THE DEMENTIAS

Hope Through Research

LEARN ABOUT:

- Types of dementia
- Risk factors
- Diagnosis and treatment
- Current research

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Introduction

A diagnosis of dementia can be frightening for those affected by the syndrome, their family members, and caretakers. Learning more about dementia can help. This booklet provides a general overview of various types of dementia, describes how the disorders are diagnosed and treated, and offers highlights of research that is supported by the National Institute of Neurological Disorders and Stroke and the National Institute on Aging, both part of the National Institutes of Health (NIH).

Alzheimer's disease (AD) is the most common form of dementia in those over the age of 65. As many as 5 million Americans age 65 and older may have AD, and that number is expected to double for every 5-year interval beyond age 65. But Alzheimer's is only one of many dementia disorders; another 1.8 million people in the U.S. have some other form of dementia. Among all people with dementia, many are believed to have a mixed type of dementia that can involve more than one of the disorders.

Age is the primary risk factor for developing dementia. For that reason, the number of people living with dementia could double in the next 40 years with an increase in the number of Americans who are age 65 or older—from 40 million today to more than 88 million in 2050. Regardless of the form of dementia, the personal, economic, and societal demands can be devastating.

Research over the past 30 years has helped us learn more about dementia—possible causes, who is at risk, and how it develops and affects the brain. This work offers the hope of better drugs and treatments for these disorders.

The Basics of Dementia

Dementia is the loss of cognitive functioning, which means the loss of the ability to think, remember, or reason, as well as behavioral abilities, to such an extent that it interferes with a person's daily life and activities. Signs and symptoms of dementia result when once-healthy neurons (nerve cells) in the brain stop working, lose connections with other brain cells, and die. While everyone loses some neurons as they age, people with dementia experience far greater loss.

Researchers are still trying to understand the underlying disease processes involved in the disorders. Scientists have some theories about mechanisms that may lead to different forms of dementias, but more research is needed to better understand if and how these mechanisms contribute to the development of dementia.

While dementia is more common with advanced age (as many as half of all people age 85 or older may have some form of dementia), it is not a normal part of aging. Many people live into their 90s and beyond without any signs of dementia.

Memory loss, though common, is not the only sign of dementia. For a person to be considered to have dementia, he or she must meet the following criteria:

- Two or more core mental functions must be impaired. These functions include memory, language skills, visual perception, and the ability to focus and pay attention. These also include cognitive skills such as the ability to reason and solve problems.
- The loss of brain function is severe enough that a person cannot do normal, everyday tasks.

In addition, some people with dementia cannot control their emotions. Their personalities may change. They can have delusions, which are strong beliefs without proof, such as the idea that someone is stealing from them. They also may hallucinate, seeing or otherwise experiencing things that are not real.

Types of Dementia

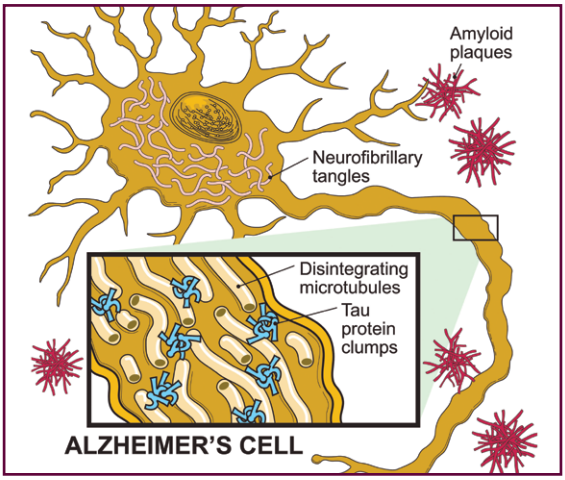
Various disorders and factors contribute to the development of dementia. Neurodegenerative disorders such as AD, frontotemporal disorders, and Lewy body dementia result in a progressive and irreversible loss of neurons and brain functions. Currently, there are no cures for these progressive neurodegenerative disorders.

However, other types of dementia can be halted or even reversed with treatment. Normal pressure hydrocephalus, for example, often resolves when excess cerebrospinal fluid in the brain is drained via a shunt and rerouted elsewhere in the body. Cerebral vasculitis responds to aggressive treatment with immunosuppressive drugs. In rare cases, treatable infectious disorders can cause dementia. Some drugs, vitamin deficiencies, alcohol abuse, depression, and brain tumors can cause neurological deficits that resemble dementia. Most of these causes respond to treatment.

Some types of dementia disorders are described below.

Tauopathies

In some dementias, a protein called tau clumps together inside nerve cells in the brain, causing the cells to stop functioning properly and die. Disorders that are associated with an accumulation of tau are called tauopathies.



In AD, the tau protein becomes twisted and aggregates to form bundles, called neurofibrillary tangles, inside the neurons. Abnormal clumps (plaques) of another protein, called amyloid, are prominent in spaces between brain cells and are a hallmark of the disease. Both plaques and tangles are thought to contribute

to reduced function and nerve-cell death in AD, but scientists do not fully understand this relationship. It is not clear, for example, if the plaques and tangles cause the disorder, or if their presence flags some other process that leads to neuronal death in AD.

Other types of tauopathies include the following disorders:

Corticobasal degeneration (CBD) is a progressive neurological disorder characterized by nerve-cell loss and atrophy (shrinkage) of specific areas of the brain, including the cerebral cortex and the basal ganglia. The disorder tends to progress gradually, with the onset of early symptoms around age 60. At first, one side of the body is affected more than the other side, but as the disease progresses both sides become impaired. An individual may have difficulty using one hand, or one's hand may develop an abnormal position.

