HEALTH AND STRESS

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STRESS, SENIOR MOMENTS AND ALZHEIMER'S DISEASE

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It's not unusual for middle-aged people to occasionally complain of forgetting a familiar name, where they left their glasses or something they meant to buy when going shopping. Memory loss for recent events like what you had for dinner two days ago tends to worsen with age and can be a daily nuisance for senior citizens. This sometimes progresses to include additional mental and emotional problems such as loss of language skills, impaired judgment, confusion, personality changes, disorientation and other disabilities characteristic of Alzheimer's Disease. Complaints and behavioral signs suggestive of Alzheimer's are seen in about 5 percent of people aged 65 to 74, increase with age, and can be found in nearly half of all super seniors 85 and older. It is estimated that over 4.5 million Americans are affected and because the over 80-age group is the most rapidly growing segment of the population; this number is predicted to increase to 13.2 million by 2050. Alzheimer's usually starts after age 60 with mild memory loss that worsens and is subsequently accompanied by signs and symptoms of mental and emotion deterioration indicative of progressive brain damage. The course of the illness varies considerably and while the average patient lives 8-10 years after the diagnosis is made, some can last as long as 20 years. Alzheimer's is currently our fourth leading cause of death with most patients succumbing to infections.

Confirming the diagnosis can be difficult and until recently, could only be convincingly established by examining the brain at autopsy. Common signs of senile dementia include asking the same questions repeatedly; getting lost in familiar places; inability to follow directions; becoming disoriented about time, people, and places; and neglecting personal safety, hygiene, and nutrition. However, these disabilities do not develop in any special sequence. Similar disturbances can also be disturbances can also be due to dehydration, vitamin and nutritional deficiencies, side effects of medications, endocrine disorders or head trauma and disappear when these problems are corrected. In addition, elderly people may have emotional problems that can easily be mistaken for dementia, especially when they are depressed, lonely, worried or bored because of difficulty coping with retirement or the loss of social support due to the death of a spouse, relative, or close friend.

ALSO INCLUDED IN THIS ISSUE

Alzheimer's is also often confused with vascular or multi-infarct dementia, another irreversible condition that is due to a series of small strokes that destroys brain tissue. The location and extent of these small strokes determine what signs and symptoms they produce and their severity. This type of dementia should be suspected when symptoms appear suddenly, especially if blood pressure is elevated. These patients are likely to show signs of improvement or remain stable for long periods of time and only get worse or develop new symptoms if more strokes occur.

The Growing Problem of MCI And The Dread Of Developing Alzheimer's

Many people also have a condition called MCI (mild cognitive impairment) manifested by difficulty in remembering recent events but who never go on to develop difficulty in concentration, loss of language skills, confusion or anything else to suggest Alzheimer's. The problem is that they are well aware of the serious mental, emotional, physical and financial effects of the disease, not only on patients, but also their families. Many suffer from severe stress because there is absolutely no way to guarantee that their symptoms will not progress to full blown Alzheimer's. As will be seen, it is now clear that **stress is a frequent cause of memory loss that can lead to a vicious and self-perpetuating cycle that makes things worse.**

Some indication of how widespread this fear is comes from a survey of 150 healthy adults aged 65 and older published in the September 2006 issue of the *Journal of the American Geriatrics Society*. Researchers reported that 98 percent said they would be willing to be tested for mild cognitive impairment if a family member felt they had memory problems. African Americans were more willing (75 percent) than whites (57 percent) to be screened at the suggestion of a family member. Ninety-nine percent would be willing to take a drug if it would halve their risk of progressing from mild cognitive impairment to Alzheimer's and 92 percent would take a medication that could delay its onset by 1 year. In an interview, the senior author indicated "We were somewhat surprised interest was this high" and was "potentially troubling because current screening tests do not meet basic scientific standards for justifying their use in standard medical practice. On the present evidence, despite the enthusiasm of the medical profession, and probably the public, screening for mild cognitive impairment is not justified." One reason for this is that "none of the available therapies for mild cognitive impairment have been shown to substantively impact the clinical course of the disease and there may be negative psychological, social, and ethical considerations from being given the label of mild cognitive impairment, which has been linked to Alzheimer disease." Another authority asked to comment on the article also warned that labeling someone as having mild cognitive impairment "may offer to otherwise normal older people a new diagnostic concern about which they did not have to previously worry about."

