

# The Dementias: Hope Through Research

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## Introduction

*A woman in her early 50s was admitted to a hospital because of increasingly odd behavior. Her family reported that she had been showing memory problems and strong feelings of jealousy. She also had become disoriented at home and was hiding objects. During a doctor's examination, the woman was unable to remember her husband's name, the year, or how long she had been at the hospital. She could read but did not seem to understand what she read, and she stressed the words in an unusual way. She sometimes became agitated and seemed to have hallucinations and irrational fears.*

This woman, known as Auguste D., was the first person reported to have the disease now known as *Alzheimer's disease*\* (AD) after Alois Alzheimer, the German doctor who first described it. After Auguste D. died in 1906, doctors examined her brain and found that it appeared shrunken and contained several unusual features, including strange clumps of protein called *plaques* and tangled fibers inside the nerve cells. Memory impairments and other symptoms of *dementia*, which means "deprived of mind," had been described in older adults since ancient times. However, because Auguste D. began to show symptoms at a relatively early age, doctors did not think her disease could be related to what was then called "*senile dementia*." The word *senile* is derived from a Latin term that means, roughly, "old age."

It is now clear that AD is a major cause of dementia in elderly people as well as in relatively young adults. Furthermore, we know that it is only one of many disorders that can lead to dementia. The U. S. Congress Office of Technology Assessment estimates that as many as 6.8 million Americans have dementia, and at least 1.8 million of those are severely affected. Studies in some communities have found that almost half of all people age 85 and older have some form of dementia. Although it is common in very elderly individuals, dementia is not a normal part of the aging process. Many people live into their 90s and even 100s without any symptoms of dementia.

Besides *senile dementia*, other terms often used to describe dementia include *senility* and *organic brain syndrome*. *Senility* and *senile dementia* are outdated terms that reflect the formerly widespread belief that dementia was a normal part of aging. *Organic brain syndrome* is a general term that refers to physical disorders (not psychiatric in origin) that impair mental functions.

Research in the last 30 years has led to a greatly improved understanding of what dementia is, who gets it, and how it develops and affects the brain. This work is beginning to pay off with better diagnostic techniques, improved treatments, and even potential ways of preventing these diseases.

*\*Terms in Italics are defined in the glossary.*

## What Is Dementia?

Dementia is not a specific disease. It is a descriptive term for a collection of symptoms that can be caused by a number of disorders that affect the brain. People with dementia have significantly impaired intellectual functioning that interferes with normal activities and relationships. They also lose their ability to solve problems and maintain emotional control, and they may experience personality changes and behavioral problems, such as agitation, delusions, and hallucinations. While memory loss is a common symptom of dementia, memory loss by itself does not mean that a person has dementia. Doctors diagnose dementia only if two or more brain functions - such as memory, language skills, perception, or cognitive skills including reasoning and judgment - are significantly impaired without loss of consciousness.

There are many disorders that can cause dementia. Some, such as AD, lead to a progressive loss of mental functions. But other types of dementia can be halted or reversed with appropriate treatment.

With AD and many other types of dementia, disease processes cause many nerve cells to stop functioning, lose connections with other neurons, and die. In contrast, normal aging does not result in the loss of large numbers of neurons in the brain.

## What Are the Different Kinds of Dementia?

Dementing disorders can be classified many different ways. These classification schemes attempt to group disorders that have particular features in common, such as whether they are progressive or what parts of the brain are affected. Some frequently used classifications include the following:

- **Cortical dementia** - dementia where the brain damage primarily affects the brain's cortex, or outer layer. Cortical dementias tend to cause problems with memory, language, thinking, and social behavior.
- **Subcortical dementia** - dementia that affects parts of the brain below the cortex. Subcortical dementia tends to cause changes in emotions and movement in addition to problems with memory.
- **Progressive dementia** - dementia that gets worse over time, gradually interfering with more and more cognitive abilities.
- **Primary dementia** - dementia such as AD that does not result from any other disease.

· **Secondary dementia** - dementia that occurs as a result of a physical disease or injury.

Some types of dementia fit into more than one of these classifications. For example, AD is considered both a progressive and a cortical dementia.

**Alzheimer's disease** is the most common cause of dementia in people aged 65 and older. Experts believe that up to 4 million people in the United States are currently living with the disease: one in ten people over the age of 65 and nearly half of those over 85 have AD. At least 360,000 Americans are diagnosed with AD each year and about 50,000 are reported to die from it.

In most people, symptoms of AD appear after age 60. However, there are some early-onset forms of the disease, usually linked to a specific gene defect, which may appear as early as age 30. AD usually causes a gradual decline in cognitive abilities, usually during a span of 7 to 10 years. Nearly all brain functions, including memory, movement, language, judgment, behavior, and abstract thinking, are eventually affected.

AD is characterized by two abnormalities in the brain: *amyloid plaques* and *neurofibrillary tangles*. Amyloid plaques, which are found in the tissue between the nerve cells, are unusual clumps of a protein called *beta amyloid* along with degenerating bits of neurons and other cells.

Neurofibrillary tangles are bundles of twisted filaments found within neurons. These tangles are largely made up of a protein called *tau*. In healthy neurons, the *tau* protein helps the functioning of microtubules, which are part of the cell's structural support and deliver substances throughout the nerve cell. However, in AD, *tau* is changed in a way that causes it to twist into pairs of helical filaments that collect into tangles. When this happens, the microtubules cannot function correctly and they disintegrate. This collapse of the neuron's transport system may impair communication between nerve cells and cause them to die.

Researchers do not know if amyloid plaques and neurofibrillary tangles are harmful or if they are merely side effects of the disease process that damages neurons and leads to the symptoms of AD. They do know that plaques and tangles usually increase in the brain as AD progresses.

In the early stages of AD, patients may experience memory impairment, lapses of judgment, and subtle changes in personality. As the disorder progresses, memory and language problems worsen and patients begin to have difficulty performing activities of daily living, such as balancing a checkbook or remembering to take medications. They also may have visuospatial problems, such as difficulty navigating an unfamiliar route. They may become disoriented about places and times, may suffer delusions (such as the idea that someone is stealing from them or that their spouse is being unfaithful), and may become short-tempered and hostile. During the late stages of the disease, patients begin to lose the ability to control motor functions. They may have difficulty swallowing and

lose bowel and bladder control. They eventually lose the ability to recognize family members and to speak. As AD progresses, it begins to affect the person's emotions and behavior. Most people with AD eventually develop symptoms such as aggression, agitation, depression, sleeplessness, or delusions.

On average, patients with AD live for 8 to 10 years after they are diagnosed. However, some people live as long as 20 years. Patients with AD often die of aspiration pneumonia because they lose the ability to swallow late in the course of the disease.

**Vascular dementia** is the second most common cause of dementia, after AD. It accounts for up to 20 percent of all dementias and is caused by brain damage from cerebrovascular or cardiovascular problems - usually strokes. It also may result from genetic diseases, endocarditis (infection of a heart valve), or amyloid angiopathy (a process in which amyloid protein builds up in the brain's blood vessels, sometimes causing hemorrhagic or "bleeding" strokes). In many cases, it may coexist with AD. The incidence of vascular dementia increases with advancing age and is similar in men and women.

Symptoms of vascular dementia often begin suddenly, frequently after a stroke. Patients may have a history of high blood pressure, vascular disease, or previous strokes or heart attacks. Vascular dementia may or may not get worse with time, depending on whether the person has additional strokes. In some cases, symptoms may get better with time. When the disease does get worse, it often progresses in a stepwise manner, with sudden changes in ability. Vascular dementia with brain damage to the mid-brain regions, however, may cause a gradual, progressive cognitive impairment that may look much like AD. Unlike people with AD, people with vascular dementia often maintain their personality and normal levels of emotional responsiveness until the later stages of the disease.

People with vascular dementia frequently wander at night and often have other problems commonly found in people who have had a stroke, including depression and incontinence.

There are several types of vascular dementia, which vary slightly in their causes and symptoms. One type, called *multi-infarct dementia (MID)*, is caused by numerous small strokes in the brain. MID typically includes multiple damaged areas, called infarcts, along with extensive lesions in the white matter, or nerve fibers, of the brain.

Because the infarcts in MID affect isolated areas of the brain, the symptoms are often limited to one side of the body or they may affect just one or a few specific functions, such as language. Neurologists call these "local" or "focal" symptoms, as opposed to the "global" symptoms seen in AD, which affect many functions and are not restricted to one side of the body.