Other signs and symptoms may include memory loss; trouble making familiar, focused movements (apraxia) such as brushing one's teeth; involuntary muscular jerks (myoclonus) and involuntary muscle contractions (dystonia); alien limb, in which the person feels as though a limb is being controlled by a force other than oneself; muscle rigidity (resistance to imposed movement); postural instability; and difficulty swallowing (dysphagia). People with CBD also may have visual-spatial problems that make it difficult to interpret visual information, such as the distance between objects.

There is no cure for CBD. Supportive therapies are available to reduce the burden of certain symptoms. For example, botulinum toxin can help control muscle contractions. Speech therapy and physical therapy may help one learn how to cope with daily activities.

Frontotemporal disorders (FTD) are caused by a family of brain diseases that primarily affect the frontal and temporal lobes of the brain; they account for up to 10 percent of all dementia cases. Some, but not all, forms

of FTD are considered tauopathies. In some cases, FTD is associated with mutations in the gene for tau (MAPT), and tau aggregates are present. However, other forms of FTD are associated with aggregates of the protein TDP-43, a mutated protein found among people with a type of ALS that is inherited. Mutations in a protein called progranulin may also play a role in some TDP43-opathies.

In FTD, changes to nerve cells in the brain's frontal lobes affect the ability to reason and make decisions, prioritize and multitask, act appropriately, and control movement. Some people decline rapidly over 2 to 3 years, while others show only minimal changes for many years. People can live with frontotemporal disorders for 2 to 10 years, sometimes longer, but it is difficult to predict the time course for an affected individual. In some cases, FTD is associated with progressive neuromuscular weakness otherwise known as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease). The signs and symptoms may vary greatly among individuals as different parts of the brain are affected. No treatment that can cure or reverse FTD is currently available.

Clinically, FTD is classified into two main types of syndromes:

- *Behavioral variant frontotemporal dementia* causes a person to undergo behavior and personality changes. People with this disorder may do impulsive things that are out of character, such as steal or be rude to others. They may engage in repetitive behavior (such as singing, clapping, or echoing another person's speech). They may overeat compulsively; lose inhibitions, causing them to say or do inappropriate things (sometimes sexual in nature); or become apathetic and experience excessive sleepiness. While they may be cognitively impaired, their memory may stay relatively intact.

- *Primary progressive aphasia (PPA)* causes a person to have trouble with expressive and receptive speaking—finding and/or expressing thoughts and/or words. Sometimes a person with PPA cannot name common objects. Problems with memory, reasoning, and judgment are not apparent at first but can develop and progress over time. PPA is a language disorder not to be confused with the aphasia that can result from a stroke. Many people with PPA, though not all, develop symptoms of dementia. In one form of PPA, called semantic PPA or semantic dementia, a person slowly loses the ability to understand single words and sometimes to recognize the faces of familiar people and common objects.

Other types of FTDs include:

- *Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17),* a rare form of dementia that is believed to be inherited from one parent and is linked to a defect in the gene that makes the tau protein. The three core features are behavioral and personality changes, cognitive impairment, and motor symptoms. People with this type of FTD often have delusions, hallucinations, and slowness of movement and tremor as seen in Parkinson's disease. Typical behavioral/personality characteristics include apathy, defective judgment, and compulsive and abusive behavior. Diagnosis of the disorder requires the confirmed presence of clinical features and genetic analysis. Palliative and symptomatic treatments such as physical therapy are the mainstays of management.
- *Pick's disease,* a tauopathy subtype of FTD characterized by hallmark Pick bodies—masses comprised of tau protein that accumulate inside nerve cells, causing them to appear enlarged or balloon-like. Some of the

symptoms of this rare neurodegenerative disorder are similar to those of AD, including loss of speech, inappropriate behavior, and trouble with thinking. However, while inappropriate behavior characterizes the early stages of Pick's disease, memory loss is often the first symptom of AD. Antidepressants and antipsychotics can control some of the behavioral symptoms of Pick's disease, but no treatment is available to stop the disease from progressing.

Progressive supranuclear palsy (PSP) is a rare brain disorder that damages the upper brain stem, including the substantia nigra (a movement control center in the midbrain). This region also is affected in Parkinson's disease, which may explain an overlap in motor symptoms shared by these disorders. Eye movements are especially affected, causing slow and then limited mobility of the eye. The most common early signs and symptoms include loss of balance, unexplained falls, general body stiffness, apathy, and depression. A person with this type of dementia may suddenly laugh or cry very easily (known as pseudobulbar affect). As the disorder progresses, people develop blurred vision and a characteristic vacant stare that involves loss of facial expression. Speech usually becomes slurred, and swallowing solid foods or liquids becomes difficult. PSP gets progressively worse, but people can live a decade or more after the onset of symptoms. Dextromethorphan, a common ingredient in cough medicine, has been approved for the treatment of pseudobulbar affect.

Argyrophilic grain disease is a common, late-onset degenerative disease characterized by tau deposits called argyrophilic grains in brain regions involved in memory and emotion. The disease's signs and symptoms are indistinguishable from late-onset AD. Confirmation of the diagnosis can be made only at autopsy.

Synucleinopathies

In these brain disorders, a protein called alpha-synuclein accumulates inside neurons. Although it is not fully understood what role this protein

plays, changes in the protein and/or its function have been linked to Parkinson's disease and other disorders.

One type of synucleinopathy, **Lewy body dementia,** involves protein aggregates called Lewy bodies, balloon-like structures that form inside of nerve cells. The initial symptoms may vary, but over time, people with these disorders develop very similar cognitive, behavioral, physical, and sleep-related symptoms. Lewy body dementia is one of the most common causes of dementia, after Alzheimer's disease and vascular disease. Types of Lewy body dementia include:

- *Dementia with Lewy bodies (DLB),* one of the more common forms of progressive dementia. Symptoms such as difficulty sleeping, loss of smell, and visual hallucinations often precede movement and other problems by as long as 10 years, which consequently results in DLB going unrecognized or misdiagnosed as a psychiatric disorder until its later stages. Neurons in the substantia nigra that produce dopamine die or become impaired, and the brain's outer layer (cortex) degenerates. Many neurons that remain contain Lewy bodies.

