



ALZHEIMER'S DISEASE: CURRENT THINKING AND ISSUES

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*A*lzheimer's disease, dementia and senility are all words that terrify us, all the more so as people are living longer and are therefore more at risk to lose their mental capabilities. Following is a detailed examination of Alzheimer's disease, how it is diagnosed and what researchers are doing to combat it.

Symptoms of Alzheimer's Disease

Unlike most diseases, the person complaining to the doctor about problems of Alzheimer's disease (AD) is not the patient, they are usually family members. This is an important point both for the families and the physician to understand. When you have a cold or a muscle pull, the patient is the only one who feels the symptoms and therefore is the best source of the information pertaining to them. Not so with AD. The family sees the declining memory and the gradual loss of mental capabilities, but the person with Alzheimer's is largely unaware of the problem. Because of this, many

times the family member will not trust or act on his or her observations about the person with AD. When asked, the patient will more than likely deny or minimize the disability. This denial is because he is *unaware* of the extent of the problem; in fact, it is one of the symptoms of AD. Therefore, the attentive physician must seek crucial information from a knowledgeable family member when confronted by a patient for memory evaluation.

Memory loss is the cardinal symptom of Alzheimer's disease and the one most easily recognized. It is commonly divided into short-term and long-term memory loss. Short-term memory loss is characterized by forgetting things he would have otherwise remembered. This would include what he ate for lunch yesterday, the phone message he took an hour ago or the plot of the movie he watched last night. Commonly family members will dismiss or ignore their first

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DIRECTOR'S MESSAGE

*A*lzheimer's disease (AD) is a brain disorder first described in 1906 by a German doctor named Alois Alzheimer. Dr. Alzheimer was examining microscopic sections from the brain of a middle-age woman who had become progressively and severely demented and then died.

Dementia is a serious brain disorder. It usually involves loss of memory followed by loss of ability to carry out daily activities. Demented persons may ask the same questions repeatedly, forgetting answers heard hours or even minutes earlier. They lose track of time and may become lost in their own neighborhoods. They lose the ability to follow simple directions. Severely demented people are unable to recognize their closest relatives, forget how to eat or dress, and may lose all but the simplest forms of language expression. They become entirely dependent and helpless, unable to sustain personal safety, hygiene or nutrition.

There are many causes of dementia, some of which are reversible. For example, symptoms of dementia may occur after a head injury or with poor nutrition or vitamin deficiency (especially a lack of B₁₂). Another cause is heavy metal (lead or mercury) poisoning. Temporary dementia may also occur with high fever or dehydration, drug reactions or insufficient thyroid hormone (hypothyroidism). In the elderly, irreversible dementia is usually due to either AD or disease of the arteries supplying the brain causing "little strokes." This latter condition is called "multi-infarct dementia." The only way to definitely determine the cause of senile dementia is to examine the patient's brain tissue.

In the original patient's brain, Dr. Alzheimer observed abnormal clumps of glassy yellowish material (amyloid plaques) and tangled black bundles of fibers (neurofibrillary tangles). Such plaques and tangles are now considered the hallmark of AD. Because the patient in question was not very old, AD was first considered a "pre-senile" or premature form of dementia. Only later was it realized that the majority of elderly people who became "senile" also have plaques and tangles in their brains, characteristic of AD.

It is now known that AD is the most common cause of irreversible, progressive dementia in the elderly. As many as 4.5 million Americans may suffer from AD. Although younger people occasionally get AD, as observed by Dr. Alzheimer, the disease is more frequent in people age 60 and older and risk of AD continues to increase with age. As many as 5 percent of people ages 65 to 74 have AD,

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DIRECTOR'S MESSAGE ... *Continued*

but this increases to nearly half of those ages 85 and older. Nonetheless, AD is not just normal brain aging. Rather, it is a disease process that occurs in some, but not all, aging brains.