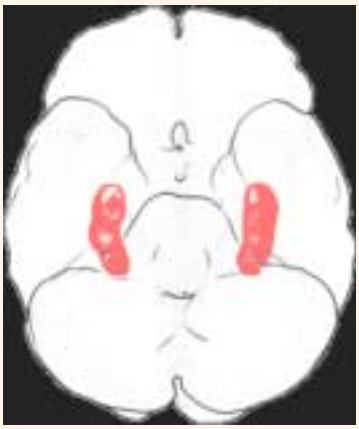
This dilemma is rapidly increasing due to the growing numbers of elderly individuals in addition to evidence that much younger people have a similar problem. **Americans in their thirties and forties are now experiencing the same memory difficulties usually seen in much older people**. One survey of physicians reported that:

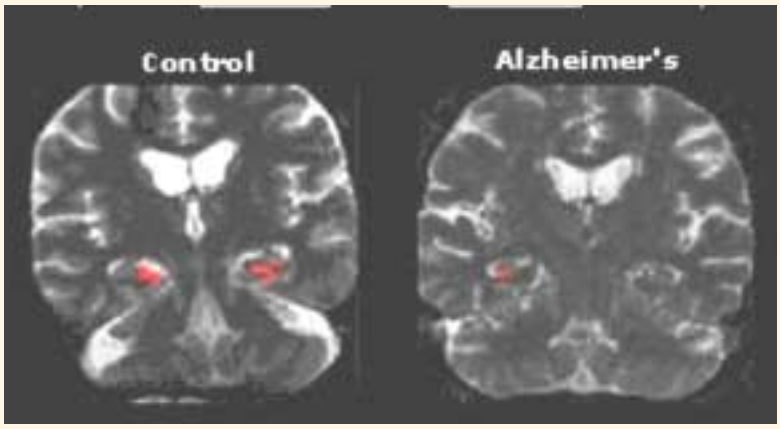
- Four out of five patients as young as 35 complain of diminished memory and concentration skills.
- Three out of four expected this trend to increase in those 35 years of age and older over the next ten years.
- Most people do not realize how prevalent this problem is. Although doctors hear numerous other complaints, 9 out of 10 state that many affected patients never discuss their memory or concentration difficulties until asked.
- Men and especially professionals appear to be at greater risk than women. Men complained of such problems more (36 percent) than women (33 percent) and white-collar workers more (32 percent) than blue-collar workers (28 percent). Single people were also slightly more prone (32 percent) compared to those who were married (30 percent).

- The most frequent factors contributing to memory loss and poor concentration were increased job stress and personal pressures (86 percent), natural aging and diminished blood supply to the brain (85 percent), taking certain prescription medications (84 percent) and not getting enough sleep (81 percent).
- With respect to treatment, they advised patients to reduce stress (89 percent), get more exercise (89 percent) and develop better sleeping habits (87%). Physicians were nearly three times more likely to treat patients with vitamins and herbal supplements than prescription drugs and six times more likely to recommend supplements than to make referrals to specialists.

Sophisticated functional MRI (fMRI) imaging findings that correlate with periodic memory tests results suggest that ten to fifteen percent of people with this type of mild cognitive impairment go on to develop Alzheimer's compared to one percent of the normal elderly population. **The bottom line is that we can't reassure anyone with symptoms of mild memory loss that this is not a precursor of Alzheimer's. Even if the latter seemed likely because of other cognitive complaints, there is little that can be done to significantly delay much less prevent its progression.**

How Stress Contributes To Loss Of Memory, Aging And Alzheimer's





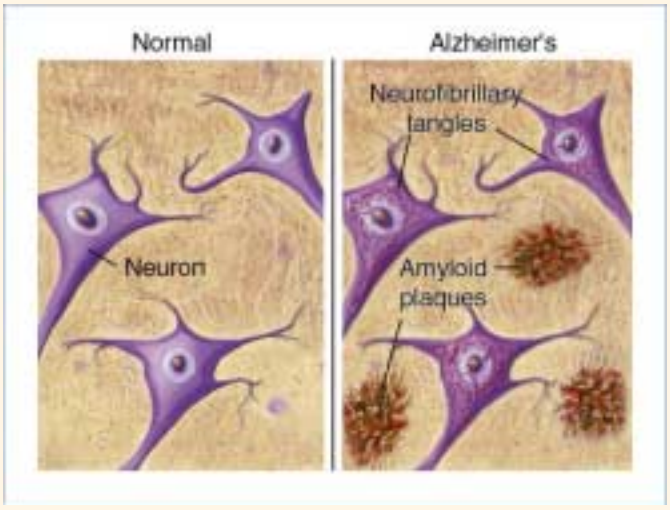
Memory for recent events is stored in the hippocampus, which, as shown above to the left, is located in the temporal lobe on each side of the brain. The name is derived from its curved shape that somewhat resembles a seahorse (Greek: *hippo*=horse, *kampos*=sea monster). As we grow older, the hippocampus starts to shrink and MRI enhancements allow us to measure these changes more accurately and show their correlation with progressive impairment of short-term memory. Some authorities believe that this shrinkage, which can go down to 10 percent of the original size, may represent one of the earliest signs of Alzheimer's, where there is severe atrophy compared to controls the same age, as illustrated on the right.