Although not all strokes cause dementia, in some cases a single stroke can damage the brain enough to cause dementia. This condition is called single-infarct dementia. Dementia is more common when the stroke takes place on the left side (hemisphere) of

the brain and/or when it involves the hippocampus, a brain structure important for memory.

Another type of vascular dementia is called *Binswanger's disease*. This rare form of dementia is characterized by damage to small blood vessels in the white matter of the brain (white matter is found in the inner layers of the brain and contains many nerve fibers coated with a whitish, fatty substance called *myelin*). Binswanger's disease leads to brain lesions, loss of memory, disordered cognition, and mood changes. Patients with this disease often show signs of abnormal blood pressure, stroke, blood abnormalities, disease of the large blood vessels in the neck, and/or disease of the heart valves. Other prominent features include urinary incontinence, difficulty walking, clumsiness, slowness, lack of facial expression, and speech difficulty. These symptoms, which usually begin after the age of 60, are not always present in all patients and may sometimes appear only temporarily. Treatment of Binswanger's disease is symptomatic, and may include the use of medications to control high blood pressure, depression, heart arrhythmias, and low blood pressure. The disorder often includes episodes of partial recovery.

Another type of vascular dementia is linked to a rare hereditary disorder called *CADASIL*, which stands for **cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy**. *CADASIL* is linked to abnormalities of a specific gene, *Notch3*, which is located on chromosome 19. This condition causes multi-infarct dementia as well as stroke, migraine with aura, and mood disorders. The first symptoms usually appear in people who are in their twenties, thirties, or forties and affected individuals often die by age 65. Researchers believe most people with *CADASIL* go undiagnosed, and the actual prevalence of the disease is not yet known.

Other causes of vascular dementia include vasculitis, an inflammation of the blood vessel system; profound hypotension (low blood pressure); and lesions caused by brain hemorrhage. The autoimmune disease lupus erythematosus and the inflammatory disease temporal arteritis can also damage blood vessels in a way that leads to vascular dementia. **Lewy body dementia (LBD)** is one of the most common types of progressive dementia. LBD usually occurs sporadically, in people with no known family history of the disease. However, rare familial cases have occasionally been reported.

In LBD, cells die in the brain's cortex, or outer layer, and in a part of the mid-brain called the substantia nigra. Many of the remaining nerve cells in the substantia nigra contain abnormal structures called Lewy bodies that are the hallmark of the disease. Lewy bodies may also appear in the brain's cortex, or outer layer. Lewy bodies contain a protein called alpha-synuclein that has been linked to Parkinson's disease and several other disorders. Researchers, who sometimes refer to these disorders collectively as "synucleinopathies," do not yet know why this protein accumulates inside nerve cells in LBD.

The symptoms of LBD overlap with AD in many ways, and may include memory impairment, poor judgment, and confusion. However, LBD typically also includes visual hallucinations, parkinsonian symptoms such as a shuffling gait and flexed posture, and

day-to-day fluctuations in the severity of symptoms. Patients with LBD live an average of 7 years after symptoms begin.

There is no cure for LBD, and treatments are aimed at controlling the parkinsonian and psychiatric symptoms of the disorder. Patients sometimes respond dramatically to treatment with antiparkinsonian drugs and/or *cholinesterase inhibitors*, such as those used for AD. Some studies indicate that neuroleptic drugs, such as clozapine and olanzapine, also can reduce the psychiatric symptoms of this disease. But neuroleptic drugs may cause severe adverse reactions, so other therapies should be tried first and patients using these drugs should be closely monitored.

Lewy bodies are often found in the brains of people with Parkinson's and AD. These findings suggest that either LBD is related to these other causes of dementia or that the diseases sometimes coexist in the same person.

**Frontotemporal dementia** (FTD), sometimes called frontal lobe dementia, describes a group of diseases characterized by degeneration of nerve cells - especially those in the frontal and temporal lobes of the brain. Unlike AD, FTD usually does not include formation of amyloid plaques. In many people with FTD, there is an abnormal form of *tau* protein in the brain, which accumulates into neurofibrillary tangles. This disrupts normal cell activities and may cause the cells to die.

Experts believe FTD accounts for 2 to 10 percent of all cases of dementia. Symptoms of FTD usually appear between the ages of 40 and 65. In many cases, people with FTD have a family history of dementia, suggesting that there is a strong genetic factor in the disease. The duration of FTD varies, with some patients declining rapidly over 2 to 3 years and others showing only minimal changes for many years. People with FTD live with the disease for an average of 5 to 10 years after diagnosis.

Because structures found in the frontal and temporal lobes of the brain control judgment and social behavior, people with FTD often have problems maintaining normal interactions and following social conventions. They may steal or exhibit impolite and socially inappropriate behavior, and they may neglect their normal responsibilities. Other common symptoms include loss of speech and language, compulsive or repetitive behavior, increased appetite, and motor problems such as stiffness and balance problems. Memory loss also may occur, although it typically appears late in the disease.

In one type of FTD called *Pick's disease*, certain nerve cells become abnormal and swollen before they die. These swollen, or ballooned, neurons are one hallmark of the disease. The brains of people with Pick's disease also have abnormal structures called Pick bodies, composed largely of the protein *tau*, inside the neurons. The cause of Pick's disease is unknown, but it runs in some families and thus it is probably due at least in part to a faulty gene or genes. The disease usually begins after age 50 and causes changes in personality and behavior that gradually worsen over time. The symptoms of Pick's disease are very similar to those of AD, and may include inappropriate social behavior, loss of mental flexibility, language problems, and difficulty with thinking and

concentration. There is currently no way to slow the progressive degeneration found in Pick's disease. However, medication may be helpful in reducing aggression and other behavioral problems, and in treating depression.

In some cases, familial FTD is linked to a mutation in the *tau* gene. This disorder, called *frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17)*, is much like other types of FTD but often includes psychiatric symptoms such as delusions and hallucinations.

*Primary progressive aphasia (PPA)* is a type of FTD that may begin in people as early as their forties. "Aphasia" is a general term used to refer to deficits in language functions, such as speaking, understanding what others are saying, and naming common objects. In PPA one or more of these functions can become impaired. Symptoms often begin gradually and progress slowly over a period of years. As the disease progresses, memory and attention may also be impaired and patients may show personality and behavior changes. Many, but not all, people with PPA eventually develop symptoms of dementia.

**HIV-associated dementia (HAD)** results from infection with the human immunodeficiency virus (HIV) that causes AIDS. HAD can cause widespread destruction of the brain's white matter. This leads to a type of dementia that generally includes impaired memory, apathy, social withdrawal, and difficulty concentrating. People with HAD often develop movement problems as well. There is no specific treatment for HAD, but AIDS drugs can delay onset of the disease and may help to reduce symptoms.

**Huntington's disease (HD)** is a hereditary disorder caused by a faulty gene for a protein called huntingtin. The children of people with the disorder have a 50 percent chance of inheriting it. The disease causes degeneration in many regions of the brain and spinal cord. Symptoms of HD usually begin when patients are in their thirties or forties, and the average life expectancy after diagnosis is about 15 years.

Cognitive symptoms of HD typically begin with mild personality changes, such as irritability, anxiety, and depression, and progress to severe dementia. Many patients also show psychotic behavior. HD causes chorea - involuntary jerky, arrhythmic movements of the body - as well as muscle weakness, clumsiness, and gait disturbances.

**Dementia pugilistica**, also called chronic traumatic encephalopathy or Boxer's syndrome, is caused by head trauma, such as that experienced by people who have been punched many times in the head during boxing. The most common symptoms of the condition are dementia and parkinsonism, which can appear many years after the trauma ends. Affected individuals may also develop poor coordination and slurred speech. A single traumatic brain injury may also lead to a disorder called *post-traumatic dementia (PTD)*. PTD is much like dementia pugilistica but usually also includes long-term memory problems. Other symptoms vary depending on which part of the brain was damaged by the injury.

**Corticobasal degeneration (CBD)** is a progressive disorder characterized by nerve cell loss and *atrophy* of multiple areas of the brain. Brain cells from people with CBD often have abnormal accumulations of the protein *tau*. CBD usually progresses gradually over

the course of 6 to 8 years. Initial symptoms, which typically begin at or around age 60, may first appear on one side of the body but eventually will affect both sides. Some of the symptoms, such as poor coordination and rigidity, are similar to those found in Parkinson's disease. Other symptoms may include memory loss, dementia, visual-spatial problems, apraxia (loss of the ability to make familiar, purposeful movements), hesitant and halting speech, *myoclonus* (involuntary muscular jerks), and *dysphagia* (difficulty swallowing). Death is often caused by pneumonia or other secondary problems such as sepsis (severe infection of the blood) or pulmonary embolism (a blood clot in the lungs). There are no specific treatments available for CBD. Drugs such as clonazepam may help with myoclonus, however, and occupational, physical, and speech therapy can help in managing the disabilities associated with this disease. The symptoms of the disease often do not respond to Parkinson's medications or other drugs.