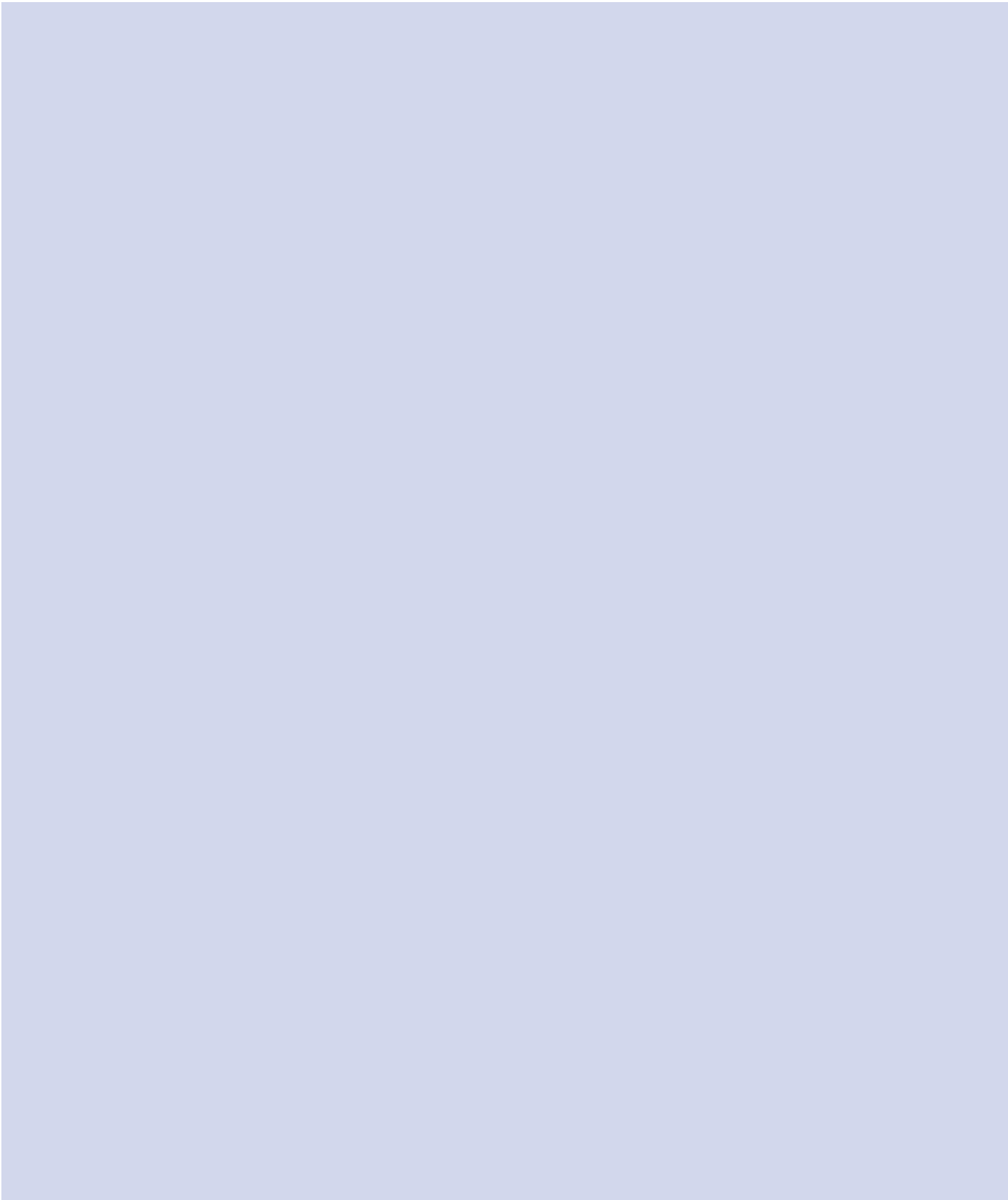
The pathological process of AD first involves the brain areas responsible for thought, memory and language. Scientists studying AD have concluded the plaques and tangles mark areas of the brain where nerve cells have died. The first nerve cells to die are those that are vital to memory and other mental abilities. As nerve cells drop out, vital connections to and from other nerve cells are lost. It is as if critical switches in a huge telephone center have burned out, so that incoming signals cannot be relayed. Thus, AD impairs thinking and memory by disrupting transmission of vital messages. Despite all we have learned about AD, we still do not fully understand the cause, nor do we yet have a cure.