  Later in the course of DLB, some signs and symptoms are similar to AD and may include memory loss, poor judgment, and confusion. Other signs and symptoms of DLB are similar to those of Parkinson's disease, including difficulty with movement and posture, a shuffling walk, and changes in alertness and attention. Given these similarities, DLB can be very difficult to diagnose. There is no cure for DLB, but there are drugs that control some symptoms. The medications used to control DLB symptoms can make motor function worse or exacerbate hallucinations.
- *Parkinson's disease dementia (PDD),* a clinical diagnosis related to DLB that can occur in people with Parkinson's disease. PDD may affect memory, social judgment, language, or reasoning. Autopsy studies show that people with PDD often have amyloid plaques and tau tangles

similar to those found in people with AD, though it is not understood what these similarities mean. A majority of people with Parkinson's disease develop dementia, but the time from the onset of movement symptoms to the onset of dementia symptoms varies greatly from person to person. Risk factors for developing PDD include the onset of Parkinson's-related movement symptoms followed by mild cognitive impairment and REM sleep behavior disorder, which involves having frequent vivid nightmares and visual hallucinations.

Vascular Dementia and Vascular Cognitive Impairment

Vascular dementia and vascular cognitive impairment (VCI) are caused by injuries to the vessels supplying blood to the brain. These disorders can be caused by brain damage from multiple strokes or any injury to the small vessels carrying blood to the brain. Dementia risk can be significant even when individuals have suffered only small strokes. Vascular dementia and VCI arise as a result of risk factors that similarly increase the risk for cerebrovascular disease (stroke), including atrial fibrillation, hypertension, diabetes, and high cholesterol. Vascular dementia also has been associated with a condition called amyloid angiopathy, in which amyloid plaques accumulate in the blood-vessel walls, causing them to break down and rupture. Symptoms of vascular dementia and VCI can begin suddenly and progress or subside during one's lifetime.

Some types of vascular dementia include:

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). This inherited form of cardiovascular disease results in a thickening of the walls of small- and medium-sized blood vessels, eventually stemming the flow of blood to the brain. It is associated with mutations of a specific gene called Notch3, which gives instructions

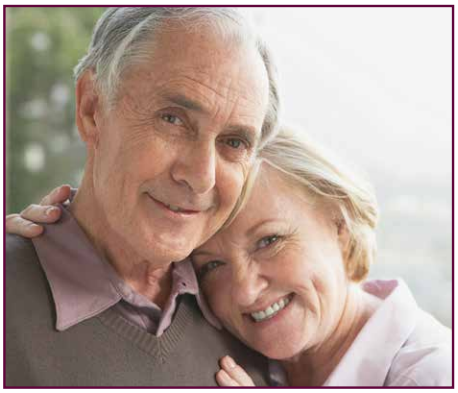
to a protein on the surface of the smooth muscle cells that surround blood vessels. CADASIL is associated with multi-infarct dementia, stroke, migraine with aura (migraine preceded by visual symptoms), and mood disorders. The first symptoms can appear in people between ages 20 and 40. Many people with CADASIL are undiagnosed. People with first-degree relatives who have CADASIL can be tested for genetic mutations to the Notch3 gene to determine their own risk of developing CADASIL.

Multi-infarct dementia. This type of dementia occurs when a person has had many small strokes that damage brain cells. One side of the body may be disproportionally affected, and multi-infarct dementia may impair language or other functions, depending on the region of the brain that is affected. Doctors call these "local" or "focal" symptoms, as opposed to the "global" symptoms seen in AD that tend to affect several functions and both sides of the body. When the strokes occur on both sides of the brain, however, dementia is more likely than when stroke occurs on one side of the brain. In some cases, a single stroke can damage the brain enough to cause dementia. This so-called single-infarct dementia is more common when stroke affects the left side of the brain—where speech centers are located—and/or when it involves the hippocampus, the part of the brain that is vital for memory.

Subcortical vascular dementia, also called Binswanger's disease. This is a rare form of dementia that involves extensive microscopic damage to the small blood vessels and nerve fibers that make up white matter, the "network" part of the brain believed to be critical for relaying messages between regions. The symptoms of Binswanger's are related to the disruption of subcortical neural circuits involving short-term memory, organization, mood, attention, decisionmaking, and appropriate behavior. A characteristic feature of this disease is psychomotor slowness, such as an increase in the time it takes for a person to think of a letter and then write it on a piece of paper.

Other symptoms include urinary incontinence that is unrelated to a urinary tract condition, trouble walking, clumsiness, slowness, lack of facial expression, and speech difficulties. Symptoms tend to begin after age 60, and they progress in a stepwise manner. People with subcortical vascular disease often have high blood pressure, a history of stroke, or evidence of disease of the large blood vessels in the neck or heart valves. Treatment is aimed at preventing additional strokes and may include drugs to control blood pressure.

Mixed Dementia



Autopsy studies looking at the brains of people who had dementia suggest that a majority of those age 80 and older probably had "mixed dementia," caused by both AD-related neurodegenerative processes and vascular disease-related processes. In fact, some studies indicate that mixed vascular-degenerative dementia is the most common cause of dementia in the elderly. In a person with mixed dementia, it may not be clear exactly how many of a person's symptoms are due to AD or another type of dementia. In one study, approximately 40 percent of people who were thought to have AD were found after autopsy to also have some form of cerebrovascular disease. Several studies have found that many of the major risk factors for vascular disease also may be risk factors for AD.