Numerous studies suggest that sustained stress is a major contributor to memory loss because chronic increases in cortisol can also cause a reduction in hippocampal size. Cortisol levels tend to be elevated in depression, which is why patients frequently have problems with concentration and memory. Following successful treatment, these and other cognitive complaints disappear as cortisol values return to normal. One report on Vietnam veterans suffering from Post Traumatic Stress Disorder similarly found that the hippocampus was significantly smaller in those who were more stressed because of greater exposure to severe combat experiences. Animal studies confirm that chronic stress causes the hippocampus to shrink and that there are analogous alterations in the prefrontal cortex, a portion of the brain crucial for concentration and decision-making. Chronic stress also impairs immune system function and contributes to inflammation, both of which are thought to contribute to the development of Alzheimer's and other age related disorders. In contrast, acute stress improves memory, enhances immune function and reduces inflammation.

Telomeres are protective shields at the end of chromosomes that prevent them from fraying during cell division, much like plastic tips safeguard the ends of shoelaces. Every time a cell divides, its chromosomes cannot be copied to their full length, leaving a tiny tip of the protective telomeres uncopied, much like a tape recorder is unable to play the first and last centimeter or so of tape in a cassette. As a result, the copy of the chromosome is incomplete and after repeated divisions the telomere progressively erodes and the cell no longer functions correctly and dies. Some cells have longer telomeres than others, which explains why cells age at different rates. Cumulative stress also contributes to aging and Alzheimer's by reducing the damage due to telomere shortening that occurs whenever a cell divides. Telomere shortening is prevented by the enzyme telomerase, which becomes depleted with aging. It is also decreased by sustained stress. Telomerase is decreased in people who are under stress for long periods of time, such as caregivers for patients with Alzheimer's and other chronic diseases. As indicated in a prior Newsletter, Alzheimer's caregivers also tend to have impaired immune system function that can persist for years after their duties cease. This may increase their susceptibility to infections and other disorders as well as accelerate aging. Conversely, telomerase is elevated in many malignancies, which explains why cancer cells can keep replicating without the repeated loss of telomere tips during cell division.

Levels of glucocorticoid hormones like cortisol have been found to be higher in patients in the early stages of Alzheimer's and recent studies in a mouse model showed that this can rapidly increase the formation of amyloid plaque and other brain lesions that are hallmarks of the disease. When researchers injected a hormone similar to cortisol for only seven days in four-month old mice, beta-amyloid, a protein that forms plaque, increased by 60 percent. The amount of hormone injected approximated the levels of cortisol that would be seen in humans under stress and while there would normally be little or no plague at this early age, the resultant plaque formation was similar to that seen in untreated nine-month old mice. When the same amount of hormone was injected into 13-month-old mice that already had some plaque deposits, there was a significant increase in these and other lesions in the brain. In addition, the increase in beta-amyloid appeared to increase the levels of stress hormones, leading to a vicious cycle that produces progressive damage. The researchers believe that the same chain of events occurs in humans and emphasized the importance of stress reduction in treating Alzheimer's, noting that **"It is remarkable that these stress hormones can have such a significant effect in such a short period of time."** The lead author also warned, "Some medications prescribed for the elderly for various conditions contain glucocorticoids. These drugs may be leading to accelerated cognitive decline in patients in the early stages of Alzheimer's."

The diagnosis of Alzheimer's is made based on two characteristic microscopic findings in the brain that are found at autopsy. These two tell tale features are the presence of amyloid plaques and neurofibrillary tangles as illustrated below.



Amyloid is a general term for fragments of protein that are normally produced in the body. Beta-amyloid is a fragment snipped from a protein called amyloid precursor protein (APP). In a healthy brain, these fragments would be broken down and eliminated. In Alzheimer's, the sticky beta-amyloid fragments accumulate to form hard, insoluble plaques.

Neurofibrillary tangles are insoluble twisted fibers that are found inside of the brain's cells. They primarily consist of a protein called tau, which forms part of a structure called a microtubule. The microtubule helps transport nutrients and other important substances from one part of the nerve cell to another. Because tau protein is abnormal in Alzheimer's, the microtubule structures collapse.

High levels of beta-amyloid are associated with reduced levels of acetylcholine, a neurotransmitter essential for memory and learning that is progressively destroyed in Alzheimer's Disease. Beta-amyloid disrupts channels carrying sodium, potassium and calcium ions, which generate the electrical charges that fire in a regular order to allow signals to pass from one nerve cell to another. When these channels are damaged the resulting imbalance interferes with proper signal transmission and nerve function. As beta-amyloid breaks down it also releases unstable oxygen-free radicals that bind to and damage other molecules and cells. Another result of oxidation is inflammation due to activation of immune system components designed to repair injury. However, when there is excess stimulation of the immune system, the resulting response increases the production of glutamate, an amino acid that can injure and destroy neurons. These various insults cause a steady and irreversible deterioration of communication between nerve cells that involve different brain areas, as depicted below.