It is clear that inheritance plays an important role in AD. Certain genes have been shown to greatly increase the risk that a person will develop AD. For example, one form (Apo-A4) of the gene for a protein called Apo-A increases the risk of AD, whereas another form (Apo-A2) appears to be protective. Persons who inherit two genes of the Apo-A4 type (one from each parent) are at very high risk for AD and develop it earlier in life. Many scientists are hard at work trying to unravel the processes leading to nerve cell loss in AD. Some believe the processing of the protein that becomes amyloid holds the key. Others think the formation of amyloid is part of a defense reaction against cell death and that other processes leading to nerve cell destruction are more important. One candidate for such a process is damage by oxygen free radicals (oxidative stress), a basic mechanism implicated in many processes related to various chronic diseases, and perhaps to aging itself.

In studies of aging dogs, animals fed diets high in antioxidant compounds developed AD-like damage to the brain either much later, or not at all, when compared to control dogs fed a normal canine diet. Humans with early signs of dementia frequently have high levels of isoprostanes, compounds that are markers of ongoing oxidative damage, in their blood, urine and spinal fluid.

Although we do not yet have truly effective treatments for AD, there do seem to be preventive effects of regular exercise – both physical and mental – and a healthy diet with lots of fruits and vegetables (natural anti-oxidants). Only with continued research, requiring support from public and private sources, will we finally determine the fundamental cause of this scourge of the elderly. KLRI has been working on better methods to define and measure ongoing oxidative stress. Perhaps this research will eventually contribute to better methods to prevent or cure AD.

***S. Mitchell Harman, MD, PhD
Director and President
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observations of memory loss problems in a loved one, typically excusing their forgetfulness with comments like, "Frank's getting old, he's supposed to forget." Or, "She's under so much stress. I'd have trouble remembering things, too." Since the patient often denies there is a problem and may actively resist being brought in for help, some patients, consequently, are reasonably advanced on initial presentation to their physician.

Long-term memory loss is less easily appreciated in the early stages, although with careful questioning, forgotten items from months or years ago can be identified. Other symptoms of AD are best understood by categories. Each category is a function that our brain performs, usually unconsciously, every day. For example, difficulty with making travel arrangements highlights problems with *planning*. Many activities requiring calculation, organization, sequencing, judgment, insight, executive functioning, spatial understanding and problem solving are also gradually impaired. Examples include getting lost while driving, inability to do the taxes or balance the checkbook, or difficulty following a recipe, calculating a tip, counting change or writing a report for the book club. Later symptoms are more apparent and more incapacitating, such as forgetting how to operate the TV remote or the microwave oven, being unable to finish a knitting project or put the doorknob back together. Less apparent is the gradual failure to even attempt previously enjoyed activities with the default being watching more TV or taking more naps. A family member who fails at a previously acquired skill or begins to neglect such activities should trigger an evaluation at his doctor's office.



Diagnosing Alzheimer's Disease

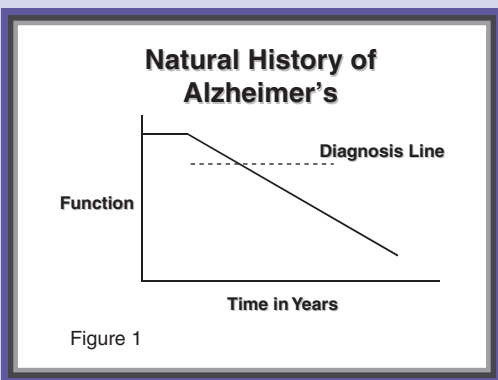
In the doctor's office, many familiar things take place, like a period of questioning with both the patient and the family member followed by a physical examination, some blood tests and likely a CAT scan or MRI scan of the brain. Here's what happens behind the scenes. First, Alzheimer's is mostly a diagnosis of exclusion, that is, there are no tests for the disease. There are only tests to eliminate other conditions that could cause similar symptoms. For example, you cannot see AD on an MRI scan. To that end, the doctor takes a careful history to confirm the presence of the cognitive (mental capacity) decline, which includes asking about many of the categories described above. The physical examination is performed to uncover other illnesses, and the blood tests will check for thyroid disorder, B₁₂ deficiency, certain rare infections, blood disorders and other such things. Lastly, the brain scan eliminates strokes, collections of fluid or blood around the brain or tumors. Once all the information is in, the physician will likely give the diagnosis of the cause or causes of the cognitive decline.