**Creutzfeldt-Jakob disease (CJD)** is a rare, degenerative, fatal brain disorder that affects about one in every million people per year worldwide. Symptoms usually begin after age 60 and most patients die within 1 year. Many researchers believe CJD results from an abnormal form of a protein called a prion. Most cases of CJD occur sporadically - that is, in people who have no known risk factors for the disease. However, about 5 to 10 percent of cases of CJD in the United States are hereditary, caused by a mutation in the gene for the prion protein. In rare cases, CJD can also be acquired through exposure to diseased brain or nervous system tissue, usually through certain medical procedures. There is no evidence that CJD is contagious through the air or through casual contact with a CJD patient.

Patients with CJD may initially experience problems with muscular coordination; personality changes, including impaired memory, judgment, and thinking; and impaired vision. Other symptoms may include insomnia and depression. As the illness progresses, mental impairment becomes severe. Patients often develop myoclonus and they may go blind. They eventually lose the ability to move and speak, and go into a coma. Pneumonia and other infections often occur in these patients and can lead to death.

CJD belongs to a family of human and animal diseases known as the *transmissible spongiform encephalopathies (TSEs)*. Spongiform refers to the characteristic appearance of infected brains, which become filled with holes until they resemble sponges when viewed under a microscope. CJD is the most common of the known human TSEs. Others include *fatal familial insomnia* and *Gerstmann-Straussler-Scheinker disease* (see below). In recent years, a new type of CJD, called variant CJD (vCJD), has been found in Great Britain and several other European countries. The initial symptoms of vCJD are different from those of classic CJD and the disorder typically occurs in younger patients. Research suggests that vCJD may have resulted from human consumption of beef from cattle with a TSE disease called bovine spongiform encephalopathy (BSE), also known as "mad cow disease."

**Other rare hereditary dementias** include Gerstmann-Straussler-Scheinker (GSS) disease, fatal familial insomnia, familial British dementia, and familial Danish dementia. Symptoms of GSS typically include *ataxia* and progressive dementia that begins when

people are between 50 and 60 years old. The disease may last for several years before patients eventually die. Fatal familial insomnia causes degeneration of a brain region called the thalamus, which is partially responsible for controlling sleep. It causes a progressive insomnia that eventually leads to a complete inability to sleep. Other symptoms may include poor reflexes, dementia, hallucinations, and eventually coma. It can be fatal within 7 to 13 months after symptoms begin but may last longer. Familial British dementia and familial Danish dementia have been linked to two different defects in a gene found on chromosome 13. The symptoms of both diseases include progressive dementia, paralysis, and loss of balance.

## Secondary Dementias

Dementia may occur in patients who have other disorders that primarily affect movement or other functions. These cases are often referred to as secondary dementias. The relationship between these disorders and the primary dementias is not always clear. For instance, people with advanced *Parkinson's disease*, which is primarily a movement disorder, sometimes develop symptoms of dementia. Many Parkinson's patients also have amyloid plaques and neurofibrillary tangles like those found in AD. The two diseases may be linked in a yet-unknown way, or they may simply coexist in some people. People with Parkinson's and associated dementia sometimes show signs of Lewy body dementia or progressive supranuclear palsy at autopsy, suggesting that these diseases may also overlap with Parkinson's or that Parkinson's is sometimes misdiagnosed.

Other disorders that may include symptoms of dementia include multiple sclerosis; presenile dementia with motor neuron disease, also called ALS dementia; olivopontocerebellar atrophy (OPCA); Wilson's disease; and normal pressure hydrocephalus (NPH).<sup>†</sup>

## Dementias in Children

While it is usually found in adults, dementia can also occur in children. For example, infections and poisoning can lead to dementia in people of any age. In addition, some disorders unique to children can cause dementia.

**Niemann-Pick disease** is a group of inherited disorders that affect metabolism and are caused by specific genetic mutations. Patients with Niemann-Pick disease cannot properly metabolize cholesterol and other lipids. Consequently, excessive amounts of cholesterol accumulate in the liver and spleen and excessive amounts of other lipids accumulate in the brain. Symptoms may include dementia, confusion, and problems with learning and memory. These diseases usually begin in young school-age children but may also appear during the teen years or early adulthood.

**Batten disease** is a fatal, hereditary disorder of the nervous system that begins in childhood. Symptoms are linked to a buildup of substances called lipopigments in the body's tissues. The early symptoms include personality and behavior changes, slow learning, clumsiness, or stumbling. Over time, affected children suffer mental impairment, seizures, and progressive loss of sight and motor skills. Eventually, children

with Batten disease develop dementia and become blind and bedridden. The disease is often fatal by the late teens or twenties.

**Lafora body disease** is a rare genetic disease that causes seizures, rapidly progressive dementia, and movement problems. These problems usually begin in late childhood or the early teens. Children with Lafora body disease have microscopic structures called Lafora bodies in the brain, skin, liver, and muscles. Most affected children die within 2 to 10 years after the onset of symptoms.

A number of other childhood-onset disorders can include symptoms of dementia. Among these are mitochondrial myopathies, Rasmussen's encephalitis, mucopolysaccharidosis III (Sanfilippo syndrome), neurodegeneration with brain iron accumulation, and leukodystrophies such as Alexander disease, Schilder's disease, and metachromatic leukodystrophy.

## What Other Conditions Can Cause Dementia?

Doctors have identified many other conditions that can cause dementia or dementia-like symptoms. Many of these conditions are reversible with appropriate treatment.

**Reactions to medications.** Medications can sometimes lead to reactions or side effects that mimic dementia. These dementia-like effects can occur in reaction to just one drug or they can result from drug interactions. They may have a rapid onset or they may develop slowly over time.

**Metabolic problems and endocrine abnormalities.** Thyroid problems can lead to apathy, depression, or dementia. Hypoglycemia, a condition in which there is not enough sugar in the bloodstream, can cause confusion or personality changes. Too little or too much sodium or calcium can also trigger mental changes. Some people have an impaired ability to absorb vitamin B<sub>12</sub>, which creates a condition called pernicious anemia that can cause personality changes, irritability, or depression. Tests can determine if any of these problems are present.

**Nutritional deficiencies.** Deficiencies of thiamine (vitamin B<sub>1</sub>) frequently result from chronic alcoholism and can seriously impair mental abilities, in particular memories of recent events. Severe deficiency of vitamin B<sub>6</sub> can cause a neurological illness called pellagra that may include dementia. Deficiencies of vitamin B<sub>12</sub> also have been linked to dementia in some cases. Dehydration can also cause mental impairment that can resemble dementia.

**Infections.** Many infections can cause neurological symptoms, including confusion or delirium, due to fever or other side effects of the body's fight to overcome the infection. Meningitis and encephalitis, which are infections of the brain or the membrane that covers it, can cause confusion, sudden severe dementia, withdrawal from social interaction, impaired judgment, or memory loss. Untreated syphilis also can damage the nervous system and cause dementia. In rare cases, Lyme disease can cause memory or thinking difficulties. People in the advanced stages of AIDS also may develop a form of dementia (*see* HIV-associated dementia, page 14). People with compromised immune

systems, such as those with leukemia and AIDS, may also develop an infection called progressive multifocal leukoencephalopathy (PML). PML is caused by a common human polyomavirus, JC virus, and leads to damage or destruction of the myelin sheath that covers nerve cells. PML can lead to confusion, difficulty with thinking or speaking, and other mental problems.

**Subdural hematomas.** Subdural hematomas, or bleeding between the brain's surface and its outer covering (the dura), can cause dementia-like symptoms and changes in mental function.

**Poisoning.** Exposure to lead, other heavy metals, or other poisonous substances can lead to symptoms of dementia. These symptoms may or may not resolve after treatment, depending on how badly the brain is damaged. People who have abused substances such as alcohol and recreational drugs sometimes display signs of dementia even after the substance abuse has ended. This condition is known as *substance-induced persisting dementia*.

**Brain tumors.** In rare cases, people with brain tumors may develop dementia because of damage to their brains. Symptoms may include changes in personality, psychotic episodes, or problems with speech, language, thinking, and memory.