Progressive Degeneration Of The Brain In Alzheimer's Disease

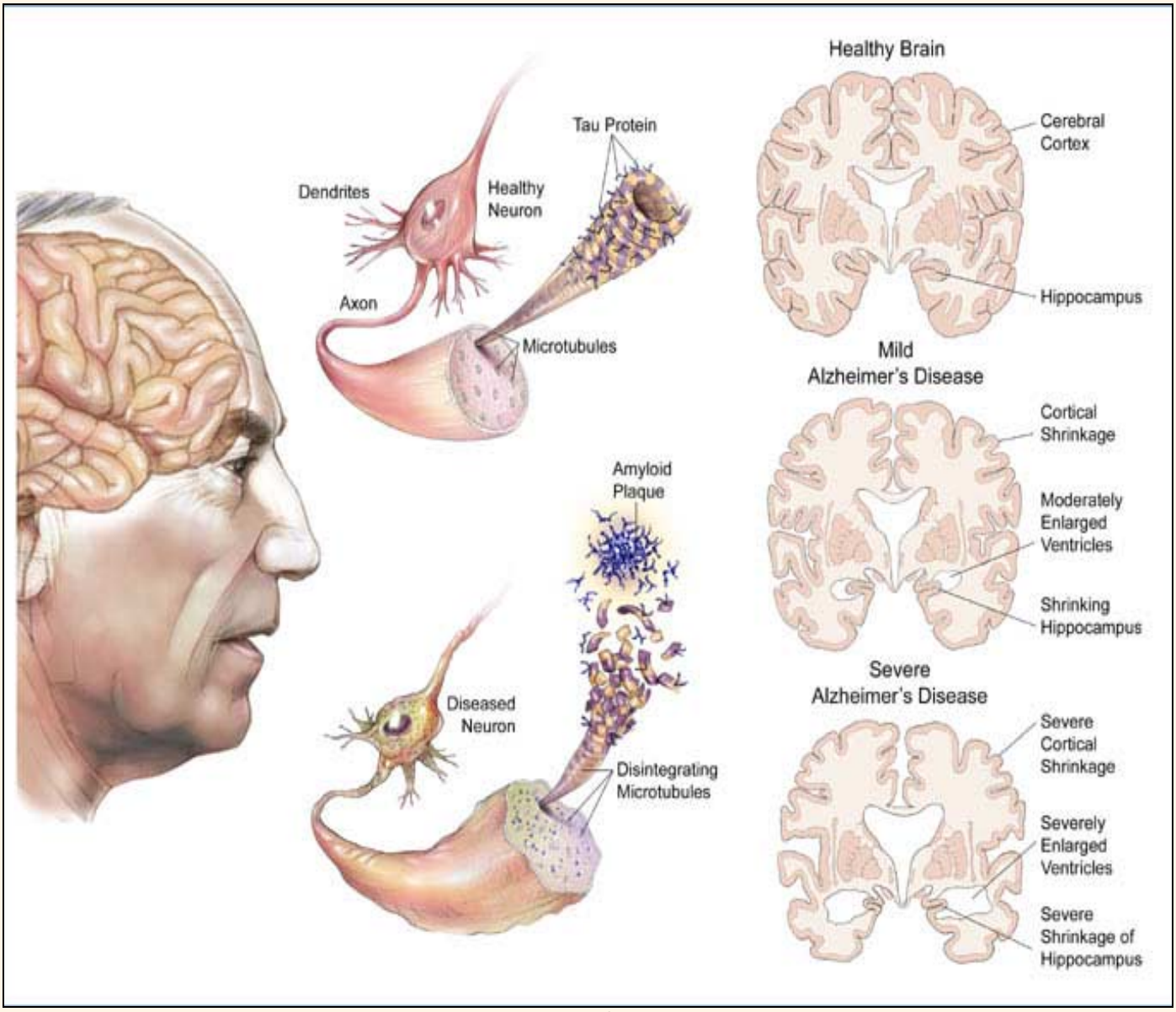


Illustration by Bob Morreale, provided courtesy of the American Health Assistance Foundation

