

ALZHEIMER'S DISEASE – WHAT IS IT?

Alzheimer's disease is a progressive brain disorder that damages and eventually destroys brain cells, leading to loss of memory, thinking and other brain functions. Alzheimer's is not a part of normal aging, but results from a complex pattern of abnormal changes. It usually develops slowly and gradually gets worse as more brain cells wither and die. Ultimately, Alzheimer's is fatal, and currently, there is no cure.

But today, there are more potential treatments in development than ever before as a result of the worldwide research effort to conquer this devastating disease. The CART Fund, Inc. is helping to move this research initiative forward by funding scientists who are searching for more answers about the cause of Alzheimer's.

Alzheimer's disease is the most common type of *dementia*, a general term used to describe various diseases and conditions that damage brain cells. Alzheimer's disease accounts for 50 to 80 percent of dementia cases. Other types include vascular dementia, mixed dementia, dementia with Lewy bodies and frontotemporal dementia.

Scientists have identified several Hallmark Alzheimer brain abnormalities, including:

Plaques, microscopic clumps of a protein called beta-amyloid peptide

Tangles, twisted microscopic strands of the protein tau (rhymes with "wow")

Loss of connections among brain cells responsible for memory, learning and communication. These connections, or synapses, transmit information from cell to cell.

Inflammation resulting from the brain's effort to fend off the lethal effects of the other changes under way

Eventual death of brain cells and severe tissue shrinkage

All these processes have a devastating impact on the brain, and over time, the brain shrinks dramatically, affecting nearly all its functions.

The most common early symptom is difficulty remembering newly learned information because Alzheimer changes typically begin in the part of the brain that affects learning.

As Alzheimer's advances through the brain it leads to increasingly severe symptoms, including disorientation, mood and behavior changes; deepening confusion about events, time and place; unfounded suspicions about family, friends and professional caregivers; more serious memory loss and behavior changes; and difficulty speaking, swallowing and walking.

Plaques and tangles tend to spread through the cortex in a predictable pattern as Alzheimer's disease progresses.

The rate of progression varies greatly. People with Alzheimer's live an average of eight years, but some people may survive up to 20 years. The course of the disease depends in part on age at diagnosis and whether a person has other health conditions.



THE CART FUND, Inc

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Coins for Alzheimer's Research Trust (The CART Fund, Inc.) is a joint project of Rotary International Districts 6900, 6910, 6920, 7670, 7680, 7690, 7710, 7720, 7730, and 7770; and the more than 600 Rotary Clubs in North Carolina, South Carolina, and Georgia.

*Credits: Our thanks to **The Alzheimer's Association** for much of the material contained in this document*

There are **10 warning signs of Alzheimer's disease.**

Along with the advice of a doctor, these signs are critical to detecting Alzheimer's.

If you or someone you know is experiencing any of the 10 signs, please see a doctor. Early diagnosis gives you a chance to seek treatment and plan for the future.

1. Memory loss that disrupts daily life

One of the most common signs of Alzheimer's is memory loss, especially forgetting recently learned information. Others include forgetting important dates or events; asking for the same information over and over; relying on memory aides (e.g., reminder notes or electronic devices) or family members for things they used to handle on their own.

What's a typical age-related change? Sometimes forgetting names or appointments, but remembering them later.

2. Challenges in planning or solving problems

Some people may experience changes in their ability to develop and follow a plan or work with numbers. They may have trouble following a familiar recipe or keeping track of monthly bills. They may have difficulty concentrating and take much longer to do things than they did before.

What's a typical age-related change? Making occasional errors when balancing a checkbook

3. Difficulty completing familiar tasks at home, at work or at leisure

People with Alzheimer's often find it hard to complete daily tasks. Sometimes, people may have trouble driving to a familiar location, managing a budget at work or remembering the rules of a favorite game.

What's a typical age-related change? Occasionally needing help to use the settings on a microwave or to record a television show.

4. Confusion with time or place

People with Alzheimer's can lose track of dates, seasons and the passage of time. They may have trouble understanding something if it is not happening immediately. Sometimes they may forget where they are or how they got there.

What's a typical age-related change? Getting confused about the day of the week but figuring it out later.

5. Trouble understanding visual images and spatial relationships

For some people, having vision problems is a sign of Alzheimer's. They may have difficulty reading, judging distance and determining color or contrast. In terms of perception, they may pass a mirror and think someone else is in the room. They may not realize they are the person in the mirror.

What's a typical age-related change? Vision changes related to cataracts.

6. New problems with words in speaking or writing

People with Alzheimer's may have trouble following or joining a conversation. They may stop in the middle of a conversation and have no idea how to continue or they may repeat themselves. They may struggle with vocabulary, have problems finding the right word or call things by the wrong name (e.g., calling a "watch" a "hand-clock").

What's a typical age-related change? Sometimes having trouble finding the right word.

7. Misplacing things and losing the ability to retrace steps

A person with Alzheimer's disease may put things in unusual places. They may lose things and be unable to go back over their steps to find them again. Sometimes, they may accuse others of stealing. This may occur more frequently over time.