**Anoxia.** Anoxia and a related term, hypoxia, are often used interchangeably to describe a state in which there is a diminished supply of oxygen to an organ's tissues. Anoxia may be caused by many different problems, including heart attack, heart surgery, severe asthma, smoke or carbon monoxide inhalation, high-altitude exposure, strangulation, or an overdose of anesthesia. In severe cases of anoxia the patient may be in a stupor or a coma for periods ranging from hours to days, weeks, or months. Recovery depends on the severity of the oxygen deprivation. As recovery proceeds, a variety of psychological and neurological abnormalities, such as dementia or psychosis, may occur. The person also may experience confusion, personality changes, hallucinations, or memory loss.

**Heart and lung problems.** The brain requires a high level of oxygen in order to carry out its normal functions. Therefore, problems such as chronic lung disease or heart problems that prevent the brain from receiving adequate oxygen can starve brain cells and lead to the symptoms of dementia.

## What Conditions Are Not Dementia?

**Age-related cognitive decline.** As people age, they usually experience slower information processing and mild memory impairment. In addition, their brains frequently decrease in volume and some nerve cells, or neurons, are lost. These changes, called age-related cognitive decline, are normal and are not considered signs of dementia.

**Mild cognitive impairment.** Some people develop cognitive and memory problems that are not severe enough to be diagnosed as dementia but are more pronounced than the cognitive changes associated with normal aging. This condition is called *mild cognitive*

*impairment*. Although many patients with this condition later develop dementia, some do not. Many researchers are studying mild cognitive impairment to find ways to treat it or prevent it from progressing to dementia.

**Depression.** People with depression are frequently passive or unresponsive, and they may appear slow, confused, or forgetful. Other emotional problems can also cause symptoms that sometimes mimic dementia.

**Delirium.** Delirium is characterized by confusion and rapidly altering mental states. The person may also be disoriented, drowsy, or incoherent, and may exhibit personality changes. Delirium is usually caused by a treatable physical or psychiatric illness, such as poisoning or infections. Patients with delirium often, though not always, make a full recovery after their underlying illness is treated.

## What Causes Dementia?

All forms of dementia result from the death of nerve cells and/or the loss of communication among these cells. The human brain is a very complex and intricate machine and many factors can interfere with its functioning. Researchers have uncovered many of these factors, but they have not yet been able to fit these puzzle pieces together in order to form a complete picture of how dementias develop.

Many types of dementia, including AD, Lewy body dementia, Parkinson's dementia, and Pick's disease, are characterized by abnormal structures called inclusions in the brain. Because these inclusions, which contain abnormal proteins, are so common in people with dementia, researchers suspect that they play a role in the development of symptoms. However, that role is unknown, and in some cases the inclusions may simply be a side effect of the disease process that leads to the dementia.

Genes clearly play a role in the development of some kinds of dementia. However, in AD and many other disorders, the dementia usually cannot be tied to a single abnormal gene. Instead, these forms of dementia appear to result from a complex interaction of genes, lifestyle factors, and other environmental influences.

Researchers have identified several genes that influence susceptibility to AD. Mutations in three of the known genes for AD - genes that control the production of proteins such as *amyloid precursor protein* (APP), *presenilin 1*, and *presenilin 2* - are linked to early-onset forms of the disease.

Variations in another gene, called *apolipoprotein E* (apoE), have been linked to an increased risk of late-onset AD. The apoE gene does not cause the disease by itself, but one version of the gene, called apoE epsilon4 (apoE E4), appears to increase the risk of AD. People with two copies of the apoE E4 gene have about ten times the risk of developing AD compared to people without apoE E4. This gene variant seems to encourage amyloid deposition in the brain. One study also found that this gene is associated with shorter survival in men with AD. In contrast, another version of the apoE gene, called apoE E2, appears to protect against AD.

Studies have suggested that mutations in another gene, called CYP46, may contribute to an increased risk of developing late-onset sporadic AD. This gene normally produces a protein that helps the brain metabolize cholesterol.

Scientists are trying to determine how beta amyloid influences the development of AD. A number of studies indicate that the buildup of this protein initiates a complex chain of events that culminates in dementia. One study found that beta amyloid buildup in the brain triggers cells called microglia, which act like janitors that mop up potentially harmful substances in the brain, to release a potent neurotoxin called peroxynitrite. This may contribute to nerve cell death in AD. Another study found that beta amyloid causes a protein called p35 to be split into two proteins. One of the resulting proteins triggers changes in the *tau* protein that lead to formation of neurofibrillary tangles. A third study found that beta amyloid activates cell-death enzymes called caspases that alter the *tau* protein in a way that causes it to form tangles. Researchers believe these tangles may contribute to the neuron death in AD.

Vascular dementia can be caused by cerebrovascular disease or any other condition that prevents normal blood flow to the brain. Without a normal supply of blood, brain cells cannot obtain the oxygen they need to work correctly, and they often become so deprived that they die.

The causes of other types of dementias vary. Some, such as CJD and GSS, have been tied to abnormal forms of specific proteins. Others, including Huntington's disease and FTDP-17, have been linked to defects in a single gene. Post-traumatic dementia is directly related to brain cell death after injury. HIV-associated dementia is clearly tied to infection by the HIV virus, although the exact way the virus causes damage is not yet certain. For other dementias, such as corticobasal degeneration and most types of frontotemporal dementia, the underlying causes have not yet been identified.

## What Are the Risk Factors for Dementia?

Researchers have identified several risk factors that affect the likelihood of developing one or more kinds of dementia. Some of these factors are modifiable, while others are not.

**Age.** The risk of AD, vascular dementia, and several other dementias goes up significantly with advancing age.

**Genetics/family history.** As described in the section "What Causes Dementia?" researchers have discovered a number of genes that increase the risk of developing AD. Although people with a family history of AD are generally considered to be at heightened risk of developing the disease themselves, many people with a family history never develop the disease, and many without a family history of the disease do get it. In most cases, it is still impossible to predict a specific person's risk of the disorder based on family history alone. Some families with CJD, GSS, or fatal familial insomnia have mutations in the prion protein gene, although these disorders can also occur in people

without the gene mutation. Individuals with these mutations are at significantly higher risk of developing these forms of dementia. Abnormal genes are also clearly implicated as risk factors in Huntington's disease, FTDP-17, and several other kinds of dementia. These dementias are described in the section "What are the different kinds of dementia?"

***Smoking and alcohol use.*** Several recent studies have found that smoking significantly increases the risk of mental decline and dementia. People who smoke have a higher risk of *atherosclerosis* and other types of vascular disease, which may be the underlying causes for the increased dementia risk. Studies also have found that drinking large amounts of alcohol appears to increase the risk of dementia. However, other studies have suggested that people who drink moderately have a lower risk of dementia than either those who drink heavily or those who completely abstain from drinking.

***Atherosclerosis.*** Atherosclerosis is the buildup of plaque - deposits of fatty substances, cholesterol, and other matter - in the inner lining of an artery. Atherosclerosis is a significant risk factor for vascular dementia, because it interferes with the delivery of blood to the brain and can lead to stroke. Studies have also found a possible link between atherosclerosis and AD.

***Cholesterol.*** High levels of low-density lipoprotein (LDL), the so-called bad form of cholesterol, appear to significantly increase a person's risk of developing vascular dementia. Some research has also linked high cholesterol to an increased risk of AD.

***Plasma homocysteine.*** Research has shown that a higher-than-average blood level of homocysteine - a type of amino acid - is a strong risk factor for the development of AD and vascular dementia.

***Diabetes.*** Diabetes is a risk factor for both AD and vascular dementia. It is also a known risk factor for atherosclerosis and stroke, both of which contribute to vascular dementia.

***Mild cognitive impairment.*** While not all people with mild cognitive impairment develop dementia, people with this condition do have a significantly increased risk of dementia compared to the rest of the population. One study found that approximately 40 percent of people over age 65 who were diagnosed with mild cognitive impairment developed dementia within 3 years.

***Down syndrome.*** Studies have found that most people with Down syndrome develop characteristic AD plaques and neurofibrillary tangles by the time they reach middle age. Many, but not all, of these individuals also develop symptoms of dementia.

## How Is Dementia Diagnosed?

Doctors employ a number of strategies to diagnose dementia. It is important that they rule out any treatable conditions, such as depression, normal pressure hydrocephalus, or vitamin B<sub>12</sub> deficiency, which can cause similar symptoms.

