DISEASES OF AGING

ALZHEIMER’S DISEASE

An introduction to aging science brought to you by the American Federation for Aging Research
Alzheimer’s disease is the most prevalent form of dementia (broadly defined as a progressive and irreversible loss of intellectual skills, including language and abstract thinking, with mood and personality change). It is a degenerative disease that destroys brain cells called neurons. Persons with Alzheimer’s lose cognitive function, including memory and language, develop mood disturbances, and gradually lose physical abilities, eventually dying of their disease.

INCIDENCE AND COSTS

Alzheimer’s disease affects 5.4 million Americans today, and by the middle of the next century, that number is estimated to more than double. It causes half of all dementias in older people, is present in 60 percent of the residents of long-term care facilities, and is among the top 10 leading causes of death in the United States in people over 65.

Care of people with Alzheimer’s disease costs more than $100 billion each year in medical and nursing care, lost productivity (due to family caregivers leaving the workforce to care for their loved one), home care, and premature deaths.

BRAIN ABNORMALITIES IN ALZHEIMER’S DISEASE

A number of abnormalities are found in the brains of patients with Alzheimer’s disease. These include:

- Loss of neurons (cells that transmit nerve impulses) from the cortex (the center of thought) and other areas associated with learning and memory.

- Elevated levels of beta amyloid, a protein that is a fragment of a larger protein called amyloid precursor protein (APP). Proteins are created from genes in our DNA, using amino acids mostly derived from meats and other food sources. There are hundreds of thousands of different proteins that can be coded from our DNA, and these do most of the functional work in neurons and all cells in our bodies. But in some cases, these proteins stop working properly and become detrimental to the neuron. The neuron then develops a loss of function and eventually dies. In Alzheimer’s brains, clumps of amyloid are surrounded by swollen nerve endings and blocked off by the feet of protective brain cells, creating plaques. Researchers are pursuing the question as to whether beta amyloid causes the disease or is a byproduct of it.

- Accumulation of the tau protein. When tau protein malfunctions in Alzheimer’s disease, it forms structures that have been dubbed “tangles.” These tangles also work to kill neurons, essentially choking them from the inside out.

- Low levels of certain chemicals called neurotransmitters (including acetylcholine, somatostatin, and corticotropin-releasing factor). These chemicals are messages that brain cells create to communicate with one another.

STAGES OF ALZHEIMER’S DISEASE

Although some variation exists from one individual to another, Alzheimer’s disease does follow a progressive course that can be divided into general stages.

- The early stage of Alzheimer’s features recent (versus distant or long-term) memory loss; language difficulty; problems with abstract thinking; diminished ability to perform normal and simple activities of daily living (AsDL); and mood changes, the most common being depression.

- The intermediate stage features worsening of memory loss; wandering and getting lost; a need for assistance with AsDL such as bathing, eating and dressing; and increased agitation. Though people at this stage of the disease can still walk, they are at greater risk for falls and injuries.
• In the severe (or terminal) stage of Alzheimer’s disease, patients are completely dependent on others. They lose all memory, cannot walk, and cannot do anything for themselves at all. They are incontinent.

• End stage Alzheimer’s disease is characterized by coma and then death.

OTHER CAUSES OF DEMENTIA

In addition to Alzheimer’s, there are several other forms of dementia, such as frontotemporal dementia; Pick’s disease; dementia with Lewy bodies; and vascular dementia (caused by multiple strokes) that may mimic some Alzheimer’s symptoms.

Dementia can also be brought on by B12 deficiency, thyroid deficiency, anemia, and hydrocephalus (fluid on the brain). These four are typically all reversible.

Delirium, which can mimic dementia, is a mental disorder that comes on rapidly and features fluctuations in cognitive skills and problems of perception, such as hallucinations. Delirium is most often the result of some other physical process, such as a toxic reaction to a medication or the symptom of an illness such as kidney failure. It too is generally reversible.

Depression can also mimic dementia by interfering with a person’s ability to concentrate and pay attention to things they are asked to remember.