What's a typical age-related change? Misplacing things from time to time, such as a pair of glasses or the remote control.

8. Decreased or poor judgment

People with Alzheimer's may experience changes in judgment or decision-making. For example, they may use poor judgment when dealing with money, giving large amounts to telemarketers. They may pay less attention to grooming or keeping themselves clean.

What's a typical age-related change? Making a bad decision once in a while.

9. Withdrawal from work or social activities

A person with Alzheimer's may start to remove themselves from hobbies, social activities, work projects or sports. They may have trouble keeping up with a favorite sports team or remembering how to complete a favorite hobby. They may also avoid being social because of the changes they have experienced.

What's a typical age-related change? Sometimes feeling weary of work, family and social obligations.

10. Changes in mood and personality

The mood and personalities of people with Alzheimer's can change. They can become confused, suspicious, depressed, fearful or anxious. They may be easily upset at home, at work, with friends or in places where they are out of their comfort zone.

What's a typical age-related change? Developing very specific ways of doing things and becoming irritable when a routine is disrupted.

The difference between Alzheimer's and typical age-related changes

Signs of Alzheimer's

Poor judgment and decision-making

Inability to manage a budget

Losing track of the date or season

Difficulty having a conversation

Misplacing things and being unable to retrace steps to find them

Typical Age-related changes

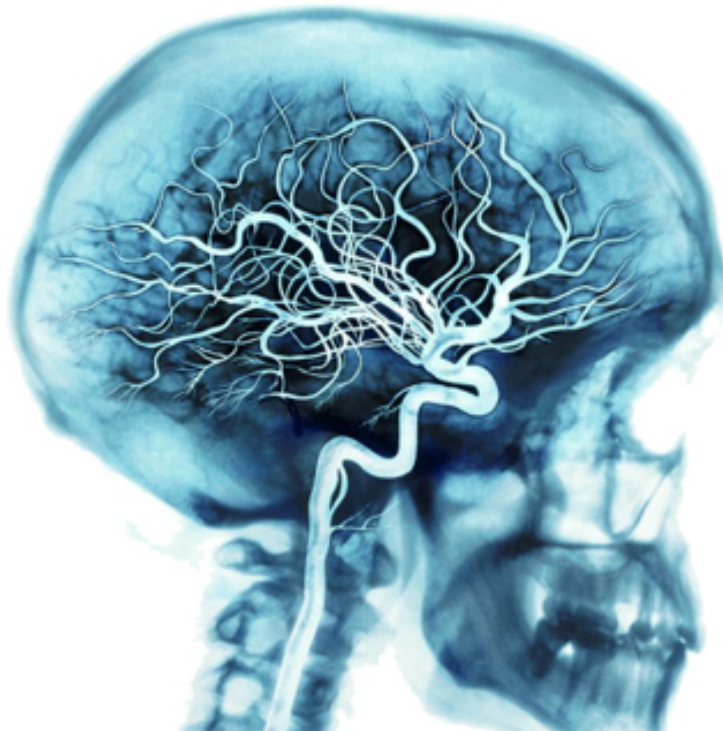
Making a bad decision once in a while

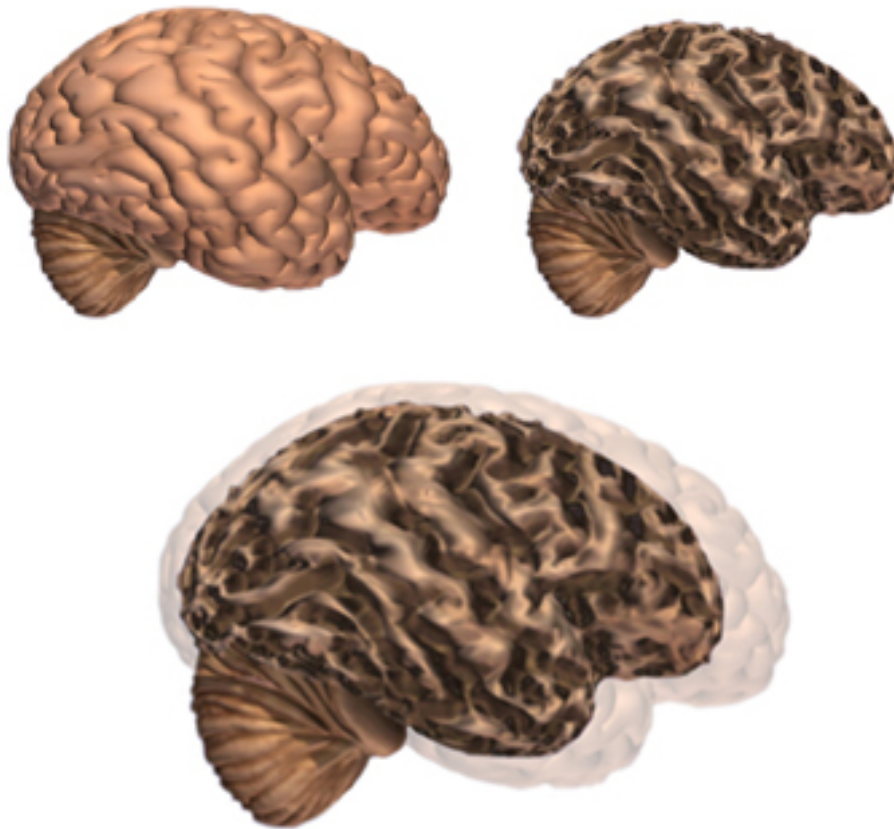
Missing a monthly payment

Forgetting which day it is & remembering later

Sometimes forgetting which word to use

Losing things from time to time



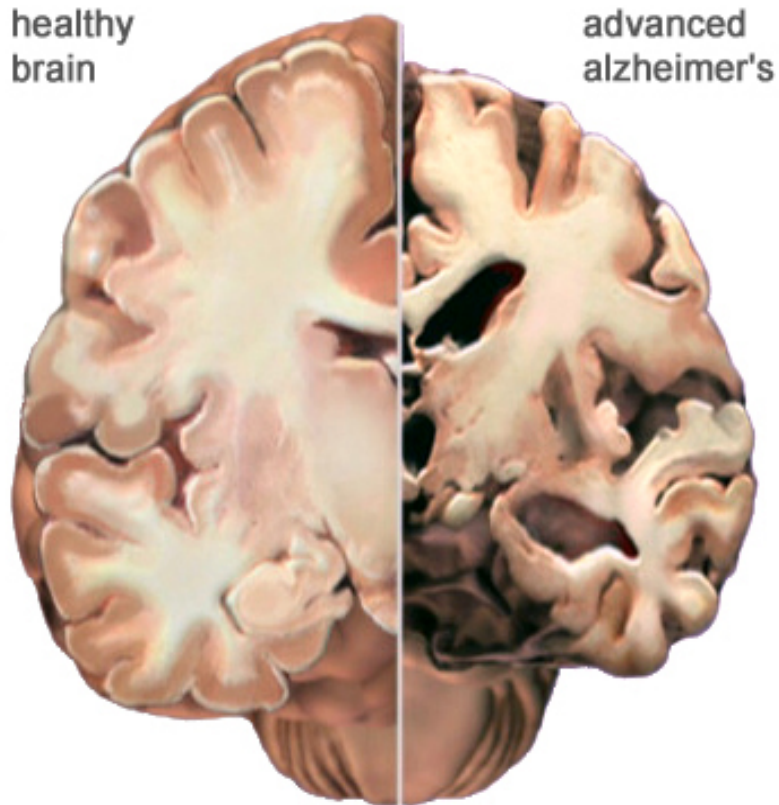


Alzheimer's disease leads to nerve cell death and tissue loss throughout the brain.
Over time, the brain shrinks dramatically, affecting nearly all its functions.

These images show:

- **A brain without the disease**
- **A brain with advanced Alzheimer's**
- **How the two brains compare**