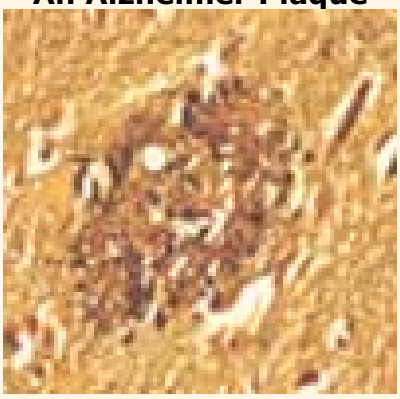
In the early stages of Alzheimer's, short-term memory begins to decline when the cells in the hippocampus degenerate and there is an increasing inability to perform routine tasks. A slow but steady overall shrinkage of brain tissue begins and the ventricles, chambers within

the brain that contain cerebrospinal fluid, become noticeably enlarged. As the disease spreads through the cerebral cortex, judgment declines, emotional outbursts may occur and language is impaired. Further progression leads to the death of more nerve cells and subsequent behavior changes, such as wandering and agitation. The ability to recognize faces and to communicate as well as bowel and bladder control is completely lost in the final stages and constant care is eventually required. This stage of complete incapacity and dependence on others may last for years before the victim succumbs to infection or some other complication. This can take a tremendous toll on spousal caregivers; even after a heart wrenching decision has been made to transfer a loved one to a nursing home or other long-term care facility.

What Causes Alzheimer's And Can It Be Prevented, Delayed Or Treated?

The only established risk factors for Alzheimer's are age, a family history and poorly understood genetic influences. The disease is named after Alois Alzheimer, a German psychiatrist and researcher who was intrigued by and carefully followed a 51 year old woman admitted to the state asylum in Frankfort in 1901 because of memory and language deficits, auditory hallucinations, delusions, paranoia and aggressive behavior. Alzheimer moved to the Munich medical school in 1903 to work with Emil Kraepelin, a founder of modern psychiatry who believed there were biologic causes for mental disorders that should be the basis for treatment in contrast to Freud's promotion of psychoanalysis. The patient died in 1906 and her brain was sent to Alzheimer, who noted severe shrinkage of the hippocampus and cerebral cortex. He also identified two microscopic changes exactly 100 years ago that are still the essential features of the disease; the neuritic plaques and neurofibrillary tangles shown below.

An Alzheimer Plaque



An Alzheimer Tangle

Alzheimer plaque may be thought of as being similar to dental plaque that forms on our teeth. The fibrillary tangles in nerves are like tangles that sometimes snarl up our hair or shoelaces. These occur in certain parts of the brain and interfere with its function in patients with Alzheimer's disease.

He subsequently published his findings and in 1910, Kraepelin coined the term "Alzheimer's Disease", implying that it was a new disorder. Alzheimer was well aware that the same symptoms and pathologic findings were frequently seen in the elderly and his intention was to demonstrate that this same senile dementia could occur at a much earlier age. Many believe Kraepelin was motivated by a desire to increase his funding, which depended on his department doing well and discovering new diseases. Young people rarely had the disorder and Alzheimer was aware of only one other case. Indeed, when I went to medical school, the disorder was still uncommon and was referred to as pre-senile dementia or pre-senile psychosis. It did not receive much attention until it affected the famous movie star Rita Hayworth when she was in her early fifties. In 1949, at the age of 31, Hayworth married Prince Ali Khan after becoming pregnant with their daughter Yasmin. She divorced him four years later and returned to her film career, which was very successful for two decades, until she had difficulty memorizing her lines, and became increasingly hostile and argumentative. Princess Yasmin Aga Khan cared for her until the end and has since devoted her life to making the public aware of this deadly disorder and raising research funds through a yearly celebrity gala, making numerous public

appearances and serving on the Board of Directors of relevant organizations and medical institutions. Today, the term Alzheimer's Disease is essentially synonymous with senile dementia, although a distinction is still made between early and late onset because of genetic differences.

A family history is found in only 10% of all patients and nearly all of these have significant symptoms before they are 65 years old. Even if only one mutated gene is inherited from either parent, there is a 50% chance of developing the disease. A large study of identical and fraternal Swedish twins 65 and older found that if one identical twin developed Alzheimer's Disease, the other had a 60% chance of getting it. If one fraternal twin developed Alzheimer's, the other had a 30% chance of being affected. Despite the fact that identical twins have the very same genes, their health patterns can differ significantly as described in an August 31,2006 *New York Times* article by Gina Kolata that is abstracted below.

(Courtesy of Josephine Tesauro)

Josephine Tesauro, left, active and healthy at 92, is part of a study trying to determine why some people age better than others, even when they are closely related. She is straight backed, firm jawed and vibrantly healthy, living alone in an immaculate brick ranch house high on a hill near McKeesport, a Pittsburgh suburb. She works part time in a hospital gift shop and drives herself to meetings of her four bridge groups, to church and to the grocery store.