It is also possible for family members or friends to perceive someone as having dementia, when in fact they may have other issues such as hearing loss, vision problems, or decreased metabolism. Often, elderly people are embarrassed to admit a decline in these areas and will attempt to mask them with false affirmative responses to questions.

ALZHEIMER’S DISEASE AND AGING

While aging is the largest risk factor for Alzheimer’s disease, it is important to note that this disease is not a normal part of aging. One in eight people 65 and older have Alzheimer’s. Six percent of men and women ages 65 to 74 have Alzheimer’s, and nearly half of those age 85 and older have the disease. In addition, two to seven percent of Alzheimer’s disease cases occur in people under the age of 65.

Diagnosing Alzheimer’s disease

Since there are multiple possible causes of dementia, Alzheimer’s often becomes a diagnosis of exclusion, that is, reached by a process of elimination. Certain factors point to it as a cause of mental decline. These include:

Patient history

Persons with Alzheimer’s disease, or more often their caregivers, will describe a pattern of loss of recent and remote memory, as well as a decline in abstract thinking abilities and poor judgment. They will also present with depression. Self-awareness is normal in the first stages. It is imperative that the physician rule out other organic causes of dementia (such as those described above), which might be mistaken for Alzheimer’s disease.

Physical examination

A complete physical examination with a thorough evaluation of blood tests must be performed. Those blood tests include a complete blood count, blood chemistry tests, thyroid function studies, folate and vitamin B12 level assessment, syphilis test, and urinalysis. Other tests such as:

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CT scans, PET scans, or MRIs of the brain can be done to evaluate for other conditions that may contribute to memory loss. Photo courtesy National Cancer Institute/Linda Bartlett.
imaging was recently approved by the FDA to diagnose definitively that someone does NOT have Alzheimer's disease.

**THE RISK FACTORS FOR ALZHEIMER’S DISEASE**

There are a number of risk factors for the development of Alzheimer’s disease. They include:

**Age**

The risk of developing Alzheimer’s disease increases with increasing age up to about age 90. Researchers estimate that as many as 50 percent of those over 85 have the disease.

**Genes and heredity**

Having a family history of Alzheimer’s disease increases your risk of developing it too. Those with one parent with the disease have a one-and-a-half times greater chance of developing it, and those with two afflicted parents have five times the average risk.

In a few families with members who develop the rare hereditary form of early onset Alzheimer’s disease, scientists have identified abnormalities in certain genes. The most common of these genes are called presenilins, which process a protein normally involved in beta amyloid generation. However, when the presenilin genes are mutated, beta amyloid production accelerates, leading to early onset of Alzheimer’s pathology. Mutations in the APP protein can also lead to earlier onset; however, a recent discovery showed that there are unique mutations in APP that can actually prevent people from developing Alzheimer’s disease.

**The gene for apolipoprotein E,** which is involved in cholesterol metabolism, comes in several different forms. These include ApoE2, ApoE3, and ApoE4. Those who inherit the ApoE4 version have a higher risk of developing Alzheimer’s disease. However, ApoE4 is “neither necessary nor sufficient” for developing Alzheimer’s disease, meaning that those who do not have ApoE4 can still get Alzheimer’s disease and those that do have ApoE4 may not end up developing dementia. However, ApoE2 appears to be protective, reducing Alzheimer’s risk. (See our Longevity Assurance Genes Center)

In January 2003, researchers published evidence that another gene related to cholesterol metabolism, CYP46, may also play a role in Alzheimer’s risk.

The study, published in the *Archives of Neurology,* showed that people with the TT variant of the CYP46 gene have increased levels of the beta-amyloid protein in brain tissue and cerebrospinal fluid, as well as a higher risk of developing Alzheimer’s. Study participants with both the APOE4 and CYP46-TT gene variants were nearly 10 times as likely as those without either gene to develop the disease. In March 2011, researchers published data in the *Nature Genetics* journal that link common variants in five genes not previously known to be associated with Alzheimer’s to confer susceptibility for late onset Alzheimer’s.