One thing to keep in mind, AD is a dementia but not all dementias are AD. How does that work? Dementias are a group of diseases of which Alzheimer's is the largest and most important one, but there are many others. A *dementia* is defined as a global, irreversible loss of cognitive ability, typically caused by a degenerative disease. Some diseases cause a reversible loss of cognitive functions, such as a severely low thyroid disorder, but it is not a dementia. Global loss indicates that a selective loss of a

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function, for example, short-term memory only, does not qualify. It also indicates a loss of previously acquired abilities.

Now that we know the symptoms and course of Alzheimer's, look at **Figure 1** for an overview of a typical case of AD. The disease pathology probably starts at least a decade before any symptoms are noticed. Even after symptoms start occurring (when the line starts its decline), it is typically some time before a diagnosis is made. After the diagnosis, the disease continues to progress over time until significant care is required, like a nursing home or its equivalent.



AD and most other dementias are degenerative diseases, characterized by progressive loss of nerve cells from the brain followed by a cascade of events. This, then, is a good time to turn to the causes of AD.

Causes of Alzheimer's Disease

Alzheimer's disease is known as a complex disease, which is to say, its causes are varied, multiple and have not yet been pinned down. But researchers do know quite a bit already.

In 1907, a hundred years ago, Alois Alzheimer published a paper detailing the progressive dementia of a 50-year-old washer woman. What set this paper

apart was Dr. Alzheimer's careful microscopic examination and description of her brain. For under his microscope, he saw the basic pathology that defines Alzheimer's and with which we still wrestle today, namely *plaques and tangles*.

Plaques are gummy deposits of a protein like substance called amyloid, which stains a reddish orange and occurs in the millions throughout the Alzheimer's brain. Surrounding them is a halo of nerve cell loss, cellular debris and some evidence of inflammation. Amyloid results from a chain of events that started out with a perfectly normal protein whose metabolism (parlance for digestion, with the constituent amino acids recycled into other proteins) was diverted and incomplete. The result is a 38 to 42 indigestible amino acid chain, called a polypeptide, left over that literally has no where to go. The neurons expel the soluble amyloid into the extracellular space after which time they meet other bits of amyloid and begin to clump together into larger and larger aggregates until it becomes insoluble and lodges to form a new plaque. The pre-plaque soluble aggregations of amyloid have been pejoratively called "toxic species," implying they cause damage even before they form the plaque. Once a plaque, it appears to continue to cause problems in the surrounding neighborhood, in part by inciting inflammatory activity that likely harms nearby neurons. The combination of the toxic soluble amyloid and the plaque-catalyzed inflammation are in part responsible for neuronal death.

The tangles are the left-over, collapsed, internal microtubular skeleton of a dead nerve cell. There are also millions of these scattered throughout the Alzheimer's brain, evidence of a previously thriving nerve cell. Microtubules not only form a structural support system for a nerve cell, they also have important transport roles as well. Think of them as

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the cell's internal super highway, roads by which nutritional and maintenance components travel around the cell. A protein called Tau is a key adjunct to the microtubular transport system. In the Alzheimer's brain, the Tau proteins become attached to multiple phosphorous atoms, which rapidly and irreversibly paralyze the Tau protein's function. The cell, without a way to move important products around the cell, then dies with the collapsed skeleton, which is the tell-tale tangle seen by Dr. Alzheimer.

Commensurate with all this pathology (and others, not discussed here) is a gradual but profound loss of neurons, with some estimates of up to a quarter of the total nerve population dead or dying. As if this were not bad enough, scientists have identified a number of "susceptibility genes," some of which have shown to increase a person's chance of getting AD. In addition, some early onset Alzheimer's, occurring before the age of 60, have a dominant gene for getting AD.

