AGEWELL®

HEALTH AND WELLNESS

MEMORY MAKEOVER® BOOK

UNRAVELING THE MYSTERY OF MEMORY LOSS

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Preface

Over the past several decades, Alzheimer's disease has emerged from obscurity. The disorder was once considered uncommon, but today it is clearly a major public health problem that severely impacts millions of older adults and their families.

This book provides updated knowledge that should prove useful for everyone interested in learning more about the condition -- including patients, family members, friends, and caregivers.

The first step to understanding Alzheimer's disease involves knowing key facts about the healthy brain. We'll describe the structure and function of the brain as a whole as well as its major parts. We'll also examine the structure and function of individual brain cells known as neurons.

The central part of the book focuses on how the brain changes during the course of Alzheimer's disease. There are illustrations showing changes in the brain as it progresses from mild to moderate to severe disease. Some of these drawings show how individual neurons change. Other drawings illustrate the protein plaques and the tangles – two hallmarks of the disease that serve to impair communication between brain cells.

The last part of the book talks about recent research advances that are helping bring us closer to the goal of controlling the disease.

Unraveling the Mystery of Memory Loss reflects our current knowledge based on recent scientific advances. We hope that this book will provide answers to some of your most pressing questions.

Introduction

Alzheimer's disease presents major problem not only for patients and families but also for our health care system and society as a whole. AD, the most common cause of dementia, affects between 2.4 million to 4.5 million people in the United States alone. But scientists agree that unless the disease can be effectively treated or prevented, the numbers will increase significantly with current population trends.

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

The number of AD caregivers will rise rapidly as the population ages and as the number of people with AD grows. During their years of AD caregiving -- spouses, relatives, and friends experience great emotional, physical, and financial challenges. As the disease runs its course and the abilities of people with AD steadily decline, family members face difficult, and often costly, decisions about the long-term care of their loved ones.

The growing number of people with AD and the costs associated with the disease also put a heavy economic burden on society. The national direct and indirect costs of caring for people with AD are estimated to be more than $100 billion a year. If current AD trends continue, total Federal Medicare spending to treat beneficiaries with the disease is estimated to increase from $62 billion in 2000 to $189 billion in 2015.

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

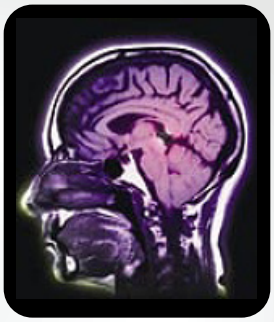
Basics of a Healthy Brain

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

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

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

THE BRAIN'S VITAL STATISTICS



Adult weight
about 3 pounds

Adult size
a medium cauliflower

Number of neurons
about 100,000,000,000 (100 billion)

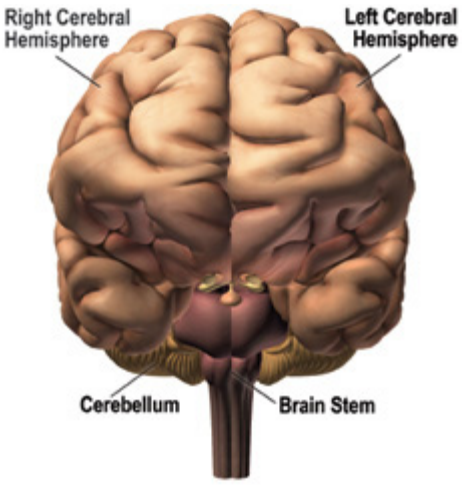
Number of synapses
(the gaps between neurons)
about 100,000,000,000,000 (100 trillion)

Number of capillaries
(tiny blood vessels)
about 400,000,000,000 (400 billion)

Inside the Human Brain

The brain has many parts, each of which is responsible for particular functions. The following section describes a few key structures and what they do.

THE MAIN PLAYERS



Two cerebral hemispheres account for 85 percent of the brain's weight. The billions of neurons in the two hemispheres are connected by thick bundles of nerve cell fibers called the corpus callosum. Scientists now think that the two hemispheres differ not so much in what they do (the "logical versus artistic" notion), but in how they process information. The left hemisphere appears to focus on details (such as recognizing a particular face in a crowd). The right hemisphere focuses on broad background (such as understanding the relative position of objects in a space). The cerebral hemispheres have an outer layer called the cerebral cortex. This is where the brain processes sensory information received from the outside world, controls voluntary movement, and regulates cognitive functions, such as thinking, learning, speaking, remembering, and making decisions. The hemispheres have four lobes, each of which has different roles:

- The frontal lobe, which is in the front of the brain, controls "executive function" activities like thinking, organizing, planning, and problem solving, as well as memory, attention, and movement.

- The parietal lobe, which sits behind the frontal lobe, deals with the perception and integration of stimuli from the senses.

- The occipital lobe, which is at the back of the brain, is concerned with vision.

- The temporal lobe, which runs along the side of the brain under the frontal and parietal lobes, deals with the senses of smell, taste, and

sound, and the formation and storage of memories.

The cerebellum sits above the brain stem and beneath the occipital lobe. It takes up a little more than 10 percent of the brain. This part of the brain plays roles in balance and coordination. The cerebellum has two hemispheres, which receive information from the eyes, ears, and muscles and joints about the body's movements and position. Once the cerebellum processes that information, it sends instructions to the body through the rest of the brain and spinal cord. The cerebellum's work allows us to move smoothly, maintain our balance, and turn around without even thinking about it. It also is involved with motor learning and remembering how to do things like drive a car or write your name.