**Gender**

Women are more likely to develop Alzheimer's disease than men. However, this may be related to the fact that women tend to live longer than men and are more likely to live into their 80s and 90s when the disease becomes more common.

**Ethnicity**

The risk of developing Alzheimer’s disease is as much as four times higher for African Americans as for Caucasians. A study published in the Journal of the American Medical Association recently compared the risk of Alzheimer’s disease among African Americans and Africans from Nigeria, and found that the risk was nearly twice as high for African Americans as for the Nigerians studied. The risk for Latinos is twice that of whites. People of Asian and Native American descent are at lower risk. It is unclear whether these differences in risk are due to genetic heritage, health, or social/cultural differences between ethnic groups. What is clear, however, is that Alzheimer’s disease affects all ethnic groups worldwide.

**Education**

One provocative study of older nuns suggested that literary acumen and education play roles in the risk for developing Alzheimer’s disease. The Nun Study, based in Wisconsin, looked at more than 100 nuns over the age of 75 (testing the 93 living subjects and reviewing autopsy results for the 14 who had died). The investigators reviewed autobiographies that the nuns had written nearly six decades earlier, and found that those women whose writing contained less complexity of ideas and simpler grammar had an increased risk for developing Alzheimer’s disease.
Head injury
A study done at Duke University reviewing the medical records of World War II veterans revealed that their risk of developing Alzheimer’s disease was increased if they had suffered serious head injury in young adulthood. The risk of Alzheimer’s disease or dementia was twice as high for those with a history of moderate head injury (loss of consciousness or amnesia for 30 minutes to 24 hours) and four times as high for those with a history of severe head injury (loss of consciousness for more than 24 hours).

Depression
Being depressed may increase your risk of developing Alzheimer’s disease, even if the depression was earlier in adulthood. A study of nearly 2,000 subjects with Alzheimer’s and their non-demented family members found that depression symptoms correlated strongly with the development of Alzheimer’s within a year. Depression symptoms that occurred more than one year—and even more than 25 years—before the onset of Alzheimer’s were also associated with increased risk, although the association was weaker.

In the elderly, the symptoms of depression can mimic the symptoms of Alzheimer’s disease. It is important that depression be ruled out when obtaining a diagnosis for an elderly person displaying symptoms of dementia.

Cardiovascular health
Scientists are finding that cardiovascular disease and Alzheimer’s disease may develop through similar pathways, as heart disease risk factors such as elevated blood pressure, homocysteine levels, and cholesterol seem to increase the risk of developing Alzheimer’s disease as well.

Homocysteine is an amino acid linked to heart disease. A deficiency of either vitamin B12 or folate can lead to higher homocysteine levels in the blood, and homocysteine has damaging effects on the central nervous system. Even borderline low levels of vitamin B12 or folate have been found to increase the risk of developing Alzheimer’s disease. Persons with elevated homocysteine levels are two to three times more likely to develop Alzheimer’s disease than those with normal levels. It is unclear if homocysteine contributes directly to Alzheimer’s disease or is an “innocent bystander” of another process contributing to the development of dementia.

High blood pressure and high cholesterol have also been linked to an increased risk of developing Alzheimer’s. Studies are now underway to investigate whether medications that control these factors could reduce a person’s risk of Alzheimer’s disease.

Research indicates that damage to the blood vessels that deliver blood, oxygen, and nutrients to the brain can increase the risk of Alzheimer’s disease. In addition to high blood pressure and blocked arteries caused by excessive cholesterol, other causes of that damage include atrial fibrillation (an abnormal heart rhythm that increases the risk of strokes caused by blood clots lodging in the circulation of the brain) and diabetes. All of these health problems increase the risk of stroke, and stroke and Alzheimer’s disease often occur in the same patient. A growing amount of research indicates that strokes are a significant risk factor for the development of Alzheimer’s disease, even if the stroke is so small as to be nearly without symptoms. Generally speaking, what is good for your heart is good for your brain.