Researchers are still working to understand how underlying disease processes in mixed dementia influence each other. It is not clear, for example, if symptoms are likely to be worse when a person has brain changes reflecting multiple types of dementia. Nor do we know if a person with multiple dementias can benefit from treating one type, for example, when a person with AD controls high blood pressure and other vascular disease risk factors.

Other Conditions That Cause Dementia

Doctors have identified many other conditions that can cause dementia or dementia-like symptoms.

Other Brain Diseases

Creutzfeldt-Jakob disease (CJD). A rare brain disorder that affects about one in every million people worldwide each year, CJD belongs to a family of diseases known as the transmissible spongiform encephalopathies, or TSEs. Spongiform refers to the fact that the brain becomes filled with microscopic swellings that give the appearance of holes, like a sponge. CJD and other TSEs are believed to be caused by infectious proteins called prions that become misfolded. Scientists believe that the presence of misfolded prions can trigger normal proteins to misfold as well, causing a chain reaction. These abnormal prion proteins tend to clump together, which is believed to be related to the brain damage.

Symptoms usually begin after age 60, and most people die within a year of onset. In most cases, CJD occurs in people who have no known risk factors for the disease; however, an estimated 5 to 10 percent of cases in the U.S. are associated with genetic mutations. In addition, a type of CJD, called variant CJD (vCJD), has been found in Great Britain and several other European countries. vCJD has been observed to affect people who are younger than those with other forms of CJD and is believed to be caused by eating beef from cattle infected with a TSE called bovine spongiform encephalopathy, more commonly known as "mad cow disease." Inherited forms of CJD include:

- *Fatal familial insomnia.* This prion disease causes a part of the brain involved in sleep to slowly degenerate. People with the disease have trouble sleeping and may show signs of poor reflexes and hallucinations.

- *Gerstmann-Straussler-Scheinker disease*. Symptoms include a loss of coordination (ataxia) and dementia that begin when people are 50 to 60 years old.

Huntington's disease. This hereditary disorder is caused by a faulty gene for a protein called huntingtin. Symptoms begin around age 30 or 40 years and include abnormal and uncontrollable movements called chorea, as well as gait changes and lack of coordination. Huntington's disease may affect a person's judgment, memory, and other cognitive functions. As the disease progresses, these cognitive problems worsen, and motor difficulties lead to complete loss of ability for self-care. Children of people with Huntington's have a 50 percent chance of having the disorder.

Secondary dementias. These dementias occur in people with disorders that damage brain tissue. Such disorders may include multiple sclerosis; meningitis; encephalitis; and Wilson's disease, in which excessive amounts of copper build up to cause brain damage. In rare cases, people with brain tumors may develop dementia because of damage to their brain circuits or a buildup of pressure inside the skull. Symptoms may include changes in personality, psychotic episodes, or problems with speech, language, thinking, and memory.

Head Injury

Chronic traumatic encephalopathy, initially known as dementia pugilistica, is caused by repeated traumatic brain injury (TBI), such as in boxers or in people who suffered multiple concussions while playing a contact sport. People with this condition often develop poor coordination, slurred speech, and other symptoms similar to those seen in Parkinson's disease, along with dementia, 20 years or more after the TBI events. This form of dementia also is characterized by brain atrophy and widespread deposits of tau aggregates. In some individuals, even just 5 to 10 years beyond the TBI events, behavioral and mood changes may occur. Dementia may not yet be present and the

brain may not have atrophied, but small focal deposits of tau are seen in the brain at autopsy.

Subdural hematoma, or bleeding between the brain's surface and its outer covering (the dura), is common in the elderly after a fall. Subdural hematomas can cause dementia-like symptoms and changes in mental function. With treatment, some symptoms can be reversed.

Reversible Dementias

Many conditions that cause dementia can be reversed with the appropriate treatment.

- Cerebral vasculitis, an inflammation and necrosis (tissue death) of blood vessel walls, can cause a form of dementia that may resolve when the person is treated with immune suppressants.
- Some studies have shown that people with depression are at increased risk of developing dementia. Severe depression can cause dementia and can be treated.
- Infections can cause confusion or delirium due to related fever or other side effects associated with the body's response to a foreign entity.
- Metabolic disorders of the nervous system, such as mitochondrial disorders, leukodystrophies, and lysosomal storage diseases, can lead to dementia.
- Metabolic problems and endocrine abnormalities such as thyroid problems, low blood sugar levels (called hypoglycemia), and low or high levels of sodium or calcium also may also cause dementia.
- Normal pressure hydrocephalus is an abnormal buildup of cerebro-spinal fluid in the brain. Elderly individuals with the condition usually have trouble with walking and bladder control before onset

of dementia. Normal pressure hydrocephalus can be treated or even reversed by implanting a shunt system to divert fluid from the brain.

- Nutritional deficiencies of vitamin B_1 (thiamine), caused by chronic alcoholism, and vitamin B_{12} deficiencies can be reversed with treatment.
- Paraneoplastic syndromes (a group of symptoms that may develop when substances released by some cancer cells disrupt the normal function of surrounding cells and tissue) can cause symptoms that resemble dementia. Such symptoms generally occur in people with cancer when the body's immune response to the cancer also ends up targeting proteins in the central nervous system. In many cases, the neurologic condition occurs before the cancer is detected. Circulating antibodies against brain proteins are common in both neurologic and cancer conditions.
- Side effects of medications or drug combinations may cause dementias that arise quickly or develop slowly over time.