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

OTHER CRUCIAL PARTS

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

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

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

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

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

THE BRAIN IN ACTION

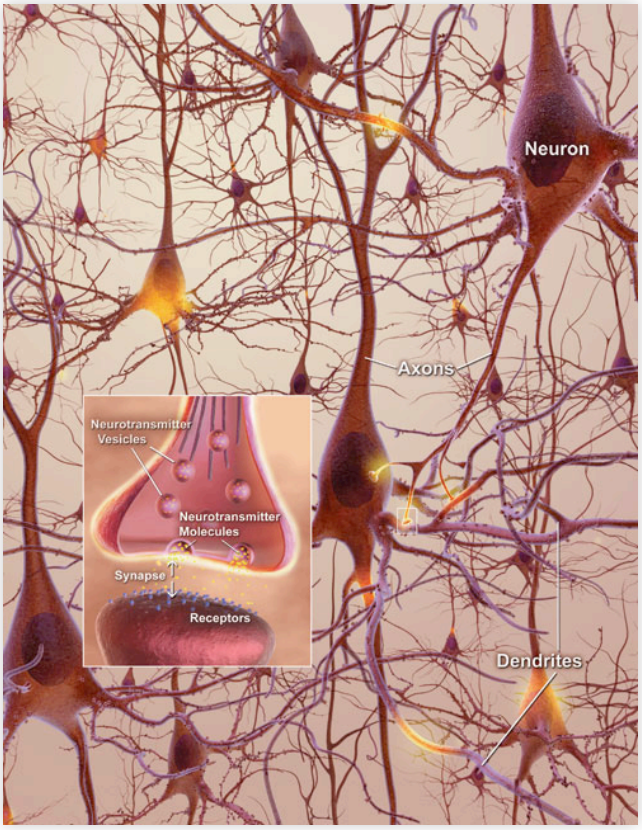
Sophisticated brain-imaging techniques allow scientists to monitor brain function in living people and to see how various parts of the brain are used for different kinds of tasks. This is opening up worlds of knowledge about brain function and how it changes with age or disease.

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

Scientists can use PET scans to see what happens in the brain when a person is engaged in a physical or mental activity, at rest, or even while sleeping or dreaming. Certain tracers can track the activity of brain chemicals, for example neurotransmitters such as dopamine and serotonin. Some of these neurotransmitters are changed with age, disease, and drug therapies.

Neurons and Their Jobs

The human brain is made up of billions of neurons. Each has a cell body, an axon, and many dendrites. The cell body contains a nucleus, which controls much of the cell's activities. The cell body also contains other structures that perform specific tasks.



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

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

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

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

COMMUNICATION

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

Neurons communicate with each other through their axons and dendrites. When a dendrite receives an incoming signal (electrical or chemical), an "action potential," or nerve impulse, can be generated in the cell body. The action potential travels to the end of the axon, and once there, the passage of either electrical current or, more typically, the release of chemical messengers, called neurotransmitters, can be triggered. The neurotransmitters are released from the axon terminal and move across a tiny gap, or synapse, to specific receptor sites on the receiving, or post-synaptic, end of dendrites of nearby neurons. A typical neuron has thousands of synaptic connections, mostly on its many dendrites, with other neurons. Cell bodies also have receptor sites for neurotransmitters.

Once the post-synaptic receptors are activated, they open channels through the cell membrane into the receiving nerve cell's interior or start other processes that determine what the receiving nerve cell will do. Some neurotransmitters inhibit nerve cell function (that is, they make it less likely that the nerve cell will send an electrical signal down its axon). Other neurotransmitters stimulate nerve cells, priming the receiving cell to become active or send an electrical signal down the axon to more neurons in the pathway. A neuron receives signals from many other neurons simultaneously, and the sum of a neuron's neurotransmitter inputs at any one instant will determine whether it sends a signal down its axon to activate or inhibit the action of other neighboring neurons.

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

METABOLISM

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

REPAIR

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

The Changing Brain in Healthy Aging

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

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

- Certain parts of the brain shrink, especially the prefrontal cortex (an area at the front of the frontal lobe) and the hippocampus. Both areas are important to learning, memory, planning, and other complex mental ac tivities.

- Changes in neurons and neurotransmitters affect communication between neurons. In certain brain regions, communication between neurons can be reduced because white matter (myelin-covered axons) is degraded or lost.

- Changes in the brain's blood vessels occur. Blood flow can be reduced because arteries narrow and less growth of new capillaries occurs.

- In some people, structures called plaques and tangles develop outside of and inside neurons, respectively, although in much smaller amounts than in AD

- Damage by free radicals increases (free radicals are a kind of molecule that reacts easily with other molecules).

- Inflammation increases (inflammation is the complex process that occurs when the body responds to an injury, disease, or abnormal situation).

What effects does aging have on mental function in healthy older people? Some people may notice a modest decline in their ability to learn new things and retrieve information, such as remembering names. They may perform worse on complex tasks of attention, learning, and memory than would a younger person. However, if given enough time to perform the task, the scores of healthy people in their 70s and 80s are often similar to those of young adults. In fact, as they age, adults often improve in other cognitive areas, such as vocabulary and other forms of verbal knowledge.

It also appears that additional brain regions can be activated in older adults during cognitive tasks, such as taking a memory test. Researchers do not fully understand why this happens, but one idea is that the brain engages mechanisms to compensate for difficulties that certain regions may be having. For example, the brain may recruit alternate brain networks in order to perform a task. These findings have led many scientists to believe that major declines in mental abilities are not inevitable as people age. Growing evidence of the adaptive ("plastic") capabilities of the older brain provide hope that people may be able to do things to sustain good brain function as they age. A variety of interacting factors, such as lifestyle, overall health, environment, and genetics also may play a role.