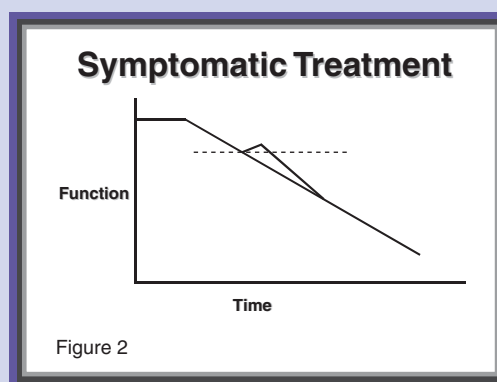
Current Treatment Strategies

When I started out as a young neurologist, there was no treatment to help the symptoms of AD. Since then, there have been a total of five medications approved by the FDA for the *symptomatic* treatment of Alzheimer's disease. They are: Cognex, Aricept, Exelon, Razadyne (formerly Reminyl) and Namenda.

The first four all work in a similar manner with Namenda working in a somewhat unique manner. All of these medications enhance or modulate certain brain chemicals that improve the function of the surviving neurons. They improve the symptoms of AD but have no appreciable effect on the disease itself. The situation is much like treating hypertension or a cold. These medications do not shorten the cold or fix the high blood pressure, but we take them anyway

because they make us feel better. In addition, the Alzheimer's medications actual ability to improve the symptoms is modest at best and is usually temporary. This has recently caused the United Kingdom to consider curbing or limiting their use, since they do have a considerable effect on the collective pocket-book.

Consider **Figure 2**, which illustrates the effect of symptomatic treatment. Note that the actual functional debility is not changed over time and there is little net effect, although even the temporary pause in apparent symptom progression can be hugely important to the family.



Unfortunately, well meaning doctors have misrepresented the medications' effect by telling their patients something like, "this will slow it down." I think this creates an unrealistic expectation for the family. All of the foregoing aside, the availability of any medicine for AD is a milestone and, in particular cases, the improvement has been gratifying, at least for a while.

Disease Modifying Approach to Alzheimer's

With the increased understanding of the pathology of AD, many pharmaceutical companies are now con-

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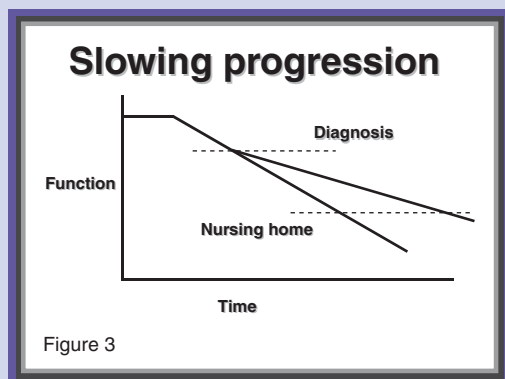
ducting clinical trials on treatments and drugs that may have an effect on the underlying pathology.

First is an immune approach. Scientists are using highly targeted antibodies thought to attack the amyloid and help clear it out of the brain. This seems to work in rat models with evidence that it works in removing the plaques. Once the antibody attaches to the amyloid in the plaque, the body uses a type of "garbage truck" cells called microglia to gobble up the antibody-amyloid pairing and gradually reduce the amyloid plaques.

Another approach notes that a hormone system in the body is out of kilter in AD patients. The medication being studied is hoped to improve the hormonal balance and help the surviving neurons better resist Alzheimer's processes.

Still another company is looking at a compound that may slow the production of amyloid in the brain, which hopefully would allow normal mechanisms to eliminate the reduced amounts of amyloid that were produced.

As seen in **Figure 3**, the power of a disease-modifying treatment may not be immediately apparent, but the payoff is potentially years of preserved function and independent living.



There are other potential disease-modifying medication candidates not described here, each with the intent to attack some fundamental aspect of Alzheimer's pathology. Like any ambitious scientific endeavor, this one is fraught with potential risks and disappointments, some of which we have already witnessed. Researchers are more optimistic than ever before about AD research; however, there has been one significant setback. Families of those with AD are not volunteering for clinical trials like they used to. The cost of finding qualified patients for AD research has tripled and the medication development timelines have more than doubled. This is significantly slowing the pace of research in AD.