Her identical twin to the right is incontinent, has had a hip replacement and suffers from a degenerative disorder that destroyed most of her vision. She also has dementia and as Josephine explained "She just does not comprehend". Researchers are searching for some explanation of how two people with the same genes, growing up in the same family, living all their lives in the same place, could age so differently?

One clue might be their different attitudes that led to differing lifestyles. Josephine had always been healthy and active, a self-described tomboy growing up who played tennis until she was 85. "I just can't sit still," she said. The New York Times article went on to explain, "She was a woman who knew her mind, so eager to go to college that she defied her father, who thought it was a waste of money, and worked her way through. She ended up with a master's degree in education and a career as a high school teacher.
Her twin was different. She was the frilly type and not much of a student. She failed a grade in high school and barely graduated." Lower educational status has been found to be a risk factor for Alzheimer's. Both Josephine and her sister married and had children. Josephine was also born first, and though many scientists believe that the first-born twin is stronger and lives longer, the Swedish twin study did not show this.

The same genes may also have different effects depending on environmental factors. One survey found that risk for Japanese men increased when they emigrated to the U.S. The disease is also much less common in West Africa than in African Americans, who have same or higher risk as American whites. The ApoE4 gene is believed to be a major risk factor for late-onset Alzheimer's while the ApoE2 gene has a protective effect. People without ApoE4 are three to five times less likely to develop Alzheimer's by age 85 whereas those with 2 copies of this gene can have a 90% risk. Early-Onset Alzheimer's, a less common but extremely aggressive form of the disease, appears to result from mutations in different genes called presenelins that seem to accelerate beta-amyloid plaque formation and apoptosis, a natural process by which cells self-destruct.

Aside from genetics, it is not clear what influences can contribute to Alzheimer's since studies are frequently confusing and even contradictory. One report found no association between the risk for dementia and a longer reproductive life in women, suggesting that longer exposure to estrogen did not protect against mental decline. Other studies suggest that estrogens may delay Alzheimer in premenopausal females but that hormonal replacement therapy had the opposite effect in older females. Theoretically, estrogens should be beneficial, since most studies show that they can:

- Protect against the memory loss and lower mental functioning associated with normal aging and may help block production of beta-amyloid, the source of the sticky plaques found in Alzheimer's brains.
- Trigger the temporary growth of nerve pathways in the memory portion of the brain and stimulate production of the neurotransmitters acetylcholine and serotonin that are depleted in Alzheimer's patients.
- Smooth, relax, and open blood vessels, which may help blood flow in the brain.
- Have antioxidant activities that help neutralize unstable oxygen-free radicals thought to damage nerve cells in the brain that cause Alzheimer's.
- However, this may depend on the age of the study group as well as whether the estrogen is synthetic or a natural derivative.

An elevated cholesterol has been implicated, which has led some to advocate treatment with statin drugs. On the other hand, cholesterol is essential for proper brain function and numerous studies suggest that a high cholesterol protects against developing Alzheimer's. In addition, statins can cause memory loss, amnesia, confusion and other cognitive deficits and any alleged benefit is likely to come from anti-inflammatory activities rather than lipid lowering. The improvement and slower progression of the disease in patients taking NSAIDs like Motrin and Aleve have also been attributed to their anti-inflammatory effects. Some studies suggest that alcohol and tobacco consumption contributes to Alzheimer's but others have found that red wine reduces risk and nicotine-like compounds actually help restore the ability to learn and remember in rats that have brain lesions similar to those found in Alzheimer's Disease. THC, the active ingredient in marijuana, may slow down progression of the disease because it prevents the neurotransmitter acetylcholine from breaking down and also blocks the development of plaque. Anything that decreases blood flow to the brain or otherwise interferes with its supply of oxygen and nutrients can increase risk of Alzheimer's as well as stroke. Common causes include atherosclerosis of the cerebral or coronary arteries, diabetes, hypertension and atrial fibrillation associated with clot formation. Several decades ago, researchers reported finding high levels of aluminum in the brains of Alzheimer's patients. Aluminum is found in drinking water, baked goods with aluminum additives, OTC drugs like antacids and buffered aspirin as well as foods cooked in aluminum pots and pans but it is not clear whether this is a causal influence or simply a tendency for aluminum to collect in the plaque lesions. Excessive amounts of zinc and copper have also been reported in plaque. Increased binding of these metals appears to result from an inflammatory response that produces a more dangerous type of beta-amyloid. *Chlamydia pneumoniae*, a common organism that causes respiratory infections can produce very powerful inflammatory effects in coronary and cerebral vessels. In addition to culturing the microbe from heart attack and stroke patients, researchers have also found it in parts of the brain affected by late-onset Alzheimer's. Some studies show that exposure to intense electromagnetic fields may also be associated with increased risk of Alzheimer's, possibly because interference with the concentration of calcium in brain cells increases the production of beta-amyloid. Although increased homocysteine levels have also been implicated, lowering these to normal with B complex vitamins has not resulted in any improvement.