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

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

- Controlling risk factors for chronic disease, such as heart disease and diabetes (for example, keeping blood cholesterol and blood pressure at healthy levels and maintaining a healthy weight)

- Enjoying regular exercise and physical activity

- Eating a healthy diet that includes plenty of vegetables and fruits

- Engaging in intellectually stimulating activities and maintaining close social ties with family, friends, and community

Hallmarks of Alzheimer's Disease

Alzheimer's disease disrupts critical metabolic processes that keep neurons healthy. These disruptions cause nerve cells in the brain to stop working, lose connections with other nerve cells, and finally die. The destruction and death of nerve cells causes the memory failure, personality changes, problems in carrying out daily activities, and other features of the disease.

The brains of people with AD have an abundance of two abnormal structures—amyloid plaques and neurofibrillary tangles—that are made of misfolded proteins. This is especially true in certain regions of the brain that are important in memory.

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

AMYLOID PLAQUES

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

We now know that some people develop some plaques in their brain tissue as they age. However, the AD brain has many more plaques in particular brain regions. We still do not know whether amyloid plaques themselves cause AD or whether they are a by-product of the AD process.

NEUROFIBRILLARY TANGLES

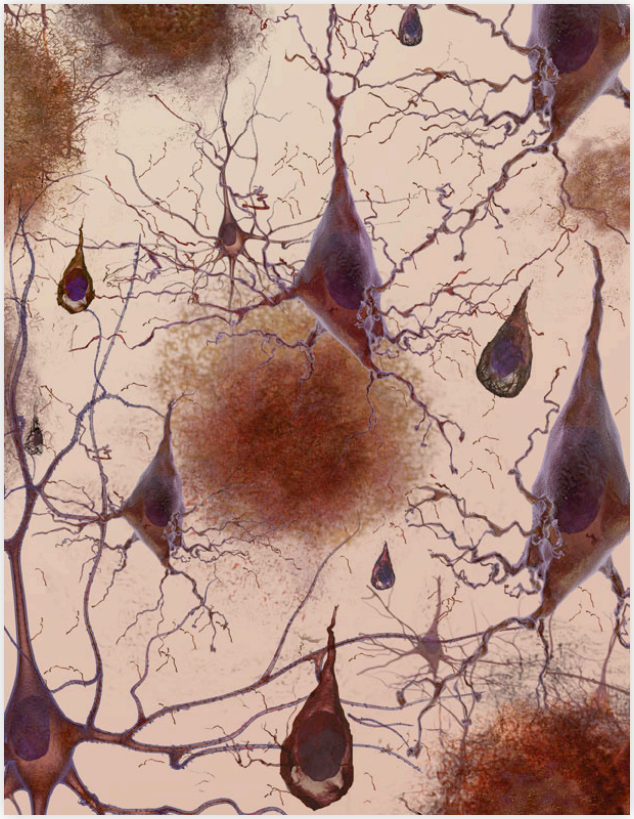
The second hallmark of AD, also described by Dr. Alzheimer, is neurofibrillary tangles. Tangles are abnormal collections of twisted protein threads found inside nerve cells. The chief component of tangles is a protein called tau.

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

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

LOSS OF CONNECTION BETWEEN CELLS AND CELL DEATH

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



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

The Changing Brain in AD

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

PRECLINICAL AD

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

Scientists believe that these brain changes begin 10 to 20 years before any clinically detectable signs or symptoms of forgetfulness appear. That's why they are increasingly interested in the very early stages of the disease process. They hope to learn more about what happens in the brain that sets a person on the path to developing AD. By knowing more about the early stages, they also hope to be able to develop drugs or other treatments that will slow or stop the disease process before significant impairment.

VERY EARLY SIGNS AND SYMPTOMS

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

Mild Cognitive Impairment

People with MCI have memory impairments, but otherwise function well and don't meet the clinical criteria for dementia. Whereas normal memory loss associated with aging may involve forgetting a name, memory loss associated with MCI is more severe and persistent.

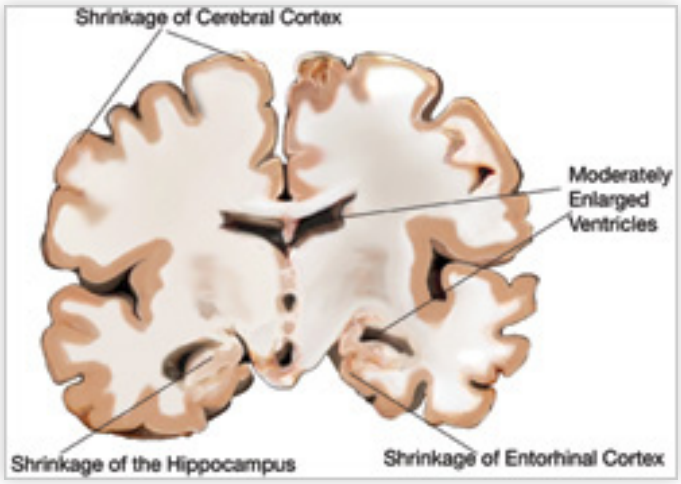
MCI is often a transition stage between normal aging and more serious problems caused by AD. Most, but not all, people with MCI get worse. According to some studies, each year about 12 to 15 percent of people with MCI develop AD. In older people with MCI, if the memory loss is slowly getting worse, the chances of developing AD are about 60 percent to 70 percent.

Research is under way on whether the drugs approved to treat symptoms of AD may help some people with MCI. Scientists hope that in the future accurate and early evaluation and treatment of people with MCI may help prevent further cognitive decline.

Other Signs of Early AD Development

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

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



Other scientists have focused on changes in sensory abilities as possible indicators of early cognitive problems. For example, in one study they found associations between a decline in the ability to detect odors and cognitive problems or dementia.

