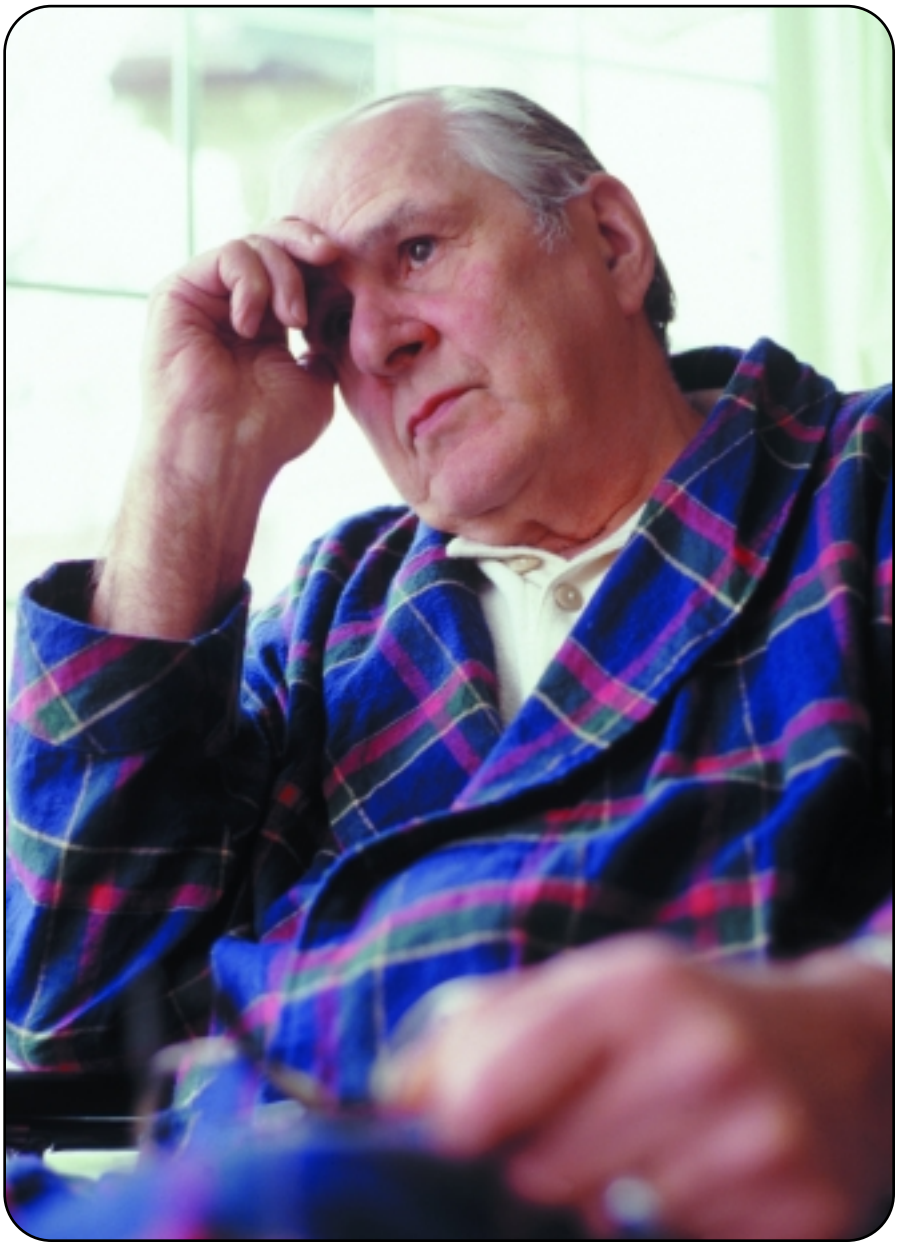
"Mom has been getting up in the night and wandering around the house. Last night, I found her all dressed and trying to get out the front door. None of us is getting any sleep anymore."

"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."

As Alzheimer's disease makes inroads into memory and mental abilities, it also begins to change a person's emotions and behaviors. Between 70 to 90 percent of people with Alzheimer's disease eventually develop one or more behavioral symptoms. These 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.

Unlike a stroke, in which damage to part of the brain occurs all at once, the damage of Alzheimer's disease spreads slowly over time and affects many different parts of the brain.