ALZHEIMER'S CHANGES THE WHOLE BRAIN

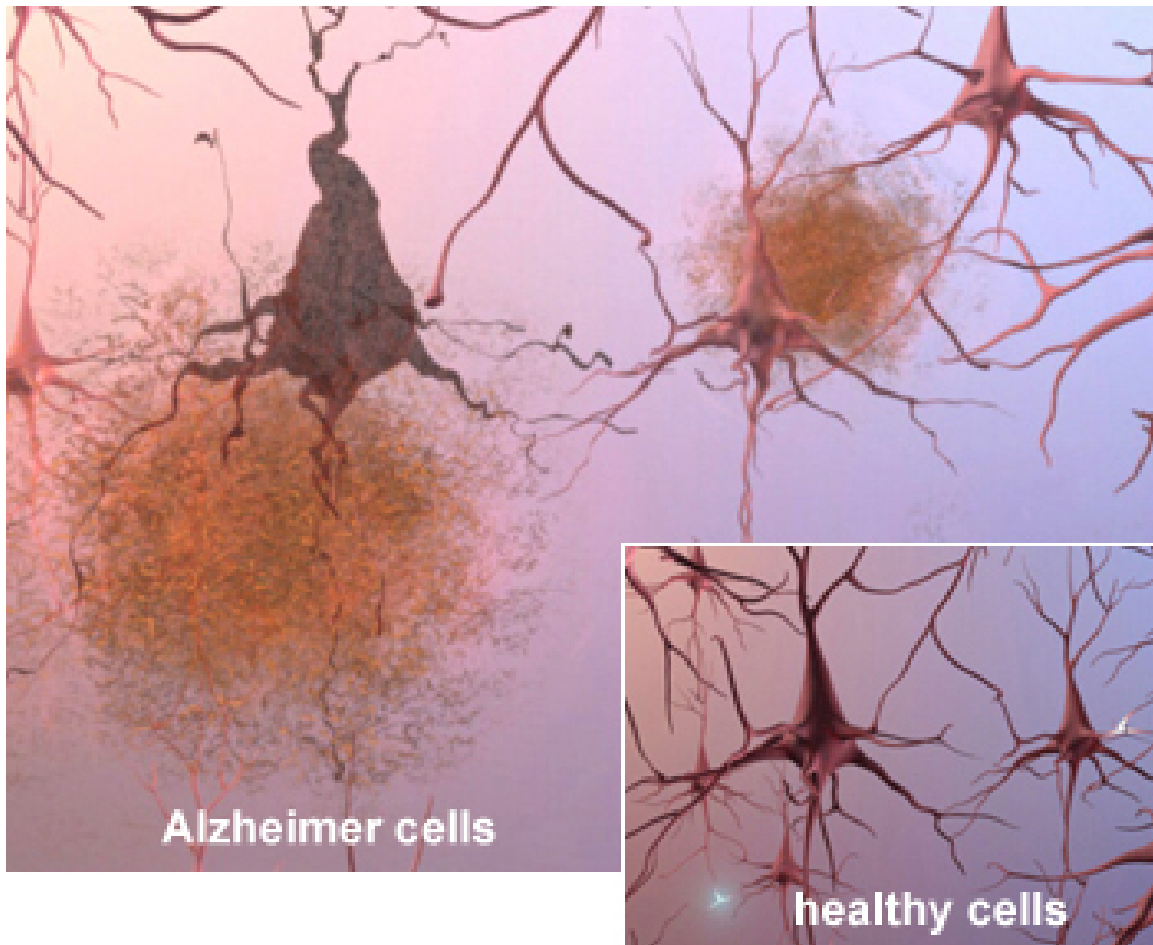


Here is another view of how massive cell loss changes the whole brain in advanced Alzheimer's disease. This slide shows a crosswise "slice" through the middle of the brain between the ears.

In the Alzheimer brain:

- The **cortex shrivels up**, damaging areas involved in thinking, planning and remembering.
- Shrinkage is especially severe in the **hippocampus**, an area of the cortex that plays a key role in formation of new memories.
- **Ventricles** (fluid-filled spaces within the brain) grow larger.

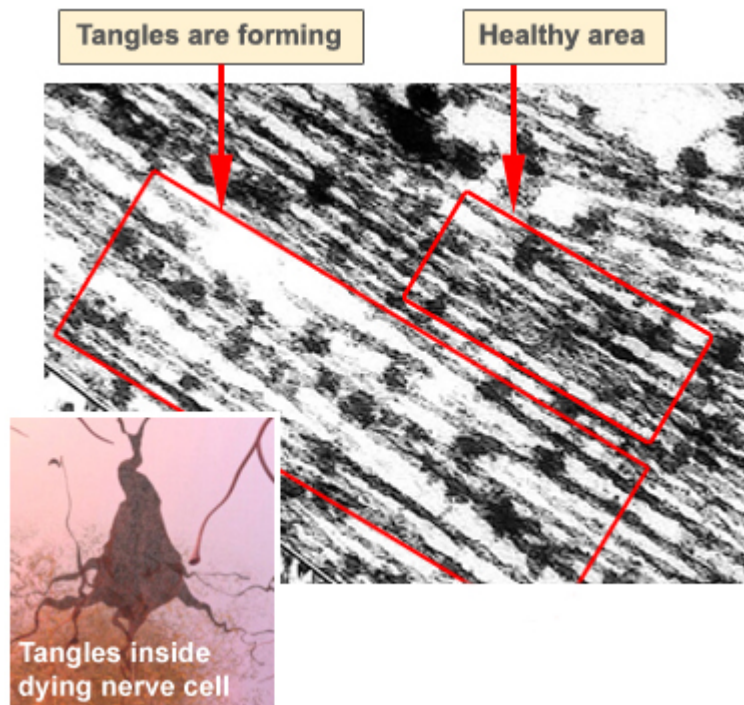
Under the microscope



Scientists can also see the terrible effects of Alzheimer's disease when they look at brain tissue under the microscope:

- **Alzheimer tissue** has many fewer nerve cells and synapses than a healthy brain.
- **Plaques**, abnormal clusters of protein fragments, build up between nerve cells.
- **Dead and dying nerve cells contain tangles**, which are made up of twisted strands of another protein.

Scientists are not absolutely sure what causes cell death and tissue loss in the Alzheimer brain, but plaques and tangles are prime suspects.



Tangles destroy a vital cell transport system made of proteins. This electron microscope picture shows a cell with some healthy areas and other areas where tangles are forming.