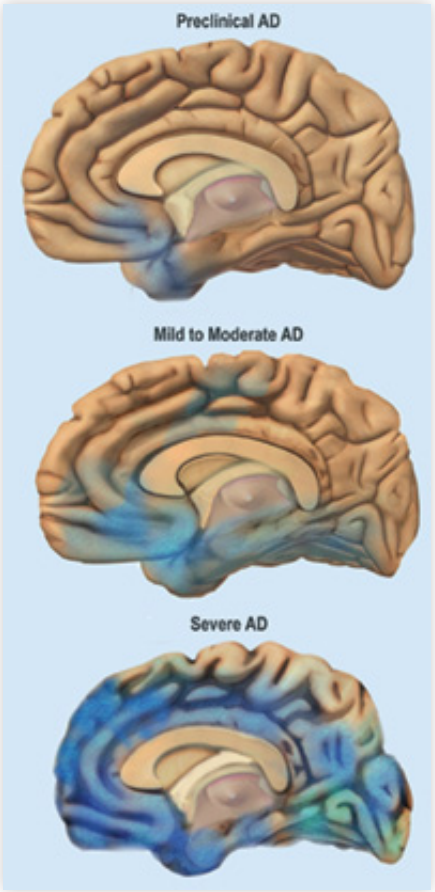
These findings are tentative, but they are promising because they suggest that, some day, it may be possible to develop ways to improve early detection of MCI or AD. These tools also will help scientists answer questions about causes and very early development of AD, track changes in brain and cognitive function over time, and ultimately track a person's response to treatment for AD.

MILD AD

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

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

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



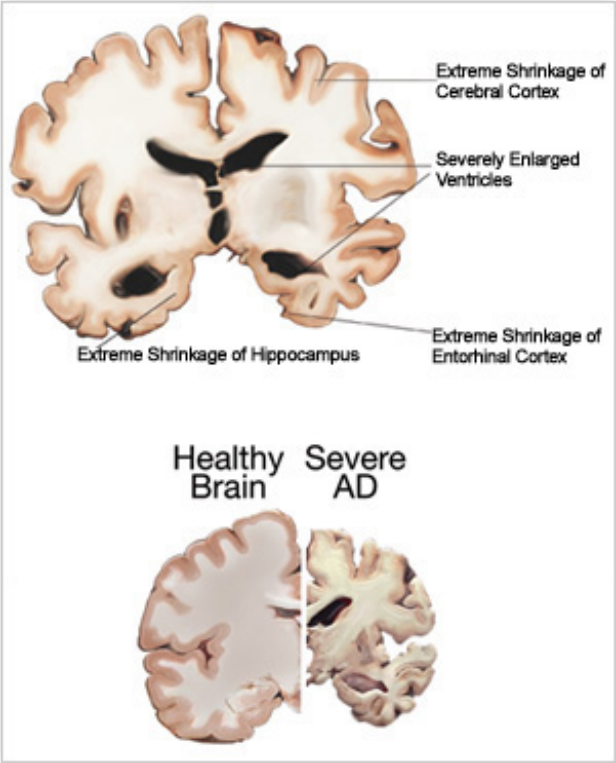
MODERATE AD

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

- Increasing memory loss and confusion
- Shortened attention span
- Inappropriate outbursts of anger
- Problems recognizing friends and family members
- Difficulty with language and problems with reading, writing, and working with numbers
- Difficulty organizing thoughts and thinking logically
- Inability to learn new things or to cope with new or unexpected situations
- Restlessness, agitation, anxiety, tearfulness, wandering—especially in the late afternoon or at night
- Repetitive statements or movement, occasional muscle twitches
- Hallucinations, delusions, suspiciousness or paranoia, irritability
- Loss of impulse control (shown through undressing at inappropriate times or places or vulgar language)
- An inability to carry out activities that involve multiple steps in sequence,

such as dressing, making a pot of coffee, or setting the table

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



SEVERE AD

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

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

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

AD Research: What We Know Today

Scientists have studied AD from many angles. They have looked at populations to see how many cases of AD occur every year and whether there might be links between the disease and lifestyles or genetic backgrounds. They also have conducted clinical studies with healthy older people and those at various stages of AD. They have done many studies with laboratory animals. They have begun to look at neuronal circuits and networks of cells to learn how AD pathology develops and spreads. They even have examined individual nerve cells to see how beta-amyloid, tau, and other molecules affect the ability of cells to function normally.

These studies have led to a fuller understanding of many aspects of the disease, improved diagnostic tests, new ways to manage behavioral aspects of AD, and a growing number of possible drug treatments. Findings from current research are pointing scientists in promising directions for the future. They are also helping researchers to ask better questions about the issues that are still unclear. In this section, we examine in greater detail what scientists are learning from their search for causes of AD, techniques to help in diagnosis, and new treatments. Results from this research will bring us closer to the day when we will be able to delay the onset, prevent, or cure the devastating disease.

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

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

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

OTHER FACTORS AT WORK IN AD

Researchers continue to investigate other possibilities that may explain how the AD process starts and develops.

Beta-Amyloid

We now know a great deal about how beta-amyloid is formed and the steps by which beta-amyloid fragments stick together in small aggregates and then gradually form into plaques. Armed with this knowledge, investigators are intensely interested in the toxic effects that beta-amyloid and plaques have on neurons. Beta-amyloid studies have moved forward to the point that scientists are now carrying out preliminary tests in humans of potential therapies aimed at removing beta-amyloid, halting its formation, or breaking down early forms before they can become harmful.

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

Tau

Tau, the chief component of neurofibrillary tangles is generating new excitement as an area of study. Scientists now speculate that tau may damage and kill neurons because it upsets the normal activity of the cell in addition to forming neurofibrillary tangles.