Environmental Factors

Environmental factors may play a role in the development of certain types of dementia. This relationship is complex, however, since a person may carry genetic mutations that influence his or her response to environmental factors. Examples of environmental factors include:

Anoxia. Anoxia and a related condition, hypoxia, are terms often used to describe a state in which there is a curtailed supply of oxygen to an organ's tissues. Anoxia and hypoxia can lead to the loss of neurons and diffuse brain injury. Characteristics of the resulting dementia include confusion, personality changes, hallucinations, or memory loss. This type of dementia commonly occurs in people who survive cardiac arrest.

Poisoning. Exposure to lead, mercury, other heavy metals, or poisonous substances can lead to symptoms of dementia. These symptoms may or may not resolve after treatment, depending on how severely the brain is damaged.

Substance abuse. People who have abused substances such as alcohol and recreational drugs sometimes display signs of dementia even after the substance abuse has stopped. This condition is known as substance-induced persisting dementia.

Infectious Disease

HIV-associated dementia (HAD) can occur in people who are positive for the human immunodeficiency virus, the virus that causes AIDS. HAD damages the brain's white matter and leads to a type of dementia associated with memory problems, social withdrawal, and trouble concentrating. People with HAD may develop movement problems as well. The incidence of HAD has dropped dramatically with the availability of effective antiviral therapies for managing the underlying HIV infection.

Risk Factors for Dementia

The following risk factors can increase a person's chance of developing one or more kinds of dementia. Some of these factors can be modified, while others cannot.

- **Age.** The risk goes up with advanced age.
- **Alcohol use.** Most studies suggest that drinking large amounts of alcohol increases the risk of dementia, while drinking a moderate amount may be protective.
- **Atherosclerosis.** The accumulation of fats and cholesterol in the lining of arteries, coupled with an inflammatory process that leads to a thickening of the vessel walls (known as atherosclerosis), can hinder blood from getting to the brain, which can lead to stroke or another brain injury. For example, high levels of low-density lipoprotein (LDL, or "bad" cholesterol) can raise the risk for vascular dementia. High LDL levels also have been linked to AD.
- **Diabetes.** People with diabetes appear to have a higher risk for dementia, although the evidence for this association is modest. Poorly controlled diabetes, however, is a well-proven risk factor for stroke and cardiovascular disease-related events, which in turn increase the risk for vascular dementia.
- **Down syndrome.** Many people with Down syndrome develop early-onset AD, with signs of dementia by the time they reach middle age.
- **Genetics.** One's likelihood of developing a genetically linked form of dementia increases when more than one family member has the disorder. But in some cases, such as with CADASIL, having just

one parent who carries a mutation increases the risk of inheriting the condition. In other instances, genetic mutations may underlie dementias in specific populations. For example, a mutation of the gene TREM2 has been found to be common among people with a form of very early onset frontotemporal dementia that runs in Turkish families.

- **Hypertension.** High blood pressure has been linked to cognitive decline, stroke, and types of dementia that affect the white matter regions of the brain.
- **Mental illness.** Depression has been associated with mild mental impairment and cognitive function decline.
- **Smoking.** Smokers are prone to diseases that slow or stop blood from getting to the brain.

Diagnosis

Doctors first assess whether the individual has an underlying treatable condition such as depression, abnormal thyroid function, drug-induced encephalopathy, normal pressure hydrocephalus, or vitamin B_{12} deficiency. Early diagnosis is important, as some causes for symptoms can be treated. In many cases, the specific type of dementia that a person has may not be confirmed until after the person has died and the brain is examined.

An assessment generally includes:

- **Patient history.** Typical questions about a person's medical and family history might include asking about whether dementia runs in the family, how and when symptoms began, and if the person is taking certain medications that might cause or exacerbate symptoms.
- **Physical exam.** Measuring blood pressure and other vital signs may help physicians detect conditions that might cause or occur with dementia. Such conditions may be treatable.
- **Neurological evaluations.** Assessing balance, sensory function, reflexes, vision, eye movements, and other functions helps identify signs of conditions that may affect the diagnosis or are treatable with drugs. Doctors also might use an electroencephalogram, a test that records patterns of electrical activity in the brain, to check for abnormal electrical brain activity.

The following procedures also may be used when diagnosing dementia:

- **Brain scans.** These tests can identify strokes, tumors, and other problems that can cause dementia. Scans also identify changes in the

brain's structure and function. The most common scans are computed tomographic (CT) scans and magnetic resonance imaging (MRI). CT scans use X-rays to produce images of the brain and other organs. MRI scans use a computer, magnetic fields, and radio waves to produce detailed images of body structures, including tissues, organs, bones, and nerves.

Other types of scans let doctors watch the brain as it functions. Two of these tests are single photon-emission computed tomography, which can be used to measure blood flow to the brain, and positron emission tomography (PET), which uses radioactive isotopes to provide pictures of brain activity. These scans are used to look for patterns of altered brain activity that are common in dementia. Researchers also use PET imaging with compounds that bind to beta-amyloid to detect levels of the protein, a hallmark of AD, in the living brain.

- **Cognitive and neuropsychological tests.** These tests measure memory, language skills, math skills, and other abilities related to mental functioning. For example, people with AD often show impairment in problem-solving, memory, and the ability to perform once-automatic tasks.
- **Laboratory tests.** Many tests help rule out other conditions. They include measuring levels of sodium and other electrolytes in the blood, a complete blood count, a blood sugar test, urine analysis, a check of vitamin B_{12} levels, cerebrospinal fluid analysis, drug and alcohol tests, and an analysis of thyroid function.
- **Presymptomatic tests.** Some dementias are associated with a known gene defect. In these cases, a genetic test could help people know if they are at risk for dementia. People should talk with family members, their primary health care professional, and a genetic counselor before getting tested.
- **Psychiatric evaluation.** This will help determine if depression or another mental health condition is causing or contributing to a person's symptoms.