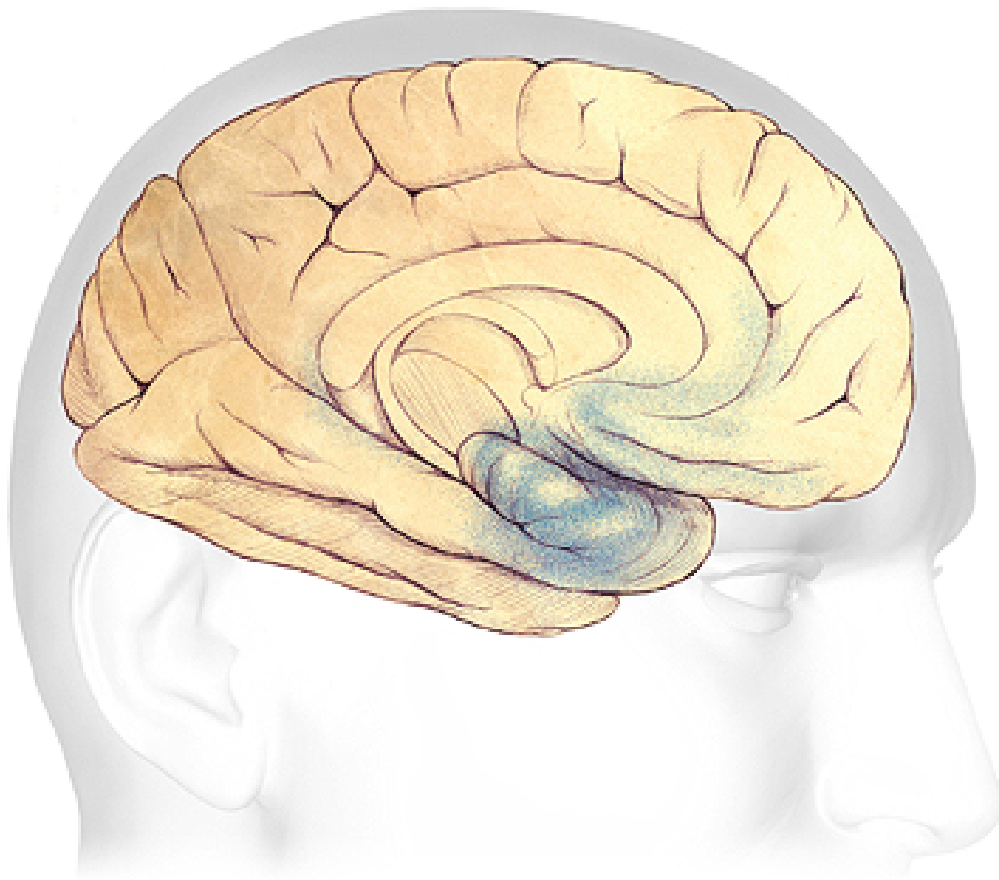
In healthy areas:

- The transport system is **organized in orderly parallel strands** somewhat like railroad tracks. Food molecules, cell parts and other key materials travel along the “tracks.”
- A protein called **tau** (rhymes with wow) helps the tracks stay straight.

In areas where tangles are forming:

- **Tau collapses into twisted strands called tangles.**
- The tracks can no longer stay straight. They **fall apart and disintegrate.**
- Nutrients and other essential supplies can no longer move through the cells, which eventually die.

More about Tangles

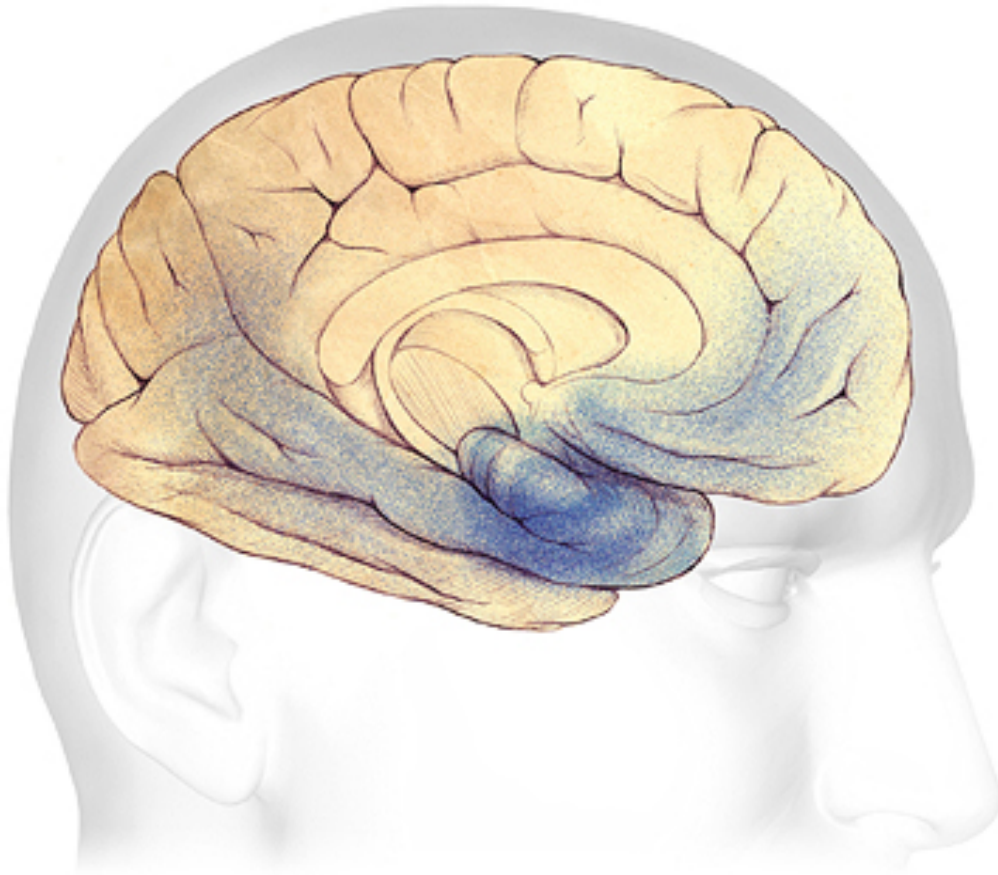


EARLY STAGE ALZHEIMER'S

In the earliest stages, before symptoms can be detected with current tests, plaques and tangles begin to form in brain areas involved in:

- **Learning and memory**
- **Thinking and planning**

[Changes may begin 20 or more years before diagnosis]



MILD TO MODERATE ALZHEIMER'S

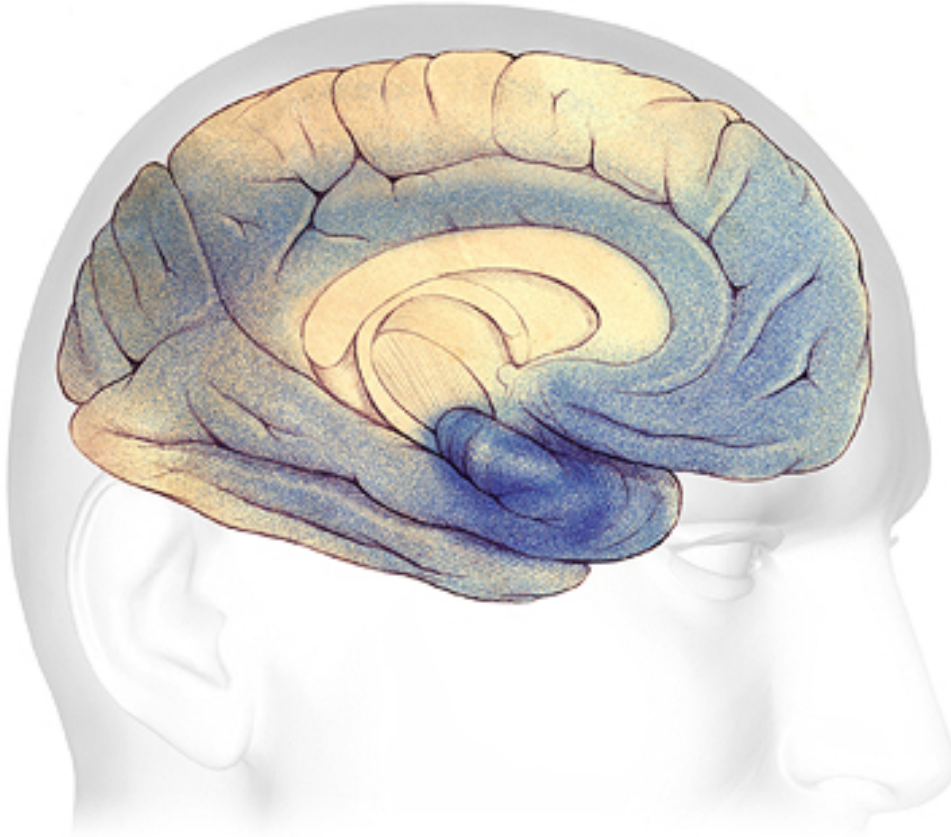
In mild to moderate stages, brain regions important in **memory** and **thinking and planning** develop more plaques and tangles than were present in early stages. As a result, individuals develop problems with memory or thinking serious enough to interfere with work or social life. They may also get confused and have trouble handling money, expressing themselves and organizing their thoughts. Many people with Alzheimer's are first diagnosed in these stages.

Plaques and tangles also spread to areas involved in:

Speaking and understanding speech

[This stage generally may last from 2 to 10 years]

Severe Alzheimer's disease



In advanced Alzheimer's disease, most of the cortex is seriously damaged. The brain shrinks dramatically due to widespread cell death. Individuals lose their ability to communicate, to recognize family and loved ones and to care for themselves.

[This stage generally last from 1 to 5 years; and is always fatal in the end.]

The Search for Causes

While scientists know Alzheimer's disease involves progressive brain cell failure, the reason cells fail isn't clear. Like other chronic conditions, experts believe that Alzheimer's develops as a complex result of multiple factors rather than any one overriding cause. Both age and genetics have been identified as risk factors, but many questions still remain. The discovery of additional risk factors will deepen our understanding of why Alzheimer's develops in some people and not others.

Age and Alzheimer's

Although Alzheimer's is not a normal part of growing older, the greatest risk factor for the disease is increasing age. After age 65, the risk of Alzheimer's doubles every five years. After age 85, the risk reaches nearly 50 percent.

Family history and Alzheimer's

Another Alzheimer risk factor is family history. Research has shown that those who have a parent, brother, sister or children with Alzheimer's are more likely to develop the disease. The risk increases if more than one family member has the illness. When diseases tend to run in families, either heredity (genetics) or environmental factors or both may play a role.