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

Protein Misfolding

Researchers have found that a number of devastating neurodegenerative diseases share a key characteristic—protein misfolding.

When a protein is formed, it “folds” into a unique three-dimensional shape that helps it perform its specific function. This crucial process can go wrong for various reasons, and more commonly does go wrong in aging cells. As a result, the protein folds into an abnormal shape—it is misfolded. In AD, the misfolded proteins are beta-amyloid and a cleaved product of tau.

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

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

The Aging Process

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

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

Mitochondria are the cell’s power plant, providing the energy a cell needs to maintain its structure, divide, and carry out its functions. Energy for the cell is produced in an efficient metabolic process. In this process, free radicals are produced. Free radicals can help cells in certain ways, such as fighting infection. However, because they are very active and combine easily with other molecules, free radicals also can damage the neuron’s cell membrane or its DNA. The production of free radicals can set off a chain reaction, releasing even more free radicals that can further damage neurons. This kind of damage is called oxidative damage. The brain’s unique `characteristics, including its high rate of metabolism and its long-lived cells, may make it especially vulnerable to oxidative damage over the lifespan. The discovery that beta-amyloid generates free radicals in some AD plaques is a potentially significant finding in the quest for better understanding of AD as well as for other neurodegenerative disorders and unhealthy brain aging.

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

Vascular Disease

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

AD and Vascular Problems in the Brain

The brain requires a constant and dependable flow of oxygen and glucose to survive and flourish. The brain's blood vessels provide the highways to deliver these vital elements to neurons and glial cells.

Aging brings changes in the brain's blood vessels—arteries can narrow and growth of new capillaries slows down. In AD, whole areas of nervous tissue, including the capillaries that supply and drain it, also are lost. Blood flow to and from various parts of the brain can be affected, and the brain may be less able to compensate for damage that accumulates as the disease progresses.

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

AD and Vascular Problems in Other Parts of the Body

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

Much of this evidence comes from epidemiologic studies, which compare the lifestyles, behaviors, and characteristics of groups of people. These studies have found, for example, that heart disease and stroke may contribute to the development of AD, the severity of AD, or the development of other types of dementia.

Studies also show that high blood pressure that develops during middle age is correlated with cognitive decline and dementia in later life.

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

Nearly one in five Americans older than age 60 has type 2 diabetes, and epidemiologic studies suggest that people with this disease may be at increased risk of cognitive problems, including MCI and AD, as they age. The higher risk associated with diabetes may be the result of high levels of blood sugar, or it may be due to other conditions associated with diabetes (obesity, high blood pressure, abnormal blood cholesterol levels, progressive atherosclerosis, or too much insulin in the blood). These findings about diabetes have spurred research on a number of fronts—epidemiologic studies, test tube and animal studies, and clinical trials. The objective of these studies is to learn more about the relationship between diabetes and cognitive problems and to find out in clinical trials whether treating the disease rigorously can positively affect cognitive health and possibly slow or prevent the development of AD.

Lifestyle Factors

We know that physical activity and a nutritious diet can help people stay healthy as they grow older. A healthy diet and exercise can reduce obesity, lower blood cholesterol and high blood pressure, and improve insulin action. In addition, association studies suggest that pursuing intellectually stimulating activities and maintaining active contacts with friends and family may contribute to healthy aging. A growing body of evidence now suggests that these lifestyle factors may be related to cognitive decline and AD. Researchers who are interested in discovering the causes of AD are intensively studying these issues, too.

Physical Activity and Exercise

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

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

- Animal studies have shown that exercise increases the number of capil laries that supply blood to the brain and improves learning and memory in older animals.

- Epidemiologic studies show that higher levels of physical activity or exercise in older people are associated with reduced risk of cognitive decline and reduced risk of dementia. Even moderate exercise, such as brisk walking, is associated with reduced risk.

- Clinical trials show some evidence of short-term positive effects of exercise on cognitive function, especially executive function (cognitive abilities involved in planning, organizing, and decision making). One trial showed that older adults who participated in a 6-month program of brisk walking showed increased activity of neurons in key parts of the brain.

More clinical trials are underway to expand our knowledge about the relationship of exercise to healthy brain aging, reduced risk of cognitive decline, and development of AD.

Diet

Researchers have explored whether diet may help preserve cognitive function or reduce AD risk, with some intriguing findings. For example, studies have examined specific foods that are rich in antioxidants and anti-inflammatory properties to find out whether those foods affect age-related changes in brain tissue. One study in mice found that diets high in DHA a type of healthy omega-3 fatty acid found in fish, reduced beta-amyloid and plaques in brain tissue.

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

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

In one of these studies, researchers worked with older adults living in New York who ate the "Mediterranean diet"—a diet with lots of fruits, vegetables, and bread; low to moderate amounts of dairy foods, fish, and poultry; small amounts of red meat; low to moderate amounts of wine; and frequent use of olive oil. The researchers found that sticking to this type of diet was associated with a reduced risk of AD and that the association seemed to be driven by the whole approach, rather than by its individual dietary components. A follow-up study found that this pattern also was associated with longer survival in people with AD.

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

Intellectually Stimulating Activities and Social Engagement

Many older people love to read, do puzzles, play games, and spend time with family and friends. All these activities are fun and help people feel alert and engaged in life. Researchers are beginning to find other possible benefits as well, for some studies have shown that keeping the brain active is associated with reduced AD risk. For example, over a 4-year period, one group of researchers tracked how often a large group of older people did activities that involved significant information processing, such as listening to the radio, reading newspapers, playing puzzle games, and going to museums. The researchers then looked at how many of the participants developed AD. The researchers found that the risk of developing AD was 47 percent lower in the people who did them the most frequently compared with the people who did the activities least frequently. Another study supported the value of lifelong learning and mentally stimulating activity by finding that, compared with older study participants who may have had AD or who had AD, healthy older participants had engaged in more mentally stimulating activities and spent more time at them during their early and middle adulthood.