(Continued on page 48)



Participating in a Clinical Trial

Rapid advances in our knowledge about AD have led to the development of many new drugs and treatment strategies. However, before these new strategies can be adopted, they must be shown to work in patients. This means that clinical trials – studies in people to rigorously test how well a treatment works – have become an increasingly important part of AD research. Advances in treatment are only possible through the participation of patients and family members in clinical trials.

Clinical trials are the primary way that researchers find out if a promising treatment is safe and effective for patients. Clinical trials also tell researchers which treatments are more effective than others. Trials take place at private research facilities, teaching hospitals, specialized AD research centers, and doctors' offices.

Participating in a clinical trial is a big step for people with AD and their caregivers. That's why physicians and clinical trials staff spend lots of time talking with participants about what it's like to be in a trial and the pros and cons of participating. Here are some things that potential participants might want to know about clinical trials.

What kind of trials are there?

- **Treatment trials with existing drugs** assess whether an already approved drug or compound is useful for other purposes. For example, one current trial is testing whether anti-inflammatory drugs already used to treat arthritis might help to prevent AD.

- **Treatment trials with experimental drugs or strategies** find out whether a brand new drug or treatment strategy can help improve cognitive function or lessen symptoms in people with AD, slow the progression to AD, or prevent it. Potential drugs tested in these trials are developed from knowledge about the mechanisms involved in the AD disease process. These compounds are rigorously tested in tissue culture and in animals for their action. 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 study team gives the treatment to a small number of volunteers and examines its action in the body, its safety, and its effects at various doses. Phase I trials generally last only a few months.

- If results show that the treatment appears safe, it will be tested in **Phase II** and **Phase III** clinical trials. These trials involve larger numbers of people over longer periods of time. In these trials, the study team wants to know whether the treatment is safe and effective and what side effects it might have.

After these phases are complete and investigators are satisfied that the treatment is safe and effective, the study team may submit its data to the Food and Drug Administration (FDA) for approval. The FDA reviews the data and decides whether to approve the drug or treatment for use in patients.

What happens when a person signs up for a clinical trial?

First it is important to learn about the study. Study staff explain the trial in detail to potential research participants and describe possible risks and benefits. Staff also talk about participants' rights as research volunteers, including their right to leave the study 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 study and any potential risks.

Once all questions have been answered and if there is still interest in being a part of the study, a patient participant is asked to sign an informed consent form. Laws and regulations regarding informed consent differ across States and research institutions, but all are intended to ensure that patient participants are protected and well cared for.

In some cases, a patient participant may no longer be able to provide informed consent because of problems with memory and confusion. In such cases, it is still possible for an authorized representative (usually a family member) to give permission for the patient to participate. For example, the patient participant may have previously included research participation as part of his or her durable power of attorney. The person (proxy) exercising the durable power of attorney can decide to let the patient participate in a trial if they are convinced that the patient would have wanted to consent if able to do so. Even so, it is still important that patients assent to be in the study, even if they can no longer formally consent to it. Different States have different laws about who is a legal representative. These laws are in a state of flux as researchers and the public grapple with the ethical issues of proxy consent.

Next, patients go through a screening process to see if they qualify to participate in the study. If they qualify and can safely participate, they can proceed with the other parts of the study.

What happens during a trial?

If participants agree to join the study and the screening process shows they're a good match, they have a "baseline" visit with the study staff. This visit generally involves a full physical exam and extensive cognitive and physical tests. This gives the study team information against which to measure future mental and physical changes. Participants also receive the test drug or treatment. As the study progresses, participating patients 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 study staff. These visits allow the investigators to assess the effects of the test drug or treatment, see how the disease is progressing, and see how the participant and the caregiver are doing.

In most clinical trials, participants are randomly assigned to a study group. One group, the test group, receives the experimental drug. Other groups may receive a different drug or a placebo (an inactive substance that looks like the study drug). Having the different groups is important because only by comparing them can researchers be confident that changes in the test group are the result of the experimental treatment and not some other factor. In many trials, no one – not even the study team – knows who is getting the experimental drug and who is getting the placebo or other drug. This is called "masking" meaning that the patient/family member and the staff are "blind" to the treatment being received.

What should people consider before participating in a clinical trial?

Expectations and motivations. Clinical trials generally don't have miraculous results. The test drug or treatment may relieve a symptom, change a clinical measurement, or reduce the risk of death. With a complex disease like AD, it is unlikely that one drug will cure or prevent the disease. Some people choose not to participate or drop out of a study because this reality doesn't meet their expectations. Others participate because they realize that even if the benefit to them may be slight, they are making a valuable contribution to knowledge that will help future patients.