Five drugs have been approved for the treatment of memory loss in Alzheimer's, four of which are designed to increase levels of acetylcholine at nerve synapses and one to inhibit the damaging effects of glutamate. None have been shown to provide impressive benefits and all have some adverse side effects. The drugs most frequently used to relieve symptoms of agitation and aggression in Alzheimer's proved to be no better than placebos according to a recent government survey and also had numerous significant side effects. These drugs are approved for other indications but not Alzheimer's but are prescribed because of pressure from desperate families who believe they will help based on hype from company sponsored media promotions. Other preventive or restorative approaches are the customary healthy lifestyle recommendations to promote longevity and reducing stress is high on this list. Meditation has been reported to improve Alzheimer's patients, increase heart rate variability and to lower insulin resistance, risk of Type 2 diabetes and other harmful effects of stress related hormones and sympathetic nervous system overactivity. With respect to the latter, vagal nerve stimulation, which stimulates parasympathetic responses has also shown promising potential in pilot studies. Yoga, listening to music, jogging, strong social support and other stress busters may also provide benefits. Avoiding cigarettes, getting enough exercise and sleep, "use it or lose it" mental exercises like doing crossword puzzles, are particularly popular remedies, as are supplements containing omega 3 fatty acids, fish oil, *Ginko biloba*, *Ginseng panax*, huperzine, Chinese moss, kava, Coenzyme Q10, DHEA, Gotu Kola, adaptogens, various vitamins and other nutrients. A diet high in olive oil, vividly colored vegetables (as well as cabbage and potatoes), fruits like apples blueberries, strawberries and pomegranates and moderate red wine intake are also recommended. Most of these supplements and foods contain flavonoids and other powerful antioxidants that can block the age promoting damage of free radicals. However, despite anecdotal reports and lavish testimonials, they have scant scientific support.

Strawberries were recently hailed as the "Holy Grail" to enhance memory because of their large content of fisetin, a potent antioxidant that impressively improved memory in mice in maze tests. **However, you would have to eat 10 lbs. of apples every day to get the same results. More is not necessarily better.** One study found that people who ate fish once a week had a 60 percent reduction in the risk of Alzheimer's compared with people who never ate fish. However, eating fish more than once a week did not appear to provide any additional benefits and might prove harmful because they contain high levels of mercury, PCBs and other contaminants.

The Commercialization And Exploitation Of Alzheimer's By Misinformation

This brings up another point. The value of eating various foods, fruits and vegetables is based on large-scale studies of dietary habits and demonstrating a statistically significant link between certain patterns and a lower incidence of a specific disease. For example, in a study published in the Oct. 24 issue of *Neurology*, researchers studied over 3,700 senior citizens who filled out a food frequency questionnaire and had completed at least two tests for memory and cognitive skills over a six-year period. The authors concluded, "Compared to people who consumed less than one serving of vegetables a day, people who ate at least 2.8 servings of vegetables a day saw their rate of cognitive change slow by roughly 40 percent. This decrease is equivalent to about 5 years of younger age." Sounds pretty impressive but few people have less than 1 vegetable serving daily and **most of us would have to eat 3 or 4 vegetable servings every day to get the same results.** In addition, important influences like exercise, stress and social support were omitted and there was insufficient data to adequately evaluate smoking, alcohol intake, educational status, medications, nutritional supplements and other relevant factors. **This study also found that fruit consumption was not associated with any cognitive benefits.** In a weak attempt to explain this, one author suggested, "It may be due to vegetables containing high amounts of vitamin E, which helps lower the risk of cognitive decline. Vegetables, but not

fruits, are also typically consumed with added fats such as salad dressings, and fats increase the absorption of vitamin E and other fat soluble antioxidant nutrients, such as carotenoids and flavonoids". However, no information was supplied about how often or how much salad dressing was consumed or what types were used. In addition, there is no evidence that vitamin E slows the loss of memory with aging or delays the onset of Alzheimer's.