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

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

- Intellectually stimulating activities and social engagement may protect the brain in some way, perhaps by establishing a cognitive reserve.

- These activities may help the brain become more adaptable and flexible in some areas of mental function so that it can compensate for declines in other areas.

- Less engagement with other people or in intellectually stimulating activities could be the result of very early effects of the disease rather than its cause.

- People who engage in stimulating activities may have other lifestyle qualities that may protect them against developing AD.

New Techniques for Diagnosis

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

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

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

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

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

Current Tools for Diagnosing AD

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

They take a detailed patient history, including:

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

They get information from family members or close friends:

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

They conduct physical and neurological examinations and laboratory tests:

- Blood and other medical tests help determine neurological functioning and identify possible non-AD causes of dementia.

They conduct neuropsychological testing:

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

They may do a computed tomography (CT) scan or a magnetic resonance imaging (MRI) test:

- CT and MRI scans can detect strokes or tumors or can reveal changes in the brain's structure that indicate early AD.

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

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

Causes of Dementia

Dementia is the loss of cognitive functioning—thinking, remembering, and reasoning—to such an extent that it interferes with a person's daily life and activities. It is not a disease itself, but a group of symptoms that often accompanies a disease or condition. Some dementias are caused by neurodegenerative diseases. Dementia also has other causes, some of which are treatable.

Neurodegenerative Diseases That Cause Dementia

- Alzheimer's disease
- Vascular dementia
- Parkinson's disease with dementia
- Frontotemporal lobar degeneration, including:
    - o Frontotemporal dementia
    - o Pick's disease

Other Causes of Dementia

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

The Search for New Treatments

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

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

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

Many clinical trials of AD interventions focus on several key areas:

- Helping people with AD maintain their mental functioning
- Managing symptoms
- Slowing, delaying, or preventing AD

HELPING PEOPLE WITH AD MAINTAIN THEIR MENTAL FUNCTIONING

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

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

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

SLOWING, DELAYING, OR PREVENTING AD

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

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

Participating in a Clinical Trial

Rapid advances in our knowledge about AD have led to the development of many promising new drugs and treatment strategies. However, before these new strategies can be used in clinical practice, they must be shown to work in people. This means that clinical trials—and volunteer participants—are an essential part of AD research. Advances in prevention and treatment are possible thanks to volunteers who participate in clinical trials.

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

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

WHAT KIND OF TRIALS ARE THERE?

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

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

WHAT ARE THE PHASES OF CLINICAL TRIALS?

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

If results show that the treatment appears to be safe, it will go on to Phase II and Phase III clinical trials. course of the disease. Phase II trials occasionally also involve the use of a placebo (an inactive substance that looks like the study drug). Results from Phase II trials give study staff an indication of the effective dose to take into Phase III trials. Phase III trials are large studies that compare an experimental treatment with a placebo or standard treatment to determine safety and efficacy (whether the treatment has the power to produce an effect).

After these phases are complete and investigators are satisfied that the treatment is safe and effective, the study team may submit its data to the FDA for approval. FDA experts review the data and decide whether to approve the drug or treatment for use in patients with the disease under study.

WHAT HAPPENS WHEN A PERSON SIGNS UP FOR A CLINICAL TRIAL?

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

After all questions have been answered, participants who are still interested in joining the trial are asked to sign an informed consent form. In some cases, a participant may no longer be able to provide informed consent because of problems with memory and thinking. In such cases, it is still possible for an authorized representative (usually a family member) to give permission for the person to participate.

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

WHAT HAPPENS DURING A TRIAL?

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

In most clinical trials, participants are assigned to different study groups. Comparing results for different groups gives researchers confidence that changes in the test group are the result of the experimental treatment and not some other factor, such as the placebo effect (this is when people feel an effect because they think they are getting the test medication even though they are really getting a placebo).

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

WHAT SHOULD PEOPLE CONSIDER BEFORE PARTICIPATING IN A CLINICAL TRIAL?

It's a good idea to consider the following before deciding to join a trial.

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

- The biggest benefit of all. Many families find that the biggest benefit of participating in a clinical trial is the regular contact with the study team. These visits provide an opportunity to get state-of-the-art AD care and to talk regularly with AD experts who have lots of practical experience and a broad perspective on the disease. The study team understands and can provide advice about the emotional and physical aspects of the person with AD and the caregivers' experience. Team members can sug gest 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.

Summary – What You Need to Know

WHAT'S NOT NORMAL

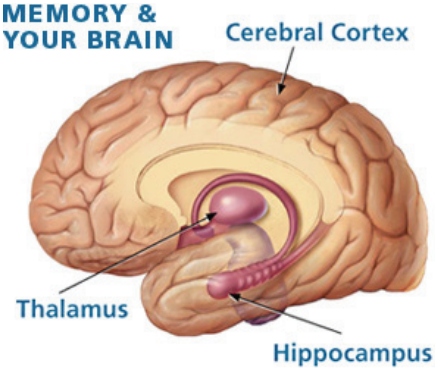
Everyone has mild memory lapses from time to time. You go from the kitchen to the bedroom to get something, only to find yourself wondering what you needed. You can't find your car keys one day and your reading glasses the next.

Lapses such as these are usually just signs of a normal brain that's constantly prioritizing, sorting, storing, and retrieving all types of information. So how do you know when memory loss is abnormal and warrants evaluation by a health professional? Here are some factors to consider:

- **Whether the memory loss disrupts daily living**
  Memory loss that prevents someone from doing activities that they had no trouble handling before—like balancing a check book, keeping up with personal hygiene, or driving around should be checked.