Early, accurate diagnosis of dementia is important for patients and their families because it allows early treatment of symptoms. For people with AD or other progressive dementias, early diagnosis may allow them to plan for the future while they can still help to make decisions. These people also may benefit from drug treatment.

The "gold standard" for diagnosing dementia, autopsy, does not help the patient or caregivers. Therefore, doctors have devised a number of techniques to help identify dementia with reasonable accuracy while the patient is still alive.

### ***Patient history***

Doctors often begin their examination of a patient suspected of having dementia by asking questions about the patient's history. For example, they may ask how and when symptoms developed and about the patient's overall medical condition. They also may try to evaluate the patient's emotional state, although patients with dementia often may be unaware of or in denial about how their disease is affecting them. Family members also may deny the existence of the disease because they do not want to accept the diagnosis and because, at least in the beginning, AD and other forms of dementia can resemble normal aging. Therefore additional steps are necessary to confirm or rule out a diagnosis of dementia.

### ***Physical examination***

A physical examination can help rule out treatable causes of dementia and identify signs of stroke or other disorders that can contribute to dementia. It can also identify signs of other illnesses, such as heart disease or kidney failure, that can overlap with dementia. If a patient is taking medications that may be causing or contributing to his or her symptoms, the doctor may suggest stopping or replacing some medications to see if the symptoms go away.

### ***Neurological evaluations***

Doctors will perform a neurological examination, looking at balance, sensory function, reflexes, and other functions, to identify signs of conditions - for example movement disorders or stroke - that may affect the patient's diagnosis or are treatable with drugs.

### ***Cognitive and neuropsychological tests***

Doctors use tests that measure memory, language skills, math skills, and other abilities related to mental functioning to help them diagnose a patient's condition accurately. For example, people with AD often show changes in so-called executive functions (such as problem-solving), memory, and the ability to perform once-automatic tasks.

Doctors often use a test called the *Mini-Mental State Examination (MMSE)* to assess cognitive skills in people with suspected dementia. This test examines orientation, memory, and attention, as well as the ability to name objects, follow verbal and written commands, write a sentence spontaneously, and copy a complex shape. Doctors also use a variety of other tests and rating scales to identify specific types of cognitive problems and abilities.

### ***Brain scans***

Doctors may use brain scans to identify strokes, tumors, or other problems that can cause dementia. Also, *cortical atrophy* -degeneration of the brain's cortex (outer layer) - is common in many forms of dementia and may be visible on a brain scan. The brain's cortex normally appears very wrinkled, with ridges of tissue (called gyri) separated by "valleys" called sulci. In individuals with cortical atrophy, the progressive loss of neurons causes the ridges to become thinner and the sulci to grow wider. As brain cells die, the ventricles (or fluid-filled cavities in the middle of the brain) expand to fill the available space, becoming much larger than normal. Brain scans also can identify changes in the brain's structure and function that suggest AD.

The most common types of brain scans are *computed tomographic (CT) scans* and *magnetic resonance imaging (MRI)*. Doctors frequently request a CT scan of the brain when they are examining a patient with suspected dementia. These scans, which use X-rays to detect brain structures, can show evidence of brain atrophy, strokes and transient ischemic attacks (TIAs), changes to the blood vessels, and other problems such as hydrocephalus and subdural hematomas. MRI scans use magnetic fields and focused radio waves to detect hydrogen atoms in tissues within the body. They can detect the same problems as CT scans but they are better for identifying certain conditions, such as brain atrophy and damage from small TIAs.

Doctors also may use *electroencephalograms (EEGs)* in people with suspected dementia. In an EEG, electrodes are placed on the scalp over several parts of the brain in order to detect and record patterns of electrical activity and check for abnormalities. This electrical activity can indicate cognitive dysfunction in part or all of the brain. Many patients with moderately severe to severe AD have abnormal EEGs. An EEG may also be used to detect seizures, which occur in about 10 percent of AD patients as well as in many other disorders. EEGs also can help diagnose CJD.

Several other types of brain scans allow researchers to watch the brain as it functions. These scans, called functional brain imaging, are not often used as diagnostic tools, but they are important in research and they may ultimately help identify people with dementia earlier than is currently possible. Functional brain scans include functional MRI (fMRI), single photon-emission computed tomography (SPECT), positron emission tomography (PET), and magnetoencephalography (MEG). fMRI uses radio waves and a strong magnetic field to measure the metabolic changes that take place in active parts of the brain. SPECT shows the distribution of blood in the brain, which generally increases with brain activity. PET scans can detect changes in glucose metabolism, oxygen metabolism, and blood flow, all of which can reveal abnormalities of brain function. MEG shows the electromagnetic fields produced by the brain's neuronal activity.

### ***Laboratory tests***

Doctors may use a variety of laboratory tests to help diagnose dementia and/or rule out other conditions, such as kidney failure, that can contribute to symptoms. A partial list of these tests includes a complete blood count, blood glucose test, urinalysis, drug and alcohol tests (toxicology screen), cerebrospinal fluid analysis (to rule out specific infections that can affect the brain), and analysis of thyroid and thyroid-stimulating

hormone levels. A doctor will order only the tests that he or she feels are necessary and/or likely to improve the accuracy of a diagnosis.

### ***Psychiatric evaluation***

A psychiatric evaluation may be obtained to determine if depression or another psychiatric disorder may be causing or contributing to a person's symptoms.

### ***Presymptomatic testing***

Testing people before symptoms begin to determine if they will develop dementia is not possible in most cases. However, in disorders such as Huntington's where a known gene defect is clearly linked to the risk of the disease, a genetic test can help identify people who are likely to develop the disease. Since this type of genetic information can be devastating, people should carefully consider whether they want to undergo such testing. Researchers are examining whether a series of simple cognitive tests, such as matching words with pictures, can predict who will develop dementia. One study suggested that a combination of a verbal learning test and an odor-identification test can help identify AD before symptoms become obvious. Other studies are looking at whether memory tests and brain scans can be useful indicators of future dementia.

## **Is There Any Treatment?**

While treatments to reverse or halt disease progression are not available for most of the dementias, patients can benefit to some extent from treatment with available medications and other measures, such as *cognitive training*.

Drugs to specifically treat AD and some other progressive dementias are now available and are prescribed for many patients. Although these drugs do not halt the disease or reverse existing brain damage, they can improve symptoms and slow the progression of the disease. This may improve the patient's quality of life, ease the burden on caregivers, and/or delay admission to a nursing home. Many researchers are also examining whether these drugs may be useful for treating other types of dementia.

Many people with dementia, particularly those in the early stages, may benefit from practicing tasks designed to improve performance in specific aspects of cognitive functioning. For example, people can sometimes be taught to use memory aids, such as mnemonics, computerized recall devices, or note taking.

Behavior modification - rewarding appropriate or positive behavior and ignoring inappropriate behavior - also may help control unacceptable or dangerous behaviors.

### ***Alzheimer's disease***

Most of the drugs currently approved by the U. S. Food and Drug Administration for AD fall into a category called cholinesterase inhibitors. These drugs slow the breakdown of the *neurotransmitter acetylcholine*, which is reduced in the brains of people with AD. Acetylcholine is important for the formation of memories and it is used in the hippocampus and the cerebral cortex, two brain regions that are affected by AD. There

are currently four cholinesterase inhibitors approved for use in the United States: tacrine (Cognex), donepezil (Precept), rivastigmine (Exelon), and galantamine (Reminyl). These drugs temporarily improve or stabilize memory and thinking skills in some individuals. Many studies have shown that cholinesterase inhibitors help to slow the decline in mental functions associated with AD, and that they can help reduce behavioral problems and improve the ability to perform everyday tasks. However, none of these drugs can stop or reverse the course of AD.

A fifth drug, memantine (Namenda), was recently approved for use in the United States. Unlike other drugs for AD, which affect acetylcholine levels, memantine works by regulating the activity of a neurotransmitter called glutamate that plays a role in learning and memory. Glutamate activity is often disrupted in AD. Because this drug works differently from cholinesterase inhibitors, combining memantine with other AD drugs may be more effective than any single therapy. One controlled clinical trial found that patients receiving donepezil plus memantine had better cognition and other functions than patients receiving donepezil alone.

Doctors may also prescribe other drugs, such as anticonvulsants, antipsychotics, sedatives, and antidepressants, to treat seizures, depression, agitation, sleep disorders, and other specific problems that can be associated with dementia.

### ***Vascular dementia***

There is no standard drug treatment for vascular dementia, although some of the symptoms, such as depression, can be treated. Most other treatments aim to reduce the risk factors for further brain damage. However, some studies have found that cholinesterase inhibitors, such as galantamine and other AD drugs, can improve cognitive function and behavioral symptoms in patients with early vascular dementia.