Uncertainty. Some families have a hard time with the uncertainties of participation – not knowing whether the person is on the test drug or the placebo, not being able to choose which study group to be in, not knowing for a long time whether the study was successful or not. Ongoing and open communication with study staff can help to counter this frustration.

Finding the right clinical trial. Some clinical trials want participants who are cognitively healthy or have

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only mild symptoms because they are testing a drug that might delay the decline in cognitive function. Other trials are interested in working with participants who have more advanced AD because they are testing a drug that might lessen behavioral symptoms, or they are testing new strategies to help caregivers. Even though a participant may not be 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 also talk on an ongoing basis with experts in AD who have lots of practical experience and a broad perspective on the disease. The study team understands and can provide advice on the emotional and physical aspects of the person with AD and the caregivers' experience. They 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 about AD clinical trials, visit the NIA's Alzheimer's Disease Education and Referral (ADEAR) Center's Clinical Trials Database website (www.alzheimers.org/trials/index.html). This website includes a list of clinical trials on Alzheimer's disease and dementia currently in progress at centers throughout the U.S. It also provides information on the phases of clinical trials and how to participate, and explains the drug development process. The site also provides links to other useful websites with related information. For additional information, visit the clinical trials websites of the Alzheimer's Association www.alz.org/ResourceCenter/ByTopic/Research.htm and the National Institutes of Health www.clinicaltrials.gov/.

Even small tasks require the brain to engage in a complex process that can involve more than one region of the brain. If this process is disrupted, 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, behavior that may seem bizarre suddenly makes sense:

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

An unknown young man suddenly appearing in her room may be threatening and terrifying to a woman who does not recognize her grandson.

Feelings of responsibility toward a long-ago night job resurface and compel a woman to get up in the night to go to work.

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.

Behavioral symptoms are one of the hardest aspects of the disease for families and other caregivers to deal with. They are emotional and upsetting. 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 they occur, and they are studying new treatments – both drug and non-drug – to deal with them.

A number of ongoing and planned clinical trials are looking at ways to treat agitation. These trials include participants who are living in nursing homes or at home. They involve the study of a variety of drugs, including a beta-blocker, an anti-seizure medication, a cholinesterase inhibitor, and an antipsychotic.

Improving Support for Families and Other Caregivers

Perhaps one of the greatest costs of Alzheimer's disease is the physical and emotional toll on family, caregivers, and friends. 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 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

Who are the **AD Caregivers?**

Caregivers vary depending on the culture and ethnic group involved. Most primary caregivers are family members.

- **Spouses:** This is the largest group of caregivers. Most are older, too, and many have their own health problems to deal with.
- **Daughters:** The second largest group of primary caregivers are 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:** Though 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, but many are older and are coping with their own frailties or health problems.
- **Grandchildren:** Older children may become major helpers in caring for a person with AD. Adolescent or young grandchildren may need extra help and support if their parents' attention is heavily focused on the ill grandparent, or if the grandparent with AD lives in the family's home.
- **Other:** Friends, neighbors, and fellow faith community members also often help care for a person with AD.

significantly more time on caregiving tasks than do caregivers of people with other types of illnesses.

Although research on caregiver support is still in its early days, we've already learned a lot about the unique aspects of caregivers' personalities and situations. For example, one study of the psychological and physical responses of AD caregivers showed that they don't all have the same response to caregiving. Certain characteristics seem to make some caregivers more vulnerable to the physical and emotional stresses associated with dementia care. These characteristics include being a male spouse, having few breaks from caregiving responsibilities, and having preexisting illnesses.

Caregiver research is also beginning to tease out characteristics of support programs that might be most useful for particular groups of caregivers. For example, peer support programs that link caregivers with trained volunteers who also have been dementia caregivers appear to help. These programs are especially good for caregivers whose social support networks are weak or who are in very stressful situations. Other research has confirmed that the information and problem-solving needs of caregivers evolve over time as the person with AD changes. Support programs can respond by offering services and information geared to different stages of the disease.