Many fruits are also rich in flavonoids, carotenoids and other antioxidants, self-report food diaries are notoriously flawed, and the study's finding that fruits had no benefit conflicts with a 10-year study of senior citizens demonstrating the ability of fruit to slow cognitive decline. In a recent report in the *Journal of Alzheimer's Disease*, Canadian researchers reported that apple juice consumption increased the production of acetylcholine in the brain and improved memory in mice with Alzheimer's-like symptoms. A prior study by another group also found that older mice without Alzheimer's on an apple enriched diet performed significantly better on memory tests than controls. It may be significant that both of these studies "were funded by unrestricted grants provided by the U.S. Apple Association and Apple Products Research and Education Council." The benefits of both fruits and vegetables have been attributed to polyphenols, antioxidants that are highly concentrated in their juices, skins and peels. These are also found in teas and wines so it is not surprising that these beverage manufacturers make similar claims. One study reported that resveratrol, a polyphenol in wine, could extend maximum lifespan by 59 percent and that it significantly delayed the age-related decline of cognitive performance in animal models. Other researchers found that resveratrol and quercetin, an antioxidant that is abundant in apples, protected brain cells in cultures from death and injury caused by oxidation and inflammation. It's difficult to determine the clinical significance of such studies. **A report on over 1000 60 to 93 year-old Asians in the July 26 issue of the *American Journal of Epidemiology* showed that those who ate curry once or more in 6 months performed much better on a standard test of cognitive function compare to others who only at curry never or rarely. Turmeric, an ingredient of curry, contains curcumin, which is thought to have powerful antioxidant and anti-inflammatory activities. Support comes from a study on genetically engineered mice confirming not only that curcumin could limit damage from oxidation but also helped to reduce amyloid plaque.** However, there are undoubtedly differences between how memory is stored and retrieved in mice and men and how brain cells react when they are in an artificial culture medium compared to their natural habitat.

There is considerable evidence and good reason to believe that oxidation and the release of free radicals that injure cells probably play an important role in the development and progression of Alzheimer's. Specific antioxidants should theoretically be able to block or reduce damage to brain cells but these have not been identified. There are also significant differences between how natural antioxidants act when given alone compared to when they are consumed in foods containing other ingredients that may have a synergistic effect. There is no evidence at present that any antioxidant supplements protect against either memory loss or Alzheimer's, save for some reports suggesting that vitamins C and E in combination (but not separately) may slow age-related mental decline. In addition, it is important to emphasize that numerous studies have shown that synthetic copies of nutrients, vitamins and other supplements do not provide the same benefits when compared to the natural version. **The latest development is a Mayo Clinic study featured on the cover of the current issue of Neurobiology of Disease proposing that memory loss in later life may be due to a central nervous system viral infection. It has been established that chronic infections caused by HIV or herpes viruses can lead to loss of brain cells but this new research studied the effect of acute infections due to picornaviruses. These are a family of pathogens that include the most common infectious viral agents in humans (rhinoviruses that cause colds, enteroviruses responsible for gastrointestinal and respiratory symptoms, etc.) that infect more**

than a billion people a year. Researchers reported that mice that contracted the virus had difficulty learning to navigate a maze designed to test memory and that the degree of impairment was directly correlated to the number of dead brain cells. Various vaccines have also been devised to delay or treat Alzheimer's but none have been successful and one had very serious side effects.

A major problem in developing effective treatments is that the course of Alzheimer's Disease varies considerably. Although deterioration is progressive it is a slow process during which patients have their ups and downs for no obvious reason. This variation makes it difficult to prove the benefits of any intervention without very long-term monitoring, much less evaluate dose-response relationships to determine what is optimal. New enhanced imaging techniques and improvements in identifying and accurately measuring relevant biomarkers might help to overcome these obstacles by providing objective benchmarks. However, these do not always correlate with clinical status and long-term studies for anything that cannot be protected by patent would be prohibitively expensive. The market for products to stave off Alzheimer's is probably billions of dollars a year and growing due to the lack of anything effective and the insatiable appetite of Americans for information on what they should do. After all, as am old saying goes, "Everyone wants to live long but nobody wants to grow old." Unfortunately, much of what is presented to the public as "news" about advances in preventing aging is actually a carefully crafted but concealed advertorial by a manufacturer anxious to cash in on this bonanza. It is also important to remember that unlike drugs, supplements are not subject to FDA regulation unless it can be proven that they are not safe. There is no guarantee that the contents of the container bear any relationship to what is on the label. Supplement manufacturers can also make any claims they choose without scientific proof as long as it is not for the diagnosis or treatment of any disease. As a result, benefits such as "improves memory and concentration" or "retards the aging process" are currently permitted in the U.S.

Humans and all organisms go through a life cycle of birth, growth, and deterioration due to aging that ends in death. How long we live is determined by heredity, which cannot be controlled, and environmental factors like death due to wars or accidents that we also may be unable to avoid. The truth is that there is no elixir of life or Fountain of Youth and that the best advice still seems to be to "moderation in everything" and adhering to healthy lifestyle practices so that you can enjoy the years that are allotted to you. It may be preferable not to deny yourself some pleasure just to spend a few more years in a nursing home. As Abraham Lincoln noted, "**In the end, it's not the years in your life that count. It's the life in your years**."

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Paul J. Rosch, M.D., F.A.C.P.
Editor-in-Chief
www.stress.org
e-mail: stress124@optonline.net