Treatment

Some dementias are treatable. However, therapies to stop or slow common neurodegenerative diseases such as AD have largely been unsuccessful, though some drugs are available to manage certain symptoms.

Most drugs for dementia are used to treat symptoms in AD. One class of drugs, called cholinesterase inhibitors, includes donepezil, rivastigmine, and galantamine. These drugs can temporarily improve or stabilize memory and thinking skills in some people by increasing the activity of the cholinergic brain network. The drug memantine is in another class of medications called NMDA receptor agonists, which prevents declines in learning and memory. NMDA receptor agonists work by regulating the activity of the neurotransmitter glutamate. When glutamate activity levels are excessive, neurons may die. Memantine may be combined with a cholinesterase inhibitor for added benefits. These drugs are sometimes used to treat other dementias as well. None of these drugs can stop or reverse the course of the disease.

- **Creutzfeldt-Jakob disease.** There are no treatments to cure or control CJD. Management focuses on reducing symptoms and making people comfortable.
- **Dementia with Lewy bodies.** Drugs available for managing DLB are aimed at relieving symptoms such as stiffness, hallucinations, and delusions. However, many of the agents for treating the physical symptoms, particularly antipsychotics, can make the mental health symptoms worse. Conversely, drugs used to treat mental health

symptoms can exacerbate physical symptoms. Studies suggest that AD drugs may benefit people with DLB.

- **Frontotemporal disorders.** There are no medications approved to treat or prevent FTD and most other types of progressive dementia. Sedatives, antidepressants, and other drugs used to treat Parkinson's and Alzheimer's symptoms may help manage certain symptoms and behavioral problems associated with the disorders.
- **Parkinson's disease dementia.** Some studies suggest that the cholinesterase inhibitors used in people with AD might improve cognitive, behavioral, and psychotic symptoms in people with Parkinson's disease dementia. The U.S. Food and Drug Administration has approved one Alzheimer's drug, rivastigmine, to treat cognitive symptoms in PDD.
- **Vascular dementia.** This type of dementia is often managed with drugs to prevent strokes. The aim is to reduce the risk of additional brain damage. Some studies suggest that drugs that improve memory in AD might benefit people with early vascular dementia. Most of the modifiable risk factors that influence development of vascular dementia and VCI are the same risk factors for cerebrovascular disease, such as hypertension, atrial fibrillation, diabetes, and high cholesterol. Interventions that address these risk factors may be incorporated into the management of vascular dementia.

Current Research

In 2012, the President announced the National Plan to Address Alzheimer's Disease, a national effort to expand research in Alzheimer's and related dementias prevention and treatment and to move the most promising drugs from discovery into clinical trials. The Plan aims to prevent and effectively treat Alzheimer's and related dementias by 2025. Its foundation is the 2011 National Alzheimer's Project Act (NAPA), which was developed to create and maintain a national strategy to overcome the disease. The National Plan calls for increased federal funding for AD research, support for those affected by AD and their families, increased public awareness about AD, and improved data collection and analysis to better understand the impact of AD on people with the disease, families, and the health and long-term care systems. These goals also apply to AD-related dementias, including dementia with Lewy bodies as well as frontotemporal, mixed (characteristics of more than one type of dementia occur simultaneously), and vascular dementias. For more information, see *http://aspe.hhs.gov/daltcp/napa/NatlPlan.pdf.*

The National Institute of Neurological Disorders and Stroke (NINDS), a component of NIH, is the leading federal funder of research on nervous system disorders. Another NIH Institute, the National Institute on Aging (NIA), is the leading federal funder of research on AD. Together, these Institutes are world leaders in supporting research on the dementias, including Lewy body dementia, frontotemporal disorders, and vascular dementia.

Although scientists have some understanding of these dementias and the mechanisms involved, ongoing research may lead to new ways to diagnose,

treat, or perhaps prevent or block disease development. Current areas of research include:

Clinical studies. Clinical studies offer an opportunity to help researchers find better ways to safely detect, treat, or prevent dementias. Various NIH Institutes support clinical studies on AD and related dementias at the NIH research campus in Bethesda, MD, and at medical research centers throughout the U.S. For information about participating in clinical studies for AD, related dementias, and other disorders, visit "NIH Clinical Research Trials and You" at *www.nih.gov/health/clinicaltrials.* For a list of AD clinical trials and studies, see *www.nia.nih.gov/alzheimers/clinical-trials.* For a comprehensive list of all trials, go to *www.clinicaltrials.gov.*

Drugs. A number of agents that might slow the progression of AD and other dementias are in various stages of testing.

The NIA-supported Alzheimer's Disease Cooperative Study (ADCS) *(www.adcs.org)* is a consortium of academic medical centers and clinics set up by NIH in 1991 to collaborate on the development of promising Alzheimer's treatments and diagnostic tools.

In the latest round of studies, the ADCS will test drug and exercise interventions in people in the early stages of the disease, examine a medication to reduce agitation in people with Alzheimer's dementia, and test a cutting-edge approach to speed testing of drugs in clinical trials. Because Alzheimer's-related brain changes begin years before symptoms appear, the A4 (Anti-amyloid Treatment in Asymptomatic Alzheimer's Disease) trial is testing a promising therapy in the early stages of the disorder. This secondary prevention trial will test an amyloid-clearing drug in the symptom-free stage of the disease in 1,000 cognitively healthy older volunteers whose brain scans show abnormal levels of amyloid accumulation. Another of the newly funded ADCS drug trials is the

Prazosin for Treating Agitation trial, which will test the use of the generic drug prazosin as a treatment for agitation that may also be well-tolerated in frail and elderly people.