One of the most difficult decisions that many families face is whether and when to place a loved one with Alzheimer's disease 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 assisted living facilities, continuing care retirement communities, nursing homes, and special care units (a separate area within a nursing home or assisted living facility designed especially for patients with dementia).

the **Realities,** the **Positives,** and the **Negatives** of **Caring** for a Person with AD

A reality check for an AD caregiver might look something like this:

- **Physical effort and time commitment:** Help with bathing, eating, dressing, and other activities of daily living takes a lot of time. As the disease progresses, the need for this kind of help increases. Behavior problems and safety concerns mean that the caregiver is always "on duty," even when not actively helping the person.

- **Financial costs:** The costs of care vary, but can be high depending on whether the person is cared for at home or in a residential care setting and how much help the caregiver has. Many caregivers give up their jobs or cut back on their work hours and this also has financial implications.

- **Psychological loss:** Caregivers often experience a profound sense of loss as the disease slowly takes their husband, wife, parent, or friend. The relationship as it once was gradually ends and plans for the future must be radically changed. Caregivers must come to terms with "the long goodbye."

Many research studies have shown that caring for a person with AD can have some negative effects on the caregiver...

- Employment complications
- Emotional distress
- Fatigue and poor physical health
- Social isolation
- Family conflict
- Less time for leisure, self, and other family members

...but research has shown that caregiving also has important positive effects:

- 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

Science on the Cutting Edge

Studying New Ways to Help Caregivers

It was midnight, the end of a long day of taking care of her husband. She was exhausted but she couldn't sleep. A year ago she would have felt totally alone, unable to share the hardships of caregiving, and desperate for ideas for how to cope better with his changeable moods and withdrawal from the world. Tonight was different. She went to the living room, switched on her computer, and plugged into a computer-based support group for family caregivers. She sent out a message and soon received replies from several fellow caregivers. They knew just what she was feeling. Their words of understanding and support eased her mind and helped give her the strength she needed for the days ahead.

Caring for a person with Alzheimer's disease has special stresses and difficulties. As a result, support groups have always been an important feature of AD caregiver programs. Conventional support groups have been enormously helpful for many caregivers, but they have a few drawbacks. Attending a group involves finding transportation and arranging for care for the person with AD. The group's meeting time may not coincide with the time that a caregiver wants advice or needs to express feelings. Some caregivers do not feel comfortable discussing their experiences publicly in a group. Members of some ethnic or cultural groups may be particularly reluctant to join a traditional support group.

In 1989, a researcher had an idea for a radically different, new kind of support system for family caregivers. She envisioned a computer-based system that would operate 24 hours a day, 7 days a week. It would provide expert medical advice and information about the latest developments in AD research. It would also include a "bulletin board" component that would allow caregivers to share ideas and give and get support by posting messages on-line. The project would provide a computer if needed and would train caregivers in how to use the equipment. From the start, she invited the local Alzheimer's Association to join her in carrying out the idea. This partnership is still flourishing today.

Although many people doubted that adult and elderly caregivers with little or no computer experience would want to go online, the project, called the Alzheimer's Disease Support Center, was a hit from the start. In fact, the bulletin board component, called the Caregiver Forum,

soon became the most popular element. Users were eager to communicate, share experiences and feelings, and learn from each other. They soon became, as they called it, a "computer family."

Scientists who have been conducting research with computer-based support systems have found they have two qualities that make them especially useful:

- They reach lots of people simultaneously. Many users can log on to get information that is posted on the system. In addition to providing lists of useful publications and materials, the systems post information on traditional support groups, daycare centers, and other services. They also provide a "Q&A" module where users can get answers to their specific caregiving questions from a team of physicians, nurses, social workers, psychologists, and staff of the Alzheimer's Association. In addition, users can browse an archive of previously asked questions and answers organized by topic. Users can also interact with each other through the bulletin board component.

- Computer-based systems address some of the drawbacks of traditional support groups. They put control of the support process in the hands of the user. Users can talk with others and get help whenever they need it, day or night. Some users log on daily; others log on only when they have a specific question or need. Because the computer is at home, they don't need to make special arrangements to get to a support group meeting. Users can express themselves publicly if they want to or they can be anonymous if that is better for them. For every user who posts messages on the system, researchers have documented that several just read what others have posted. These users seem to benefit from the sense of kinship with others facing similar situations and may in time begin to participate more actively.