The progression of vascular dementia can often be slowed significantly or halted if the underlying vascular risk factors for the disease are treated. To prevent strokes and TIAs, doctors may prescribe medicines to control high blood pressure, high cholesterol, heart disease, and diabetes. Doctors also sometimes prescribe aspirin, warfarin, or other drugs to prevent clots from forming in small blood vessels. When patients have blockages in blood vessels, doctors may recommend surgical procedures, such as carotid endarterectomy, stenting, or angioplasty, to restore the normal blood supply. Medications to relieve restlessness or depression or to help patients sleep better may also be prescribed.

### ***Other dementias***

Some studies have suggested that cholinesterase inhibitors, such as donepezil (Aricept), can reduce behavioral symptoms in some patients with Parkinson's dementia.

At present, no medications are approved specifically to treat or prevent FTD and most other types of progressive dementia. However, sedatives, antidepressants, and other medications may be useful in treating specific symptoms and behavioral problems associated with these diseases.

Scientists continue to search for specific treatments to help people with Lewy body dementia. Current treatment is symptomatic, often involving the use of medication to control the parkinsonian and psychiatric symptoms. Although antiparkinsonian medication may help reduce tremor and loss of muscle movement, it may worsen symptoms such as hallucinations and delusions. Also, drugs prescribed for psychiatric symptoms may make the movement problems worse. In general, newer antipsychotic medications are more successful than older drugs such as haloperidol. Several studies have suggested that cholinesterase inhibitors may be able to improve cognitive function and behavioral symptoms in patients with Lewy body disease.

There is no known treatment that can cure or control CJD. Current treatment is aimed at alleviating symptoms and making the patient as comfortable as possible. Opiate drugs can help relieve pain, and the drugs clonazepam and sodium valproate may help relieve myoclonus. During later stages of the disease, treatment focuses on supportive care, such as administering intravenous fluids and changing the person's position frequently to prevent bedsores.

## Can Dementia be Prevented?

Research has revealed a number of factors that may be able to prevent or delay the onset of dementia in some people. For example, studies have shown that people who maintain tight control over their glucose levels tend to score better on tests of cognitive function than those with poorly controlled diabetes. Several studies also have suggested that people who engage in intellectually stimulating activities, such as social interactions, chess, crossword puzzles, and playing a musical instrument, significantly lower their risk of developing AD and other forms of dementia. Scientists believe mental activities may stimulate the brain in a way that increases the person's "cognitive reserve" - the ability to cope with or compensate for the pathologic changes associated with dementia.

Researchers are studying other steps people can take that may help prevent AD in some cases. So far, none of these factors has been definitively proven to make a difference in the risk of developing the disease. Moreover, most of the studies addressed only AD, and the results may or may not apply to other forms of dementia. Nevertheless, scientists are encouraged by the results of these early studies and many believe it will eventually become possible to prevent some forms of dementia. Possible preventive actions include:

*Lowering homocysteine.* In one study, elevated blood levels of the amino acid homocysteine were associated with a 2.9 times greater risk of AD and a 4.9 times greater risk of vascular dementia. A preliminary study has shown that high doses of three B vitamins that help lower homocysteine levels - folic acid, B<sub>12</sub>, and B<sub>6</sub> - appear to slow the progression of AD. Researchers are now conducting a multi-center clinical trial to test this effect in a larger group of patients.

*Lowering cholesterol levels.* Research has suggested that people with high cholesterol levels have an increased risk of developing AD. Cholesterol is involved in formation of amyloid plaques in the brain. Mutations in a gene called CYP46 and the apoE E4 gene variant, both of which have been linked to an increased risk of AD, are also involved in

cholesterol metabolism. Several studies have also found that the use of drugs called statins, which lower cholesterol levels, is associated with a lower likelihood of cognitive impairment.

*Lowering blood pressure.* Several studies have shown that antihypertensive medicine reduces the odds of cognitive impairment in elderly people with high blood pressure. One large European study found a 55 percent lower risk of dementia in people over 60 who received drug treatment for hypertension. These people had a reduced risk of both AD and vascular dementia.

*Exercise.* Regular exercise stimulates production of chemicals called growth factors that help neurons survive and adapt to new situations. These gains may help to delay the onset of dementia symptoms. Exercise also may reduce the risk of brain damage from atherosclerosis.

*Education.* Researchers have found evidence that formal education may help protect people against the effects of AD. In one study, researchers found that people with more years of formal education had relatively less mental decline than people with less schooling, regardless of the number of amyloid plaques and neurofibrillary tangles each person had in his or her brain. The researchers think education may cause the brain to develop robust nerve cell networks that can help compensate for the cell damage caused by AD.

*Controlling inflammation.* Many studies have suggested that inflammation may contribute to AD. Moreover, autopsies of people who died with AD have shown widespread inflammation in the brain that appeared to be caused by the accumulation of beta amyloid. Another study found that men with high levels of C-reactive protein, a general marker of inflammation, had a significantly increased risk of AD and other kinds of dementia.

*Nonsteroidal anti-inflammatory drugs (NSAIDs).* Research indicates that long-term use of NSAIDs - ibuprofen, naproxen, and similar drugs - may prevent or delay the onset of AD. Researchers are not sure how these drugs may protect against the disease, but some or all of the effect may be due to reduced inflammation. A 2003 study showed that these drugs also bind to amyloid plaques and may help to dissolve them and prevent formation of new plaques.

The risk of vascular dementia is strongly correlated with risk factors for stroke, including high blood pressure, diabetes, elevated cholesterol levels, and smoking. This type of dementia may be prevented in many cases by changing lifestyle factors, such as excessive weight and high blood pressure, which are associated with an increased risk of cerebrovascular disease. One European study found that treating isolated systolic hypertension (high blood pressure in which only the systolic or top number is high) in people age 60 and older reduced the risk of dementia by 50 percent. These studies strongly suggest that effective use of current treatments can prevent many future cases of vascular dementia.

## What Kind of Care Does a Person with Dementia Need?

People with moderate and advanced dementia typically need round-the-clock care and supervision to prevent them from harming themselves or others. They also may need assistance with daily activities such as eating, bathing, and dressing. Meeting these needs takes patience, understanding, and careful thought by the person's caregivers.

A typical home environment can present many dangers and obstacles to a person with dementia, but simple changes can overcome many of these problems. For example, sharp knives, dangerous chemicals, tools, and other hazards should be removed or locked away. Other safety measures include installing bed and bathroom safety rails, removing locks from bedroom and bathroom doors, and lowering the hot water temperature to 120°F (48.9°C) or less to reduce the risk of accidental scalding. People with dementia also should wear some form of identification at all times in case they wander away or become lost. Caregivers can help prevent unsupervised wandering by adding locks or alarms to outside doors.

People with dementia often develop behavior problems because of frustration with specific situations. Understanding and modifying or preventing the situations that trigger these behaviors may help to make life more pleasant for the person with dementia as well as his or her caregivers. For instance, the person may be confused or frustrated by the level of activity or noise in the surrounding environment. Reducing unnecessary activity and noise (such as limiting the number of visitors and turning off the television when it's not in use) may make it easier for the person to understand requests and perform simple tasks. Confusion also may be reduced by simplifying home decorations, removing clutter, keeping familiar objects nearby, and following a predictable routine throughout the day. Calendars and clocks also may help patients orient themselves.

People with dementia should be encouraged to continue their normal leisure activities as long as they are safe and do not cause frustration. Activities such as crafts, games, and music can provide important mental stimulation and improve mood. Some studies have suggested that participating in exercise and intellectually stimulating activities may slow the decline of cognitive function in some people.

Many studies have found that driving is unsafe for people with dementia. They often get lost and they may have problems remembering or following rules of the road. They also may have difficulty processing information quickly and dealing with unexpected circumstances. Even a second of confusion while driving can lead to an accident. Driving with impaired cognitive functions can also endanger others. Some experts have suggested that regular screening for changes in cognition might help to reduce the number of driving accidents among elderly people, and some states now require that doctors report people with AD to their state motor vehicle department. However, in many cases, it is up to the person's family and friends to ensure that the person does not drive.

The emotional and physical burden of caring for someone with dementia can be overwhelming. Support groups can often help caregivers deal with these demands and they can also offer helpful information about the disease and its treatment. It is important

that caregivers occasionally have time off from round-the-clock nursing demands. Some communities provide respite facilities or adult day care centers that will care for dementia patients for a period of time, giving the primary caregivers a break. Eventually, many patients with dementia require the services of a full-time nursing home.