Generally speaking, what is good for your heart is good for your brain. Photo courtesy National Cancer Institute.
HOW CAN YOU PREVENT ALZHEIMER’S DISEASE?

Right now there are no foolproof ways to prevent Alzheimer’s disease. However, there are changes you can make to your lifestyle that may reduce your risk of developing the disease or delay its onset.

Keep your brain active
In 2003, a study published in the New England Journal of Medicine made headlines when it found that mentally stimulating leisure activities, such as reading, playing card and board games, or doing crossword puzzles, were associated with a reduced risk of dementia. Since then, other studies have confirmed that keeping your brain active, whether through mentally stimulating hobbies or through challenging work, can stave off Alzheimer’s disease. This may be because intellectually stimulating activity can help spur the brain to produce new neurons and create more connections between brain cells.

Keep your body active
Physical exercise also helps the brain stay healthy by increasing blood flow to the brain. Laboratory studies in mice as well as surveys of human populations suggest that exercising can reduce a person’s risk of developing Alzheimer’s disease or other forms of dementia. Exercise can also help control obesity, diabetes, and cardiovascular problems such as high blood pressure and high cholesterol, all of which may contribute to Alzheimer’s risk.

Keep your heart healthy
Some familiar factors that affect both cardiovascular disease and Alzheimer’s disease are blood pressure, high cholesterol, and stroke. These risk factors can be modified by eating properly and getting regular exercise. As mentioned above, scientists are studying whether medications that control blood pressure or cholesterol, such as diuretics or statins, can also reduce a person’s risk of Alzheimer’s disease.

Because high blood levels of homocysteine, usually caused by a deficiency of vitamin B12 or folate, can be damaging to the heart and the central nervous system, researchers are testing whether supplementing older adults with vitamin B12 or folate could reduce the risk of developing Alzheimer’s or slow the progress of the disease once it has begun.

TREATMENTS FOR ALZHEIMER’S DISEASE

Alzheimer’s disease is currently incurable, and current medications only slow down the worsening of symptoms, not the progression of the disease. Many of the medications that have been developed act to increase the amount of acetylcholine in the brain. Acetylcholine is a chemical message that is sent from one neuron (brain cell) to another in areas of the brain used for memory. Other medications being tested for the prevention and treatment of Alzheimer’s disease include anti-inflammatory drugs, estrogen, antioxidants, and medications that treat blood vessel risk factors, such as high blood pressure and high cholesterol. Behavioral programs are also an important part of any treatment plan for the person with Alzheimer’s disease.

Cholinergic medications
Levels of acetylcholine, a chemical messenger in the brain, are lower in patients with Alzheimer’s disease. As a consequence, most of the medications currently available serve to increase its levels by inhibiting acetylcholinesterase, a protein that breaks acetylcholine down into its components. This treatment can improve behavior and thinking in patients with Alzheimer’s disease. Medications in this category have similar efficacy and include:

- Tacrine. This was the first drug in this class to be approved for use but is now rarely used due to excessive side effects.
- Donepezil. This drug has benefits similar to tacrine’s but is much less toxic to the liver. It is taken only once a day and may be slightly more effective than tacrine.
- Rivastigmine. This is a twice-a-day medication that was approved in 2000 for the treatment of mild to moderate symptoms of Alzheimer’s disease. In preliminary trials, rivastigmine was associated with greater improvement in performance tests than any other drug in its class.
- Galantamine (also called galanthamine). This drug was approved in 2001 by the Food and Drug Administration after a number of studies showed that it offered benefit to persons with Alzheimer’s disease. Galantamine is available in either once-a-day or twice-a-day doses.

Memantine
Memantine was approved in the United States in October 2003 to treat moderate to severe Alzheimer’s disease after studies showed that it delayed progression of the disease. Memantine has been widely used in Europe to treat dementia. It helps regulate glutamate, another important chemical...
messenger in areas of the brain associated with memory. Memantine can help Alzheimer’s patients slightly improve their ability to perform daily activities and slow their rate of cognitive decline. It has not been shown to have a significant effect on mild Alzheimer’s disease; however the use of Memantine in combination with one of the drugs described above has been shown to be more effective than either alone.