One of the most fascinating findings from this project was how quickly users overcame the potential barriers posed by an electronic communication system. Here are just a few of the techniques users have adopted to "humanize" the system, especially the Caregiver Forum:

- Using punctuation keys, users have incorporated an array of icons into their messages to represent faces and gestures. They also intentionally misspell words and manipulate the placement of letters. All of these devices help users convey their feelings.

:-) :)ing :-o :-I ( )s [hugs]

"I am sooooooo tired."

"It was reeeeeeeeeally scary."

"...this is one way I have to think not to go way
D
O
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N"

- Users talk about all sorts of things, not just caregiving issues. Sharing details of everyday life – weddings, children's activities, hobbies, even the weather – seems to help users reduce their feelings of isolation and brings a sense of normality and balance to their relationships with others.

- Friendships begun over the computer have blossomed into regular meetings for meals and get-togethers.

In 2000, the NIA funded a follow-up study to the original project. Called Computer Mediated Support for Family Caregivers, or CO-MES, the study is exploring how best to use computers to provide information and support to family caregivers. The study team is trying to learn more about who uses this type of support and whether computer-based groups help to lessen the negative effects of caregiving. Two types of computer-based groups are being studied – a group led by a family caregiver and a group led by a nurse. Many of the system's features are the same as before, though users now access the system through the Internet. The system also now has a chat room, which allows users to have "real-time" conversations. At the same time, the original computer-based support group continues to operate.

Glossary

Acetylcholine – a neurotransmitter that plays an important role in learning and memory.

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

Amyloid plaques – largely insoluble deposits found in the spaces between nerve cells in the brain that are made of beta-amyloid, other molecules, and different kinds of nerve and non-nerve cells.

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

Axon – the long, tube-like part of a neuron that transmits outgoing signals to other cells.

Beta-amyloid – a part of the APP protein found in the insoluble deposits outside neurons and that forms the core of plaques.

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

Cerebellum – the part of the brain that is 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, decisionmaking, emotions, movement, and sensory functions.

Chromosome – a threadlike structure in the nucleus of a cell that contains DNA, sequences of which make up genes; most human cells contain 23 pairs of chromosomes.

Clinical trial – a research study involving humans that rigorously tests how well an intervention works.

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

Corpus callosum – the thick bundle of nerves that connects the two hemispheres of the cerebral hemispheres.

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

Dendrite – the branchlike extension of neurons that receive messages from other neurons.

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

Early-onset Alzheimer's disease – a rare form of AD that usually begins to affect 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 first begins.

Enzyme – a substance that causes or speeds up a chemical reaction.

Free radical – a highly reactive oxygen molecule that combines easily with other molecules, sometimes causing damage to cells.

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

Genetic risk factor – a change in a cell's DNA that does not cause a disease but may increase the chance that a person will develop a disease.

Glial cell – a specialized cell that supports, protects, or nourishes nerve cells.

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

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

Late-onset Alzheimer's disease – the most common form of AD; it occurs in people aged 65 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 – 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 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).

Microtubules – the internal support structure for neurons that guides nutrients and molecules from the body of the cell to the end of the axon and back.

Mutation – a rare change in a cell's DNA that can cause a disease.

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.

Neurofibrillary tangles – collections of twisted *tau* found in the cell bodies of neurons in AD.

Neuron – a nerve cell in the brain.

Neurotransmitter – a chemical messenger between neurons; a substance that is released by the axon on one neuron and excites or inhibits activity in a neighboring neuron.

Nucleus – the organ within a cell that contains the chromosomes and controls many of its activities.

Positron emission tomography (PET) – an imaging technique 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 in brain tissues.

Single photon emission computerized 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 is a principal component of the paired helical filaments in neurofibrillary tangles; *tau* helps to maintain the structure of microtubules in normal nerve cells.

Thalamus – a small organ in the front of the cerebral hemispheres that sends sensory information to the cerebral cortex and sends other information back to the body.

Transgenic mice – mice that have had a human gene (like APP) inserted into their chromosomes. Mice carrying the mutated human APP gene often develop plaques in their brains as they age.

Ventricle – cavity within the brain that contains cerebrospinal fluid. During AD, brain tissue shrinks and the ventricles enlarge.

For More Information

Organizations

Alzheimer's Association. The Alzheimer's Association is a national, nonprofit 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.