Genetics (heredity) and Alzheimer's

There are two categories of genes that influence whether a person develops a disease: (1) risk genes and (2) deterministic genes. Researchers have identified Alzheimer genes in both categories.

Risk genes increase the likelihood of developing a disease, but do not guarantee it will happen. Researchers have found several genes that increase the risk of Alzheimer's. APOE-e4 is the first risk gene identified, and remains the gene with strongest impact on risk. APOE-e4 is one of three common forms of the APOE gene; the others are APOE-e2 and APOE-e3.

Everyone inherits a copy of some form of APOE from each parent. Those who inherit one copy of APOE-e4 have an increased risk of developing Alzheimer's. Those who inherit two copies have an even higher risk, but not a certainty. In addition to raising risk, APOE-e4 may tend to make symptoms appear at a younger age than usual. Scientists estimate that APOE-e4 is implicated in about 20 percent to 25 percent of Alzheimer cases.

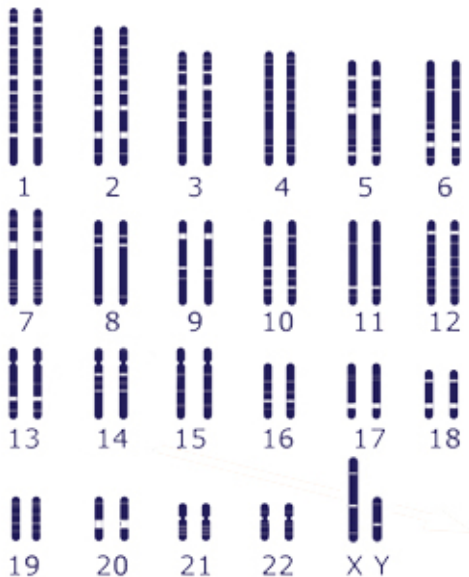
Deterministic genes directly cause a disease, guaranteeing that anyone who inherits one will develop a disorder. Scientists have found rare genes that cause Alzheimer's in only a few hundred extended families worldwide. These genes, which are estimated to account for less than 5 percent of Alzheimer's cases, cause familial early-onset forms in which symptoms usually develop between a person's early 40s and mid-50s.

Although the genes that cause "familial Alzheimer's" are rare, their discovery has provided important clues that help our understanding of Alzheimer's. All of these genes affect processing or production of beta-amyloid, the protein fragments that are the main component of plaques. Beta-amyloid is a prime suspect in the decline and death of brain cells. Several drugs now in development target beta-amyloid as a potential strategy to stop Alzheimer's disease or significantly slow its progression.

Genetic tests are available for both APOE-e4 and the rare genes that directly cause Alzheimer's. However, health professionals do not currently recommend routine genetic testing for Alzheimer's disease. Testing for APOE-e4 is sometimes included as a part of research studies.

A closer look at genes linked to Alzheimer's

The 23 human chromosome pairs contain all of the 30,000 genes that code the biological blueprint for a human being. This illustration highlights the chromosomes containing each of the three genes that cause familial Alzheimer's and the gene with the greatest impact on Alzheimer risk.



23 chromosome pairs

Amyloid precursor protein (APP), discovered in 1987, is the first gene with mutations found to cause an inherited form of Alzheimer's.

Presenilin-1 (PS-1), identified in 1992, is the second gene with mutations found to cause early-onset of Alzheimer's. Variations in this gene are the most common cause of early-onset Alzheimer's.

Presenilin-2 (PS-2), 1993, is the third gene with mutations found to cause early-onset Alzheimer's.

Apolipoprotein E-e4 (APOE4), 1993, is the first gene variation found to increase risk of Alzheimer's and remains the risk gene with the greatest known impact. Having this mutation, however, does not mean that a person will develop the disease.

CART Fund helps by funding basic scientific research

Scientists have developed animal models of Alzheimer's by genetically engineering mice to carry the human genes that cause rare inherited forms of the disease. These mice provide an invaluable means for researchers to study potential new treatments and approaches to prevention. In 1987, The Alzheimer's Association funded the proof-of-concept work that laid the foundation for developing future Alzheimer mouse models. Several CART-funded researchers are using a "triple-transgenic" mouse, widely considered the best animal model currently available, in their research projects.

Current Alzheimer Treatments

Although there is no cure, Alzheimer medications can temporarily slow the worsening of symptoms and improve quality of life for those with Alzheimer's and their caregivers.