**Alternative therapies**
In facing the frustrations of coping with a disease such as Alzheimer’s, people are often tempted to turn to alternative therapies—especially when conventional treatment doesn’t seem to be helping. Before turning to any of the alternatives listed below, however, it’s important to emphasize that you need to consult with your physician about their use. First, their effectiveness is far from established. Second, as with any medication, they can produce side effects, especially when used in combination with certain prescription drugs.

**Vitamin E**
Vitamin E has been touted as a possible preventive or progression-slowing treatment for Alzheimer’s disease because of its antioxidant effects. Antioxidants are substances that combat the effects of oxidative damage in our bodies. Oxidative damage to proteins and DNA occurs when our cells utilize oxygen to produce energy. Toxic byproducts of that process are called reactive oxygen species, a kind of free radical. Natural substances in the body (antioxidants) act to scavenge these dangerous molecules and render them less harmful, but this protection fails over time. Oxidative damage has been implicated as a possible cause or contributor to the damage in Alzheimer’s disease.

Studies of vitamin E’s effects on Alzheimer’s disease have been mixed, with some showing a benefit and others showing no significant effect. Because vitamin E can have side effects, such as bleeding in people who take blood-thinning medications (Warfarin), you should discuss vitamin E supplementation with your doctor. Also, vitamin E may interfere with the effects of some cholesterol-lowering medications.

**Gingko biloba**
Gingko biloba is an herb that may increase blood flow to the brain. Some studies have suggested benefit in Alzheimer’s disease, but these studies were conducted in Europe, where the content and dosage of herbal supplements is much more consistently regulated than in the United States. Gingko biloba can also increase the risk of bleeding and should not be taken without first checking with your doctor.

**Behavioral programs**
Simple steps can be taken to reduce the confusion and agitation that persons with Alzheimer’s disease may experience. Large calendars, digital clocks and familiar objects in a simple, uncluttered environment are useful. Setting up a daily routine and using written reminders can help the person with Alzheimer’s stay more active. Exercise, occupational therapy, group therapy, music, and family activities are often helpful too. Removal of knives, scissors, and other sharp instruments can prevent self-inflicted injuries. It is also important to remove items like fake fruit and other items that can produce confusion and potentially be hazardous.

As the disease progresses, the person with Alzheimer’s disease can become progressively more agitated. Simple distractions, such as touching and talking, can often calm them. When persons with Alzheimer’s disease have difficulty keeping facts straight (such as wanting to go visit a deceased parent), caregivers are encouraged to redirect and empathize with the person instead of correcting them. Home movies and videos can be soothing as well.

In later stages of the disease, the caregivers must assume full responsibility for all aspects of daily living. Alzheimer’s patients need help with dressing, bathing, and eating. They must be prevented from driving. As the disease progresses, wandering can become a serious problem. Door locks and alarms may be needed; identification bracelets, such as those issued by the Alzheimer’s Association are also recommended.

**End of life care**
How quickly someone progresses to the late stages of Alzheimer’s disease varies from person to person. In the later stages of the disease, patients may become totally incontinent (cannot control their urine or bowels). They may become bedridden, with the risk of pressure sores and pain from muscle contractures. They may lose the ability to swallow and may not be able to eat or drink. Though many spouses and children strive for years to keep their loved ones with Alzheimer’s disease at home, most patients come to require around the clock nursing care. Families must make critical decisions about end of life care (feeding tubes, respirator use, antibiotic use, and hospitalization). Many families choose to have the medical care of their loved
No one can provide care for a person with Alzheimer’s without help. Doctors, nurses, hospital social service departments, local elderly service administrations, local support groups, and the Internet can provide referrals for assistance to caregivers.