Alzheimer's Association
919 North Michigan Avenue, Suite 1100
Chicago, IL 60611-1676
1-800-272-3900
Website: *www.alz.org*

Alzheimer's Disease Cooperative Study. The Alzheimer's Disease Cooperative Study (ADCS) is a cooperative agreement between the National Institute on Aging (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 of 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's Disease Cooperative Study
University of California, San Diego
9500 Gilman Drive - 0949
La Jolla, CA 92093-0949
858-622-5880
Website: *http://antimony.ucsd.edu/*

Alzheimer's Disease Education and Referral (ADEAR) Center. The ADEAR Center, part of the NIA, provides publications and information on AD, including booklets on caregiving, fact sheets and reports on research findings, a database of clinical trials, recommended reading lists, and the *Progress Report on Alzheimer's Disease*. Information specialists provide referrals to local AD resources.

Alzheimer's Disease Education and Referral (ADEAR) Center
PO Box 8250
Silver Spring, MD 20907
1-800-438-4380
Website: *www.alzheimers.org*

Children of Aging Parents. Children of Aging Parents is a nonprofit organization that provides information and referrals for nursing homes, retirement communities, elderlaw attorneys, adult day-care centers, medical insurance providers, respite care, assisted living centers, and State and county agencies. Also offered are fact sheets on various topics, a bimonthly newsletter, conferences and workshops, support group referrals, and a speaker's bureau.

Children of Aging Parents
1609 Woodbourne Road, Suite 302A
Levittown, PA 19057-1511
1-800-227-7294
Website: *www.caps4caregivers.org*

For More Information

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Alzheimer's Association
225 N. Michigan Avenue, Suite 1700
Chicago, IL 60601
1-800-272-3900
Website: *www.alz.org*

Alzheimer's Disease Cooperative Study. The Alzheimer's Disease Cooperative Study (ADCS) is a cooperative agreement between the National Institute on Aging (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 of 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.

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Children of Aging Parents
1609 Woodbourne Road, Suite 302A
Levittown, PA 19057-1511
1-800-227-7294
Website: *www.caps4caregivers.org*

Eldercare Locator. The 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.

Eldercare Locator
1-800-677-1116
Website: *www.eldercare.gov*

Family Caregiving Alliance. The Family Caregiver Alliance (FCA) is a nonprofit organization that offers support services for those caring for adults with AD, stroke, traumatic brain injuries, and other cognitive disorders. FCA programs and services include an Information Clearinghouse for FCA's publications.

Family Caregiving Alliance
690 Market Street, Suite 600
San Francisco, CA 94104
415-434-3388
Website: *www.caregiver.org*

National Institute on Aging (NIA). Part of the National Institutes of Health (NIH), the NIA is the Federal government's lead agency for research on AD. NIA also offers information about health and aging, including the *Age Page* series and the NIA *Exercise Kit*, which contains an 80-page exercise guide and 48-minute closed-captioned video. Caregivers can find many *Age Pages* on the website.

National Institute on Aging
Information Center
PO Box 8057
Gaithersburg, MD 20898-8057
1-800-222-2225
1-800-222-4225 (TTY)
Website: *www.nia.nih.gov*

National Library of Medicine. Part of NIH, the National Library of Medicine is the world's largest medical library with 6 million items, including books, journals, technical reports, manuscripts, microfilms, photographs and images. A large searchable health information database of biomedical journals, called MEDLINE/PubMed is accessible via the Internet. A service called MEDLINEplus links the public to general information about AD and caregiving, plus many other sources of consumer health information, including a searchable clinical trials database located at *http://clinicaltrials.gov*.

National Library of Medicine
8600 Rockville Pike
Bethesda, MD 20894
1-888-346-3656
Website: *www.nlm.nih.gov*

Partnership for Caring. Partnership For Caring (PFC) is a nonprofit organization that works to improve how people die in our society. PFC operates an information hotline dealing with end-of-life issues and provides State-specific living wills, medical powers of attorney, and other information materials. PFC also provides education and consultation services to doctors, nurses, social workers, attorneys, and clergy concerning end-of-life decisions.

Partnership for Caring
1620 Eye Street NW, Suite 202
Washington, DC 20006
1-800-989-9455
Website: *www.partnershipforcaring.org*

Well Spouse Foundation. Well Spouse Foundation is a nonprofit organization that gives support to spouses and partners of the chronically ill and/or disabled. Well Spouse maintains support groups, publishes a bimonthly newsletter, and helps organize letter writing programs to help members deal with the effects of isolation.