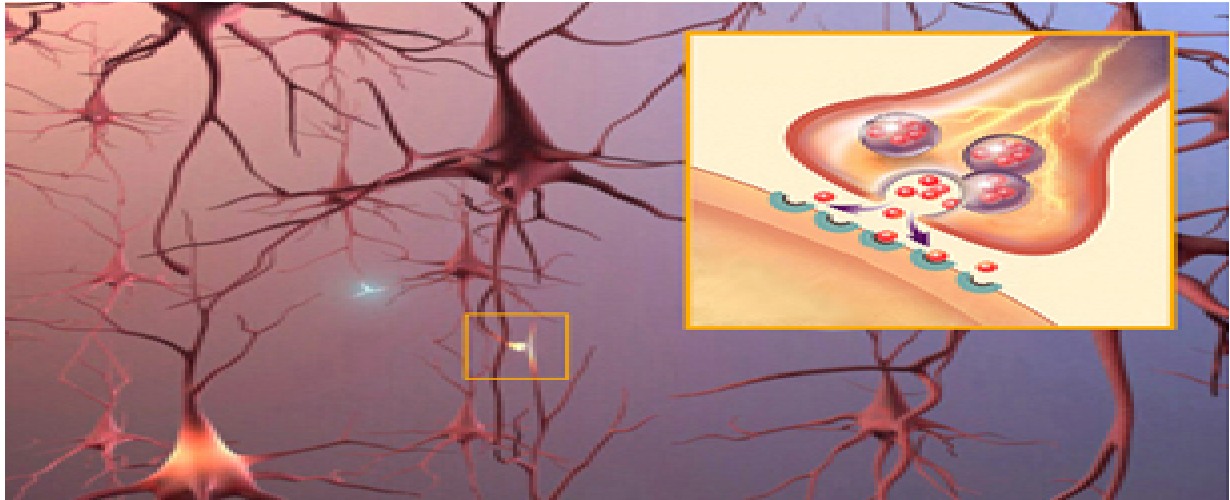
FDA-approved drugs

The U.S. Food and Drug Administration (FDA) has approved five medications (listed below) to treat the symptoms of Alzheimer's disease.

Drug name	Brand name	Approved For	FDA Approved
1. donepezil	Aricept	All stages	1996
2. galantamine	Razadyne	Mild to moderate	2001
3. memantine	Namenda	Moderate to severe	2003
4. rivastigmine	Exelon	Mild to moderate	2000
5. tacrine	Cognex	Mild to moderate	1993

How Alzheimer drugs work

To understand how Alzheimer's medications work, you first need to understand the communication network in the brain. The picture below depicts nerve cells, or *neurons*, in the brain. Neurons are the chief cells destroyed by Alzheimer's disease.



In the brain, **neurons** connect and communicate at **synapses**, where tiny bursts of chemicals called **neurotransmitters** carry information from one cell to another. Alzheimer's disrupts this process, and eventually destroys synapses and kills neurons, damaging the brain's communication network.

Current FDA-approved Alzheimer drugs support this communication process through two different mechanisms:

- 1) *Cholinesterase inhibitors* work by slowing down the disease activity that breaks down a key neurotransmitter. *Donepezil*, *galantamine*, *rivastigmine* and *tacrine* are cholinesterase inhibitors.
- 2) *Memantine*, the fifth Alzheimer drug, is an *NMDA (N-methyl-D-aspartate) receptor antagonist*, which works by regulating the activity of glutamate, a chemical messenger involved in learning and memory. *Memantine* protects brain cells against excess glutamate, a chemical messenger released in large amounts by cells damaged by Alzheimer's disease and other neurological disorders. Attachment of glutamate to cell surface "docking sites" called NMDA receptors permits calcium to flow freely into the cell. Over time, this leads to chronic overexposure to calcium, which can speed up cell damage. *Memantine* prevents this destructive chain of events by partially blocking the NMDA receptors.

On average, the five approved Alzheimer drugs are effective for about six to 12 months for about half of the individuals who take them.

Future treatment breakthroughs

Researchers are looking for new ways to treat Alzheimer's.

Current drugs help mask the symptoms of Alzheimer's, but do not treat the underlying disease.

A breakthrough Alzheimer drug would treat the underlying disease and stop or delay the cell damage that eventually leads to the worsening of symptoms.

Many experts believe such a breakthrough is possible within the next few years. There are several promising drugs in development and testing

2010 CART Grant Recipients – brief layman's description of research projects

Paul Murphy, University of Kentucky

Alzheimer's disease is sometimes called "the diabetes" of the brain, because, like diabetes, it is common and shares some common features including accumulation of proteinaceous deposits called amyloid. Moreover, until recently, it wasn't apparent that diabetes itself is a risk factor for AD, and insulin, a key hormone regulating the body's ability to respond to glucose ("sugar") levels in the blood and centrally involved in the pathogenesis of diabetes, also has important effects on brain cells and the cellular and molecular processes involved in AD. Dr. Murphy's exciting research proposal will study the shared mechanisms involved in AD and diabetes, and another new link between them – obesity.

Luigi Puglielli, University of Wisconsin

Accumulation of a toxic protein fragment known as the amyloid beta peptide (A β) in the brain is believed to play an important role in Alzheimer's disease, and as such, there is worldwide interest in developing new ways to reduce the build up A β in the brain as a therapeutic strategy for prevention and treatment of AD. Dr. Puglielli's CART research grant takes an entirely novel and promising approach to reducing amyloid production in the brain. His research will capitalize on promising preliminary findings and discovery of new drug-like compounds that appear to change the activity of another key protein, called BACE1 (the Beta Amyloid Converting Enzyme). Further development of these and other related compounds in this research could lead to new drugs that reduce A β production in a more safe way than other strategies under development.

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