A list of caregiver organizations and support groups is included at the end of this booklet.

## What Research Is Being Done?

Current research focuses on many different aspects of dementia. This research promises to improve the lives of people affected by the dementias and may eventually lead to ways of preventing or curing these disorders.

### *Causes and prevention*

Research on the causes of AD and other dementias includes studies of genetic factors, neurotransmitters, inflammation, factors that influence programmed cell death in the brain, and the roles of *tau*, beta amyloid, and the associated neurofibrillary tangles and plaques in AD. Some other researchers are trying to determine the possible roles of cholesterol metabolism, oxidative stress (chemical reactions that can damage proteins, DNA, and lipids inside cells), and microglia in the development of AD. Scientists also are investigating the role of aging-related proteins such as the enzyme telomerase.

Since many dementias and other neurodegenerative diseases have been linked to abnormal clumps of proteins in cells, researchers are trying to learn how these clumps develop, how they affect cells, and how the clumping can be prevented.

Some studies are examining whether changes in white matter - nerve fibers lined with myelin - may play a role in the onset of AD. Myelin may erode in AD patients before other changes occur. This may be due to a problem with oligodendrocytes, the cells that produce myelin.

Researchers are searching for additional genes that may contribute to AD, and they have identified a number of gene regions that may be involved. Some researchers suggest that people will eventually be screened for a number of genes that contribute to AD and that they will be able to receive treatments that specifically address their individual genetic risks. However, such individualized screening and treatment is still years away.

Insulin resistance is common in people with AD, but it is not clear whether the insulin resistance contributes to the development of the disease or if it is merely a side effect.

Several studies have found a reduced risk of dementia in people who take cholesterol-lowering drugs called statins. However, it is not yet clear if the apparent effect is due to the drugs or to other factors.

One clinical trial is testing estrogen to see if it can help prevent AD. Early studies of estrogen looked promising. However, a clinical study of several thousand postmenopausal women aged 65 or older found that combination therapy with estrogen and progestin substantially increased the risk of AD. The study is continuing to examine whether taking estrogen alone may decrease the risk of AD.

A 2003 study found that people with HIV-associated dementia have different levels of activity for more than 30 different proteins, compared to people who have HIV but no

signs of dementia. The study suggests a possible way to screen HIV patients for the first signs of cognitive impairment, and it may lead to ways of intervening to prevent this form of dementia.

### ***Diagnosis***

Improving early diagnosis of AD and other types of dementia is important not only for patients and families, but also for researchers who seek to better understand the causes of dementing diseases and find ways to reverse or halt them at early stages. Improved diagnosis can also reduce the risk that people will receive inappropriate treatments.

Some researchers are investigating whether three-dimensional computer models of PET and MRI images can identify brain changes typical of early AD, before any symptoms appear. This research may lead to ways of preventing the symptoms of the disease.

One study found that levels of beta amyloid and *tau* in spinal fluid can be used to diagnose AD with a sensitivity of 92 percent. If other studies confirm the validity of this test, it may allow doctors to identify people who are beginning to develop the disorder before they start to show symptoms. This would allow treatment at very early stages of the disorder, and may help in testing new treatments to prevent or delay symptoms of the disease. Other researchers have identified factors in the skin and blood of AD patients that are different from those in healthy people. They are trying to determine if these factors can be used to diagnose the disease.

### ***Treatment***

Researchers are continually working to develop new drugs for AD and other types of dementia. Many researchers believe a vaccine that reduces the number of amyloid plaques in the brain might ultimately prove to be the most effective treatment for AD. In 2001, researchers began one clinical trial of a vaccine called AN-1792. The study was halted after a number of people developed inflammation of the brain and spinal cord. Despite these problems, one patient appeared to have reduced numbers of amyloid plaques in the brain. Other patients showed little or no cognitive decline during the course of the study, suggesting that the vaccine may slow or halt the disease. Researchers are now trying to find safer and more effective vaccines for AD.

Researchers are also investigating possible methods of gene therapy for AD. In one case, researchers used cells genetically engineered to produce nerve growth factor and transplanted them into monkeys' forebrains. The transplanted cells boosted the amount of nerve growth factors in the brain and seemed to prevent degeneration of acetylcholine-producing neurons in the animals. This suggests that gene therapy might help to reduce or delay symptoms of the disease. Researchers are now testing a similar therapy in a small number of patients. Other researchers have experimented with gene therapy that adds a gene called neprilysin in a mouse model that produces human beta amyloid. They found that increasing the level of neprilysin greatly reduced the amount of beta amyloid in the mice and halted the amyloid-related brain degeneration. They are now trying to determine whether neprilysin gene therapy can improve cognition in mice.

A clinical trial called the Vitamins to Slow Alzheimer's Disease (VITAL) study is testing whether high doses of three common B vitamins - folic acid, B<sub>12</sub>, and B<sub>6</sub> - can reduce homocysteine levels and slow the rate of cognitive decline in AD.

Since many studies have found evidence of brain inflammation in AD, some researchers have proposed that drugs that control inflammation, such as NSAIDs, might prevent the disease or slow its progression. Studies in mice have suggested that these drugs can limit production of amyloid plaques in the brain. Clinical trials are now studying whether NSAIDs and related drugs can slow or prevent development of AD in humans.

Other clinical trials for AD are investigating whether antipsychotic drugs are useful in treating symptoms of AD, whether use of a shunt to increase the flow of cerebrospinal fluid and improve clearance of potential neurotoxins can halt or slow progression of the disease, and whether insulin-sensitizing drugs may be useful in treating AD.

Some researchers are investigating the effects of two drugs, pentoxifylline and propentofylline, to treat vascular dementia. Pentoxifylline improves blood flow, while propentofylline appears to interfere with some of the processes that cause cell death in the brain.

One study is testing the safety and effectiveness of donepezil (Aricept) for treating mild dementia in patients with Parkinson's dementia, while another is investigating whether skin patches with the drug selegiline can improve mental function in patients with cognitive problems related to HIV.

## How Can I Help Research?

People with dementia and others who wish to help research on dementing disorders may be able to do so by participating in clinical studies designed to learn more about the disorders or to test potential new therapies. Information about many such studies is available free of charge from the Federal government's database of clinical trials, [clinicaltrials.gov](http://clinicaltrials.gov) (<http://clinicaltrials.gov>).

Information about clinical trials specific to AD is available from the Alzheimer's Disease Clinical Trials Database ([www.alzheimers.org/trials](http://www.alzheimers.org/trials)), a joint project of the U. S. Food and Drug Administration and the National Institute on Aging (NIA) that is maintained by the NIA's Alzheimer's Disease Education and Referral Center.

For clinical trials taking place at the National Institutes of Health, additional information is available from the following office:

**Patient Recruitment and Public Liaison Office**

Clinical Center

National Institutes of Health

Building 61, 10 Cloister Court

Bethesda, Maryland 20892-4754

800-411-1222

**TTY:** 301-594-9774 (local), 866-411-1010 (toll free)

[www.cc.nih.gov](http://www.cc.nih.gov)

Voluntary health organizations may be able to provide information about additional clinical studies.

Another important way that people can help dementia research is by arranging to donate their brains to brain and tissue banks after they die. Tissue from these banks is made available to qualified researchers so that they can continue their studies of how these diseases develop and how they affect the brain. Brain banks accepting donations include the following:

**National Disease Research Interchange**

1880 JFK Boulevard  
6th Floor  
Philadelphia, Pennsylvania 19103  
800-222-NDRI (6374)  
215-557-7361  
[www.ndri.com](http://www.ndri.com)

**Human Brain and Spinal Fluid Resource Center**

Neurology Research (127A)  
W. Los Angeles Healthcare Center  
11301 Wilshire Blvd. Bldg. 212  
Los Angeles, CA 90073  
310-268-3536  
24-hour pager: 310-636-5199  
Email: [RMNbbank@ucla.edu](mailto:RMNbbank@ucla.edu)  
<http://www.loni.ucla.edu/~nnrsb/NNRSB>

**Brain Endowment Bank**

University of Miami  
1501 N. W. Ninth Avenue, #4013  
Miami, Florida 33136  
800-UM-BRAIN (862-7246)  
305-243-6219

**Harvard Brain Tissue Resource Center**

McLean Hospital  
115 Mill Street  
Belmont, Massachusetts 02478  
800-BRAIN BANK (272-4622)  
617-855-2400  
[www.brainbank.mclean.org](http://www.brainbank.mclean.org)

People who have more than one family member affected by AD also may be able to help research by contributing blood samples to a gene bank. A large initiative to collect such samples was announced in 2003. This large gene bank should accelerate research efforts

to identify genes that play a role in AD. People interested in participating in this gene bank can learn more about it at the address and telephone numbers below:

**Alzheimer's Disease Genetics Initiative**

National Cell Repository for Alzheimer's Disease (NCRAD)

Indiana University

Indianapolis, Indiana 46202-5251

800-526-2839

317-274-7360

## Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN

P.O. Box 5801

Bethesda, MD 20824

(800) 352-9424

<http://www.ninds.nih.gov>

Information also is available from additional organizations listed at

[http://www.ninds.nih.gov/disorders/alzheimersdisease/detail\\_alzheimersdisease.htm](http://www.ninds.nih.gov/disorders/alzheimersdisease/detail_alzheimersdisease.htm).