One with late-stage Alzheimer’s disease focus more on maintaining comfort, dignity, and quality of life rather than performing tests and undergoing treatments. Ideally, the patient, the family and the physician have come to these decisions well in advance, and are all in agreement.

Caregivers and family members of persons with Alzheimer’s can be devastated by the slow deterioration and loss of their loved ones. No one can provide care for a person with Alzheimer’s without help. Doctors, nurses, hospital social service departments, local elderly service administrations, local support groups, and the Internet can provide referrals for assistance to caregivers.

**THE DIFFERENCE BETWEEN NORMAL AGE-RELATED MEMORY LOSS AND ALZHEIMER’S DISEASE**

How do you tell the difference between normal age-related memory loss and Alzheimer’s disease? Many older adults complain about memory loss and think it is the first sign of Alzheimer’s disease. This is not the case. Some memory problems are serious, but others are not. A more sluggish ability to recall things, for example, may be part of normal, age-related memory loss. Forgetting where you placed your keys is not as important as knowing what to do with them when you find them.

There is a condition in between normal age-related memory loss and dementia called mild cognitive impairment (MCI). Doctors may diagnose MCI if an older person exhibits memory problems that
seem worse than those associated with normal aging, but not severe enough to be called dementia. Unlike persons with Alzheimer’s disease, older adults with MCI can think and reason normally, and they can perform their usual daily activities without difficulty. Doctors generally diagnose this condition based on self-reporting of memory problems, confirmed by another person and by an assessment test.

People with MCI are at a higher risk of developing Alzheimer’s disease within a few years. In fact, many researchers believe that mild cognitive impairment is actually a very early stage of Alzheimer’s disease. However, not all people with MCI go on to develop Alzheimer’s disease.

People who are worried about memory problems should see their doctor. If the problem is serious or unclear, the doctor may do a complete medical examination for memory loss, as well as blood and urine tests, and tests of mental abilities. A brain scan may also be done to rule out other disorders.

For more information on telling the difference between normal memory loss and Alzheimer’s, please see the National Institute on Aging’s helpful publication, Understanding Memory Loss.

THE FUTURE OF ALZHEIMER’S DISEASE RESEARCH

What is the future of Alzheimer’s disease research? Future research will seek to improve prevention, diagnosis, and treatment. Researchers believe that preventing Alzheimer’s disease or delaying its onset are likely to be more achievable than treating the disease once it has already taken hold, although scientists are working on both goals.

Diagnosis

Researchers are getting close to improving early diagnosis of Alzheimer’s disease. Refinements in imaging techniques like MRI and PET may soon allow doctors to identify patients at risk for Alzheimer’s disease and its probable precursor, mild cognitive impairment (MCI), well before the onset of symptoms. Scientists have also identified biological markers for Alzheimer’s disease that can be detected in the blood, urine, spinal fluid, and even the lens of the eye, and they are working to refine identifying and measuring these biomarkers for practical application in diagnosing the disease. In addition, imaging technologies that allow scientists to view plaques and tangles in the brains of living patients will help them evaluate whether or not potential treatments are preventing, slowing, or halting the progression of the disease in patients’ brains.

Prevention

Evidence is accumulating that lifestyle changes can help prevent Alzheimer’s disease or delay its onset, and researchers are likely to refine these recommendations as they learn more. In addition, progress in research into treatments that might be able to prevent or delay Alzheimer’s disease suggests that effective preventive medications or vaccines may be available within a decade. Scientists are also refining their knowledge of which genes are implicated in the development of Alzheimer’s disease. This may eventually help them identify persons at a higher risk of developing the disease who might benefit from preventive therapies.

Treatment

Current therapies focus on treating symptoms and have demonstrated little long-term efficacy. As researchers continue to break down the physiological processes underlying the development of the disease (particularly the production of beta amyloid and tau in the brain), they hope to find ways—likely through medications or vaccines—to halt the disease in its tracks, rather than simply limiting its symptoms. It is unlikely that scientists will soon develop methods of reversing damage already done by the disease in the brains of current patients.