Well Spouse Foundation
63 West Main Street, Suite H
Freehold, NJ 07728
1-800-838-0879
Website: *www.wellspouse.org*

Recommended Reading

Check with your local library, bookseller or with major Internet book distributors for the following:

Ballard, E.L., Poer, C.M. ***Lessons Learned: Shared Experiences in Coping***. Durham, NC: The Duke Family Support Program. 1999. Available from the Alzheimer's Disease Education and Referral (ADEAR) Center, PO Box 8250, Silver Spring, MD 20907-8250. 1-800-438-4380.

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.

Davies, H.D., Jensen, M.P. ***Alzheimer's: The Answers You Need***. Forest Knolls, CA: Elder Books. 1998.

This book is designed for people in the early stages of AD. It provides information about the nature and causes of AD, the symptoms and how to deal with them, the assessment process, taking part in a drug research program, continuing to work, handling finances, driving, and the effects of AD on a spouse and other family members.

Mace, N.L., Rabins, P.V. ***The 36 Hour Day: A Family Guide To Caring for Persons With Alzheimer's Disease, Related Dementing Illnesses, and Memory Loss in Later Life***. 3rd ed. Baltimore, MD: Johns Hopkins University Press. 1999.

This practical and detailed reference book provides a wealth of information to families on caring for persons with AD or related disorders. The book presents background information on dementia, brain disorders, and the causes of dementia, and gives practical suggestions and advice on how families and caretakers can deal with problems.

McKhann, G., Albert, M. ***Keeping Your Brain Young: The Complete Guide to Physical and Emotional Health and Longevity***. Hoboken, NJ: John Wiley and Sons. 2002.

This book examines scientific research and case histories to summarize the most effective ways to reduce the impact of physical changes to the brain as we age. The authors offer techniques to improve memory and recommend mental and physical exercise programs. Their strategies to stay healthy also include a well-balanced diet, proper sleep, and getting treatment for depression, vision and hearing loss, and other health problems. The book also discusses brain disorders.

Petersen, R., ed. ***Mayo Clinic on Alzheimer's Disease***. Rochester, MN: Mayo Clinic Health Information. 2002.

This book discusses current knowledge of AD and its relationship to other forms of dementia. It also provides an overview of treatment and caregiving, using the experience of physicians, psychiatrists, neurologists, and allied healthcare professionals at the Mayo Clinic. Topics include how the brain works and what can go wrong; how AD affects a person; diagnosis treatments; research; and caregiving.

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, to 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, NY: Random House, Inc. 2001.

An eloquent and moving description of Alzheimer's disease, *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. The author, calling AD a "death by a thousand subtractions," describes the science of AD in terms that are easy for those who know nothing about AD to understand.

Snowdon, D. ***Aging With Grace: What the Nun Study Teaches Us About Leading Longer, Healthier, and More Meaningful Lives***. New York, NY: Random House, Inc. 2001.

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 allowed 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 to AD, and the role of heredity and lifestyle in healthy aging.

Tanzi, R.E., Parson, A.B. ***Decoding Darkness: The Search for the Genetic Causes of Alzheimer's Disease***. Cambridge, MA: Perseus Publishing. 2000.

This book presents a history of the medical journey to find the genetic causes of AD. It describes the experiences of Dr. Rudy Tanzi, a pioneer in the search to identify AD genes. The book is easy to read and examines the complex research involved in molecular genetics. The authors speculate that AD may ultimately be effectively treated and even prevented.

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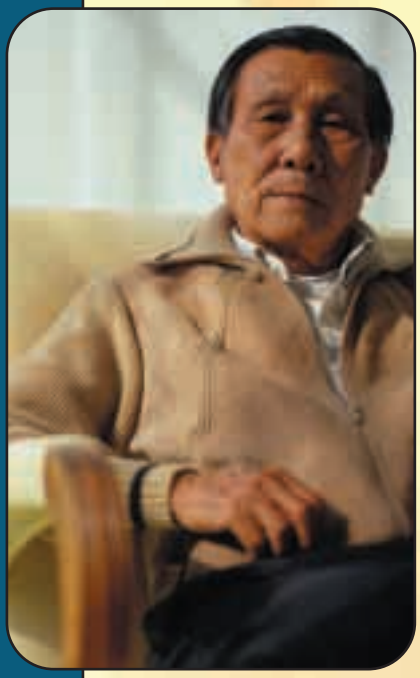

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