Exercise. Researchers are assessing the effectiveness of a supervised aerobic exercise program to enhance general cognition in adults with age-related cognitive decline. They predict that greater cognitive gains will be made by individuals with more fitness gains. Another study will determine if exercise prevents memory loss from getting worse, and if it improves daily functioning and attitudes of those with probable AD. Researchers also hope to gain a better understanding of the effects of exercise and cognitive training on improving brain function in healthy older adults who may be at risk for developing AD.

Genetics. Several genes—most notably ApoE and the gene for tau (MAPT)—have been implicated in AD and other forms of dementia. Many dementia-related disorders share genetic and other characteristics of AD. Some families share a particular genetic mutation that causes dementia. Researchers are using samples of a person's genetic material, or genome, to identify genes that may be responsible for the development of dementia and AD. For example, NIH-funded researchers recently examined ApoE's role in the development of late-onset AD and found that one of the three forms of the ApoE gene triggers an inflammatory reaction and damages the blood vessels that feed the brain. Other researchers have identified a gene variant of TREM2 that is involved with a form of frontotemporal dementia that runs in families. Additional research may identify novel genes involved with FTD and other neurodegenerative diseases, perhaps leading to therapeutic approaches where delivery of normal genes would improve or restore normal brain function.

Imaging. Clinical imaging may help researchers better understand changes in the brains of people with dementia, as well as help diagnose these disorders. Magnetic resonance imaging may reveal structural and functional differences in the brains of individuals with Parkinson's disease dementia and AD and identify small vessel disease. PET scanning uses ligands—radioactive molecules that bind to proteins to show chemical functions of tissues and organs in the body—to help produce images of brain activity. Scientists funded by NIA are testing new PET ligands that bind to beta-amyloid for early detection of Alzheimer's-type pathology and cognitive decline. Studies of PET ligands that bind to aggregates of tau are ongoing in people with very early-stage AD.

International efforts. The International Alzheimer's Disease Research Portfolio (IADRP) helps individuals learn about AD research at public and private organizations in the U.S. and abroad. It also helps organizations leverage resources and avoid duplication of effort. The Common Alzheimer's Disease Research Ontology—a classification system that allows organizations to integrate and compare research portfolios—was developed by NIA, NIH, and the Alzheimer's Association. For more information about IADRP, see *http://iadrp.nia.nih.gov/cadro-web/about*.

Proteins. One feature that several major dementias have in common is an excess in the brain of certain proteins or protein fragments that have taken abnormal forms thought to be toxic to brain cells. NIH-funded research projects are aimed at better understanding the toxic effects of protein buildup and how it is related to the development of AD and related dementias. Some of these protein abnormalities can be detected in cerebrospinal fluid.

For example, an abnormally high accumulation of beta-amyloid protein in the brain is a hallmark of AD. NINDS-funded researchers are determining which neural pathways are affected by beta-amyloid and contribute to the development of Alzheimer's pathology and symptoms. NINDS funding also led to a genetically engineered rat model of AD that has the full array of brain changes associated with the human disease and may be used to better define causes and effects of AD related to beta-amyloid accumulation. Funding also was provided by NIA, the National Institute of Mental Health (also part of NIH), and other organizations.

In FTD, AD, and other neurodegenerative diseases, the protein tau collects in abnormal tangled masses of filaments that disrupt nerve signaling, cause cell death, and impair cognition. NINDS-funded researchers are determining whether specific forms of tau interfere with nerve cell signaling and decrease memory function. Others are studying how tau pathology spreads from cell to cell. Tau-related investigations are aimed at identifying common mechanisms of FTD, as well as biomarkers (signs that may indicate disease risk and progression, and improve diagnosis) that will speed the development of novel therapeutics for PDD and other forms of dementia.

Similarly, the abnormal accumulation of the protein alpha-synuclein is a hallmark of Parkinson's disease and Lewy body dementia. Scientists hope to identify what causes alpha-synuclein to form abnormal aggregates and become toxic to nerve cells, and to understand why the aggregation is an age-related phenomenon in Parkinson's disease and other synuclein-related disorders.

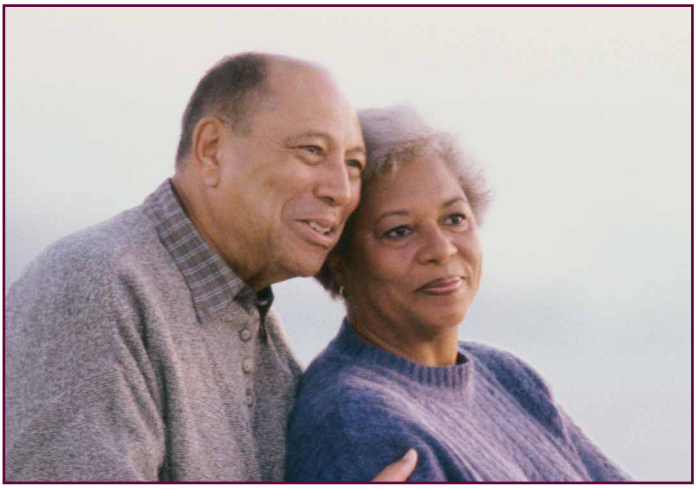
Sleep. The sleep and wakefulness cycle plays an integral, but not well understood, role in many dementias, including dementia with Lewy bodies, AD, prion dementias, and PDD. Sleep studies in individuals during periods of excessive daytime sleepiness and nocturnal sleep can help determine if fluctuations in mental status among people with

DLB are related to excessive daytime sleepiness. Sleep studies also can assess whether declining cognition is predicted by sleep-related and neurobehavioral markers in parkinsonism.