## Glossary

**acetylcholine** - a neurotransmitter that is important for the formation of memories. Studies have shown that levels of acetylcholine are reduced in the brains of people with Alzheimer's disease.

**Alzheimer's disease** - the most common cause of dementia in people aged 65 and older. Nearly all brain functions, including memory, movement, language, judgment, behavior, and abstract thinking, are eventually affected.

**amyloid plaques** - unusual clumps of material found in the tissue between nerve cells. Amyloid plaques, which consist of a protein called beta amyloid along with degenerating bits of neurons and other cells, are a hallmark of Alzheimer's disease.

**amyloid precursor protein** - a normal brain protein that is a precursor for beta amyloid, the abnormal substance found in the characteristic amyloid plaques of Alzheimer's disease patients.

**apolipoprotein E** - a gene that has been linked to an increased risk of Alzheimer's disease. People with a variant form of the gene, called apoE epsilon 4, have about ten times the risk of developing Alzheimer's disease.

**ataxia** - a loss of muscle control.

**atherosclerosis** - a blood vessel disease characterized by the buildup of plaque, or deposits of fatty substances and other matter in the inner lining of an artery.

**beta amyloid** - a protein found in the characteristic clumps of tissue (called plaques) that appear in the brains of Alzheimer's patients.

**Binswanger's disease** - a rare form of dementia characterized by damage to small blood vessels in the white matter of the brain. This damage leads to brain lesions, loss of memory, disordered cognition, and mood changes.

**CADASIL** - a rare hereditary disorder which is linked to a type of vascular dementia. It stands for cerebral **a**utosomal **d**ominant **a**rteriopathy with **s**ubcortical **i**nfarct and **l**eukoencephalopathy.

**cholinesterase inhibitors** - drugs that slow the breakdown of the neurotransmitter acetylcholine.

**cognitive training** - a type of training in which patients practice tasks designed to improve mental performance. Examples include memory aids, such as mnemonics, and computerized recall devices.

**computed tomographic (CT) scans** - a type of brain scan that uses X-rays to detect brain structures.

**cortical atrophy** - degeneration of the brain's cortex (outer layer). Cortical atrophy is common in many forms of dementia and may be visible on a brain scan.

**cortical dementia** - a type of dementia in which the damage primarily occurs in the brain's cortex, or outer layer.

**corticobasal degeneration** - a progressive disorder characterized by nerve cell loss and atrophy in multiple areas of the brain.

**Creutzfeldt-Jakob disease** - a rare, degenerative, fatal brain disorder believed to be linked to an abnormal form of a protein called a prion.

**dementia** - a term for a collection of symptoms that significantly impair thinking and normal activities and relationships.

**dementia pugilistica** - a form of dementia caused by head trauma such as that experienced by boxers. It is also called chronic traumatic encephalopathy or Boxer's syndrome.

**electroencephalogram (EEG)** - a medical procedure that records patterns of electrical activity in the brain.

**fatal familial insomnia** - an inherited disease that affects a brain region called the thalamus, which is partially responsible for controlling sleep. The disease causes dementia and a progressive insomnia that eventually leads to a complete lack of sleep.

**frontotemporal dementias** - a group of dementias characterized by degeneration of nerve cells, especially those in the frontal and temporal lobes of the brain.

**FTDP-17** - one of the frontotemporal dementias, linked to a mutation in the *tau* gene. It is much like other types of the frontotemporal dementias but often includes psychiatric symptoms such as delusions and hallucinations.

**Gerstmann-Straussler-Scheinker disease** - a rare, fatal hereditary disease that causes ataxia and progressive dementia.

**HIV-associated dementia** - a dementia that results from infection with the human immunodeficiency virus (HIV) that causes AIDS. It can cause widespread destruction of the brain's white matter.

**Huntington's disease** - a degenerative hereditary disorder caused by a faulty gene for a protein called huntington. The disease causes degeneration in many regions of the brain and spinal cord and patients eventually develop severe dementia.

**Lewy body dementia** - one of the most common types of progressive dementia, characterized by the presence of abnormal structures called Lewy bodies in the brain. In many ways the symptoms of this disease overlap with those of Alzheimer's disease.

**magnetic resonance imaging (MRI)** - a diagnostic imaging technique that uses magnetic fields and radio waves to produce detailed images of body structures.

**mild cognitive impairment** - a condition associated with impairments in understanding and memory not severe enough to be diagnosed as dementia, but more pronounced than those associated with normal aging.

**Mini-Mental State Examination** - a test used to assess cognitive skills in people with suspected dementia. The test examines orientation, memory, and attention, as well as the ability to name objects, follow verbal and written commands, write a sentence spontaneously, and copy a complex shape.

**multi-infarct dementia** - a type of vascular dementia caused by numerous small strokes in the brain.

**myelin** - a fatty substance that coats and insulates nerve cells.

**neurofibrillary tangles** - bundles of twisted filaments found within neurons, and a characteristic feature found in the brains of Alzheimer's patients. These tangles are largely made up of a protein called *tau*.

**neurotransmitter** - a type of chemical, such as acetylcholine, that transmits signals from one neuron to another. People with Alzheimer's disease have reduced supplies of acetylcholine.

**organic brain syndrome** - a term that refers to physical disorders (not psychiatric in origin) that impair mental functions.

**Parkinson's dementia** - a secondary dementia that sometimes occurs in people with advanced Parkinson's disease, which is primarily a movement disorder. Many Parkinson's patients have the characteristic amyloid plaques and neurofibrillary tangles found in Alzheimer's disease, but it is not yet clear if the diseases are linked.

**Pick's disease** - a type of frontotemporal dementia where certain nerve cells become abnormal and swollen before they die. The brains of people with Pick's disease have abnormal structures, called Pick bodies, inside the neurons. The symptoms are very similar to those of Alzheimer's disease.

**plaques** - unusual clumps of material found between the tissues of the brain in Alzheimer's disease. *See also* amyloid plaques.

**post-traumatic dementia** - a dementia brought on by a single traumatic brain injury. It is much like dementia pugilistica, but usually also includes long-term memory problems.

**presenilin 1 and 2** - proteins produced by genes that influence susceptibility to early-onset Alzheimer's disease.

**primary dementia** - a dementia, such as Alzheimer's disease, that is not the result of another disease.

**primary progressive aphasia** - a type of frontotemporal dementia resulting in deficits in language functions. Many, but not all, people with this type of aphasia eventually develop symptoms of dementia.

**progressive dementia** - a dementia that gets worse over time, gradually interfering with more and more cognitive abilities.

**secondary dementia** - a dementia that occurs as a consequence of another disease or an injury.

**senile dementia** - an outdated term that reflects the formerly widespread belief that dementia was a normal part of aging. The word *senile* is derived from a Latin term that means, roughly, "old age."

**subcortical dementia** - dementia that affects parts of the brain below the outer brain layer, or cortex.

**substance-induced persisting dementia** - dementia caused by abuse of substances such as alcohol and recreational drugs that persists even after the substance abuse has ended.

**tau protein** - a protein that helps the functioning of microtubules, which are part of the cell's structural support and help to deliver substances throughout the cell. In Alzheimer's disease, *tau* is changed in a way that causes it to twist into pairs of helical filaments that collect into tangles.

**transmissible spongiform encephalopathies** - part of a family of human and animal diseases in which brains become filled with holes resembling sponges when examined under a microscope. CJD is the most common of the known transmissible spongiform encephalopathies.

**vascular dementia** - a type of dementia caused by brain damage from cerebrovascular or cardiovascular problems - usually strokes. It accounts for up to 20 percent of all dementias.

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