- **How often the memory lapses occur**
  It is one thing to occasionally forget where you parked your car, but it's not normal to forget where you parked every day or to forget appointments over and over. Frequent memory lapses are likely to be noticeable because they tend to interfere with daily living.

- **The kinds of things forgotten**
  It's normal to forget the name of someone you just met, but may not be normal to permanently forget the name of a close friend or relative. Most people have trouble remembering some details of a conversation, but forgetting whole conversations could signal a problem. Other red flags are frequently repeating yourself or asking the same questions in the same conversation.



Cerebral Cortex
Previously formed memories are thought to be stored in the cerebral cortex.

Thalamus
Areas of the thalamus are considered to have a role in the formation of new memories partly through their connections with the hippocampus, and partly because the thalamus is considered to be important for mental alertness.

Hippocampus
The hippocampus is believed to have a critical role in the formation of new memories.

- **Signs of confusion and disorientation**
  Serious memory lapses may cause individuals to get lost in a familiar place or put something in an inappropriate place because they can't remember where it goes. Putting the car keys in the refrigerator is an example.

- **Memory loss getting worse**
  Memory loss that gets progressively worse over time should be evaluated by a health professional.

POSSIBLE CAUSES OF MEMORY LOSS

Anything that affects the process of thinking, learning, and remembering can affect memory. Doctors use a combination of strategies to gain better insight into what's going on.

Doctors evaluate memory loss by taking a medical history, asking questions to test mental ability, conducting a physical and neurological examination, and performing blood and urine tests. Brain imaging, using computerized axial tomography (CAT) scans or magnetic resonance imaging (MRI), can help to identify strokes and tumors, which can sometimes cause memory loss. The goal is to rule out factors that are potentially reversible and determine if the memory loss is due to a more serious brain disease.

The causes of memory loss include the following treatable conditions:

- **Medications.** Examples of medications that can interfere with memory include over-the-counter and prescription sleeping pills, over-the-counter antihistamines, anti-anxiety medications, antidepressants, medications used to treat delusional thinking, and pain medicines.

- **Alcohol and illicit drug use.** Heavy alcohol use can cause deficiencies in vitamin B1 (thiamine), which can harm memory. Both alcohol and illicit drugs can change chemicals in the brain that affect memory.

- **Stress.** Stress, particularly due to emotional trauma, can cause memory loss.

- **Depression.** Depression can cause a lack of attention and focus that can affect memory. Treating the depression will often improve both mood and the memory problems.

- Head injury. A blow to the head can cause a loss of consciousness and memory loss. Memory loss from head trauma typically stays the same or gradually gets better, but not worse.

- Infections. People with HIV, tuberculosis, syphilis, herpes, and other infections of the lining or substance of the brain may experience memory problems.

- Thyroid dysfunction. An underactive or overactive thyroid can interfere with remembering recent events.

- Sleep deprivation. Lack of quality sleep—whether from stress, insomnia, or sleep apnea—can affect memory.

- Nutritional deficiencies. Deficiencies of vitamins B1 and B12 can affect memory. Such deficiencies can be treated orally or by injection.

- Mild cognitive impairment. Mild cognitive impairment (MCI) is a condition characterized by a memory deficit beyond that expected for age, which is not sufficient to impair day-to-day activities.

WHAT IS DEMENTIA?

Dementia is a term used for a condition in which there is increasing impairment of memory and other aspects of thinking that are sufficiently severe to impair day-to-day activities. There are many causes of dementia, but the most common by far is Alzheimer's disease (AD), in which there is a progressive loss of brain cells accompanied by other abnormalities of the brain. A diagnosis of AD is made by confirming that a patient has dementia and by excluding other conditions, such as brain tumors, vitamin deficiencies, and hypothyroidism.

MILD COGNITIVE IMPAIRMENT

People with MCI have memory impairments, but otherwise function well and don't meet the clinical criteria for dementia. Whereas normal memory loss associated with aging may involve forgetting a name, memory loss associated with MCI is more severe and persistent.

MCI is often a transition stage between normal aging and more serious problems caused by AD. Most, but not all, people with MCI get worse. According to some studies, each year about 12 to 15 percent of people with MCI develop AD.

In older people with MCI, if the memory loss is slowly getting worse, the chances of developing AD are about 60 percent to 70 percent.

Research is under way on whether the drugs approved to treat symptoms of AD may help some people with MCI. Scientists hope that some day, accurate and early evaluation and treatment of people with MCI may help prevent further cognitive decline.

ALZHEIMER'S DISEASE

AD is the most common form of dementia in people older than age 65, and affects more than 5 million Americans, according to the Alzheimer's Association. AD is a progressive, neurodegenerative disease characterized in the brain by abnormal protein deposits (amyloid plaques) and tangled bundles of fibers within nerve cells (neurofibrillary tangles). The biggest risk factors are age and family history. Having a history of serious concussion is also a risk factor.

AD gradually destroys a person's memory and ability to learn, reason, make judgments, communicate, and carry out daily activities. Memory loss becomes severe and is marked by disorientation, general confusion, and an inability to recall recent events. A person with mild-to-moderate AD may remember things that happened to them a long time ago, but they might get lost easily in a familiar place. People with AD may also experience changes in personality and behavior, such as withdrawal and suspicion. They eventually experience a loss of speech and movement, incapacitation, and death. Some facts about AD treatment follow:

- **Most clinical trials** of drug treatments for memory loss focus on people with AD.