Stem cells. Scientists are exploring various types of cells, including stem cells, to discover nerve cell mechanisms that lead to the initiation and progression of AD and other forms of dementia. Significant research efforts have focused on induced pluripotent stem cells (iPSC), which can be "reprogrammed" from skin cells into any cell type in the body, including nerve cells. NINDS funds three research consortia to develop well-characterized iPSC for amyotrophic lateral sclerosis (ALS), Huntington's disease, and Parkinson's disease. These cells can then be used by the research community to study the effects of mutant genes and misfolded proteins on nerve cell function and health, as well as to test potential drugs and therapies for AD and related dementias.

Conclusion

Currently, there are no cures for the common dementias caused by progressive neurodegeneration, including AD, frontotemporal disorders, and Lewy body dementia. However, some forms of dementia are treatable. A better understanding of dementia disorders, as well as their diagnosis and treatment, will make it possible for affected individuals and their caretakers to live their lives more fully and meet daily challenges. NIH, primarily through research activities funded by NINDS and NIA, continues to make discoveries in the lab, design therapeutic approaches to dementias, and create tools and resources to help speed the development of treatments that can be used in practice. These discoveries may eventually lead to ways to slow disease progression or even cure and prevent the dementias.



Glossary

Alpha-synuclein—a protein that is implicated in abnormal clumps called Lewy bodies, which are seen in the brains of people with Parkinson's disease and some dementias. Disorders in which alpha-synuclein accumulates inside nerve cells are called synucleinopathies.

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

Amyloid—a protein found in the characteristic clumps of tissue (called plaques) that appear in the brains of people with Alzheimer's disease.

Chronic traumatic encephalopathy—a form of dementia caused by repeated traumatic brain injury.

Corticobasal degeneration—a progressive disorder characterized by nerve cell loss and atrophy in multiple areas of the brain.

Dementia—a term for a collection of symptoms that significantly impair thinking and normal activities and relationships.

Dementia with Lewy bodies—a type of Lewy body dementia that is a common form of progressive dementia.

Frontotemporal disorders—a group of dementias characterized by degeneration of nerve cells, especially those in the frontal and temporal lobes of the brain.

HIV-associated dementia—a dementia that results from infection with the human immunodeficiency virus that causes AIDS.

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.

Mixed dementia—dementia in which one form of dementia and another condition or dementia cause damage to the brain, for example, Alzheimer's disease and small vessel disease or vascular dementia.

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

Neurofibrillary tangles—bundles of twisted filaments found in nerve cells in the brains of people with Alzheimer's disease. These tangles are largely made up of a protein called tau.

Parkinson's disease dementia—a secondary dementia that sometimes occurs in people with advanced Parkinson's disease. Many people with Parkinson's have the amyloid plaques and neurofibrillary tangles found in Alzheimer's disease, but it is not clear if the diseases are linked.

Tau—a protein that helps the functioning of microtubules, which are part of the cell's structural support and help deliver substances throughout the cell. In Alzheimer's disease, tau twists into filaments that become tangles. Disorders associated with an accumulation of tau, such as frontotemporal dementia, are called tauopathies.

Vascular dementia—a type of dementia caused by brain damage from cerebrovascular or cardiovascular problems, usually strokes.

Resources

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
1-800-352-9424 (toll-free)
www.ninds.nih.gov

Information on dementia is also available from the following organizations:

Alzheimer's Disease Education and Referral (ADEAR) Center National Institute on Aging

P.O. Box 8250
Silver Spring, MD 20907-8250
1-800-438-4380 (toll-free)
www.nia.nih.gov/alzheimers

Alzheimer's Association

225 North Michigan Avenue, Floor 17
Chicago, IL 60601-7633
1-800-272-3900 (toll-free, 24-hour helpline)
1-312-335-5886 (TDD)
www.alz.org

Alzheimer's Foundation of America

322 Eighth Avenue, 7th Floor
New York, NY 10001
1-866-232-8484 (toll-free)
www.alzfdn.org

Alzheimer's Drug Discovery Foundation
57 West 57th Street, Suite 904
New York, NY 10019
1-212-901-8000
www.alzdiscovery.org

Association for Frontotemporal Degeneration
Radnor Station Building #2, Suite 320
290 King of Prussia Road
Radnor, PA 19087
1-866-507-7222 (toll-free)
www.theaftd.org

BrightFocus Foundation
22512 Gateway Center Drive
Clarksburg, MD 20871
1-800-437-2423 (toll-free)
www.brightfocus.org/alzheimers

John Douglas French Alzheimer's Foundation
11620 Wilshire Boulevard, Suite 270
Los Angeles, CA 90025
1-310-445-4650
www.jdfaf.org

Lewy Body Dementia Association
912 Killian Hill Road, S.W.
Lilburn, GA 30047
1-404-935-6444
1-800-539-9767 (toll-free LBD Caregiver Link)
www.lbda.org

National Institute of Mental Health

6001 Executive Boulevard, Room 8184
Bethesda, MD 20892-9663
1-866-415-8051 (toll-free)
1-301-443-8431 (TTY)
www.nimh.nih.gov

National Organization for Rare Disorders

55 Kenosia Avenue
Danbury, CT 06810
1-800-999-NORD (1-800-999-6673) (toll-free)
www.rarediseases.org

The Dementias: Hope Through Research was jointly produced by the National Institute of Neurological Disorders and Stroke and the National Institute on Aging, both part of the National Institutes of Health.

Also available from NIA are publications and information about Alzheimer's disease as well as the booklets *Frontotemporal Disorders: Information for Patients, Families, and Caregivers* and *Lewy Body Dementia: Information for Patients, Families, and Professionals.*

For additional copies of this publication or further information, contact:

National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov
1-800-352-9424

National Institute on Aging
Alzheimer's Disease Education and Referral Center
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1-800-438-4380

NIH Publication No. 13-2252
September 2013