- Five drugs are approved by FDA to treat the symptoms of AD, but there is no cure for the disease. Four of **these drugs are known as cholin esterase inhibitors** and they work in a similar way - Cognex (tacrine), Exelon (rivastigmine), and Razadyne (galantamine). Cholinesterase inhibitors prevent the breakdown of acetylcholine, a chemical that nerves use to communicate with each other. These drugs may help delay or decrease the severity of symptoms for a limited time in some people. Side effects of cholinesterase inhibitors are gastrointestinal, such as nausea and diarrhea.

- **Namenda (memantine)**, approved for moderate-to-severe AD, is believed to block the action of glutamate, a brain chemical that may be overactive in people with AD. Namenda may help some patients maintain certain daily functions a little longer. Common side effects include dizziness, headache, constipation, and confusion. Sometimes, Namenda is prescribed along with a cholinesterase inhibitor.

- **Behavioral symptoms of AD** may include agitation, sleeplessness, anxiety, and depression, which can be treated.

- **Inhibiting and/or decreasing amyloid** is an intense area of research because amyloid is the major component of the plaques that develop in the brains of people with AD and is associated with nerve cell death. Drugs called secretase inhibitors are being developed and tested to block beta-amyloid formation. Also under study is immunotherapy against beta amyloid—it's possible that a vaccine may help reduce deposits of amyloid.

OTHER DISEASES THAT CAUSE DEMENTIA

Dementia is diagnosed when two or more brain functions, such as memory and language skills, are significantly impaired, according to criteria set forth by the National Institute of Neurological Disorders and Stroke. In practice, doctors use the same drugs that are used to treat AD to treat some other types of dementia.

Vascular dementia. In people who have vascular dementia, also called multi-infarct dementia, arteries to the brain become blocked or narrowed. As a result, changes in the blood supply to the brain occur or multiple strokes disrupt blood flow to the brain. Symptoms may be similar to those of AD, although they usually occur more abruptly. Treatment focuses on preventing future strokes by controlling risk factors such as smoking, diabetes, and high blood pressure.

Lewy body dementia. This progressive brain disease is caused by a buildup of protein deposits called Lewy bodies. It involves progressive cognitive decline, problems with alertness and attention, recurrent visual hallucinations, and motor problems similar to those seen with Parkinson's disease, such as rigidity. Treatment aims to control symptoms of the disorder. Antipsychotic medications for hallucinations aren't typically prescribed because there is a risk of the hallucinations becoming worse.

Parkinson's disease with dementia. Parkinson's disease results from the loss of dopamine-producing brain cells. The primary symptoms are trembling in the hands, arms, legs, jaw, and face; body stiffness; and slowness of movement and impaired balance and coordination. Memory loss sometimes occurs with late-stage Parkinson's disease. Exelon (rivastigmine), which is approved for mild-to-moderate AD, is also approved by FDA for the treatment of dementia with Parkinson's disease.

Frontotemporal dementia. This type of dementia is associated with the shrinking of the frontal and temporal anterior lobes of the brain. Symptoms involve either impulsive or listless behavior, and may include socially inappropriate behavior. Some forms of frontotemporal dementia consist of progressive loss of language functions. No treatment has been shown to slow the progression. Antidepressants and behavior modification may improve some symptoms.

Social interaction has been associated with a lower risk of dementia.

RESOURCES FOR COPING

Coping with memory loss can be frustrating for both the person affected and family members and caregivers. Some families use memory aids to help quality of life, such as color coding and labeling items in the home with safety notes and directions for use, and using alarms and talking clocks to keep track of time and remember medication doses. Families also may experience anger, exhaustion, irritability, and other symptoms of caregiver stress.

CAN MEMORY LOSS BE PREVENTED?

There is no conclusive evidence that the herb ginkgo biloba prevents memory loss. And research has shown that the combination of estrogen and progestin increased the risk of dementia in women older than age 65.

So what can you do to prevent memory loss? Clinical trials are under way to test specific interventions. While those tests are being conducted, you may want to consider hints from animal and observational studies of promising approaches. These steps are already beneficial in other ways and may help reduce the risk of developing memory problems.

- **Lower cholesterol and high blood pressure.** A number of studies in recent years have suggested that vascular diseases—heart disease and stroke—may contribute to the development of AD, the severity of AD, or the development of multi-infarct dementia (also called vascular dementia).

- **Don't smoke or abuse alcohol.** According to a research report from Harvard Medical School, smokers perform worse than nonsmokers in studies of memory and thinking skills. Heavy alcohol use can also impair memory.

- **Get regular exercise.** Physical activity may help maintain blood flow to the brain and reduce risk factors associated with dementia.

- **Maintain healthy eating habits.** According to a study published in the Oct. 24, 2006, issue of Neurology, eating vegetables may help slow down the rate of cognitive change in adults. Researchers studied 3,718 residents in Chicago who were older than age 65. Of the types of vegetables, green leafy vegetables had the strongest association with slowing the rate of cognitive decline. Also reducing foods high in saturated fat and cholesterol and eating fish with beneficial omega-3 fatty acids, such as salmon and tuna, may benefit brain health. An NIA-funded clinical trial to test the effects of omega-3 fatty acids in people with AD is now recruiting patients nationwide.

- **Maintain social interactions.** Social interaction can help reduce stress levels and has been associated with a lower risk of dementia. Researchers found that loneliness is associated with an increased risk of late-life dementia.

- **Keep your brain active.** Some experts suggest that challenging the brain with such activities as reading, writing, learning a new skill, playing games, and gardening stimulates brain cells and the connections between the cells, and may be associated with a lower risk of dementia.

In this book, we've overviewed basics about the healthy brain -- what it looks like and how it works. We've also examined how it changes during the course of Alzheimer's disease. Our knowledge about AD is advancing rapidly, and current research advances hold the promise of more effective treatment. But we need to continue building on current knowledge to successfully manage and control this devastating disease.