What Can You Do?

Science has spent billions in research dollars proving the benefits of what your grandmother told you to do: eat your vegetables, get plenty of exercise and sleep, and keep your mind and body busy.

Higher education, an active life, regular exercise, keeping your mind challenged (more than a crossword a day!), and eating vegetables with antioxidants all seem to stave off, at least a little bit, the likelihood of getting AD. There is some evidence

that copper in tap water may accelerate AD. So put on your walking shoes, put a book-on-tape in your iPod, take a bag of mini carrots and a bottle of water, and head over to a seminar at the Kronos Longevity Research Institute. Your mind and body will thank you for years to come.

Louis Kirby, MD, is a scientific advisor for Kronos Longevity Research Institute and is also the Medical Director at Pivotal Research.



NUTRITIONAL FACTORS IN THE DEVELOPMENT OF ALZHEIMER'S DISEASE

In the United States, an estimated 4.5 million Americans are affected by Alzheimer's disease (AD) today. While there are no proven cures or treatments, fortunately, there are some foods or, more specifically, nutrients that seem to have protective effects.

There are a number of prospective or long-term studies that have been in progress for decades, including the Baltimore Longitudinal Study of Aging, the Nurses' Health Study, the Normative Aging Study, the Chicago Health and Aging Project, the Cache County Study and the Framingham Study. In these studies, diet intake information has been collected periodically over many years, so diet intake was measured before there was any sign of the disease. People who have developed AD can be compared to an age-matched group of those who have not. While this type of study cannot definitely say that specific food choices are the cause of the development of the disease, various assessments of risk can be calculated. Some specific foods and nutrients that have been associated with a reduced risk of developing AD are discussed below.

Calories/Energy/Fat

People living in countries such as China and Japan where average intake of energy (total calories) is low

and obesity rare are much less likely to develop AD than people living in countries where energy intake is high such as the United States and Western Europe. High meat or saturated fat intake may contribute to the increased risk of AD. Vegetarians are less likely to develop the disease than those eating lots of meat. One possible explanation for this finding is that high calorie, high saturated fat diets promote oxidative damage in the brain and these diets are low in

antioxidants such as vitamins A (carotenes), C, and E found in fruits and vegetables. While there are many other differences in these populations, an American study following people for four years found that those consuming lower total energy were less likely to develop the disease. An abnormality in a protein in the blood that helps remove cholesterol

(Apolipoprotein E) is found in some people with AD and may help to explain this finding.

Fish

Many studies have found that those who consume fish regularly, especially cold water fish like salmon, are protected from heart disease. A Chicago study of 815 older Americans found those who consumed fish at least once a week also had a 60% lower risk of developing AD than those who rarely ate fish. Certain



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Nutritional Factors ... *Continued from Page 8*

salad dressings and nuts may also reduce risk. These foods contain specific types of fat (omega 3 fatty acids), which are protective.

Wine

Several population studies report that moderate drinkers are less likely to develop AD than tea totalers. The key word is moderate and the effects seen may be due to consumption of red wine and not other alcoholic beverages. Red wine and grapes contain an antioxidant compound (resveratrol) that may break down the amyloids in the brain. Studies on cell lines are difficult to apply to real life consumption of people, but results are encouraging. Excessive alcohol intake causes mental deterioration, so more is not better.

Antioxidant Vitamins

Antioxidant vitamins C and E and vegetable forms of vitamin A (carotenes) help to rid the body of toxic compounds called oxidants such as peroxide (think rust). Alzheimer's patients have lower blood levels of vitamins C and E than age-matched people without the disease. Results testing the protective effects of antioxidant vitamins have been inconsistent. Average follow-up periods from initial intake assessment to diagnosis were 3-6 years. Both supplement and total diet intakes have been analyzed. Some found a protective effect with C or E or the



combination of the two and some did not. A study of 5,395 people found significant protective effects for total intakes of vitamin C or E and a Utah study of 4,740 people found a protective effect in those consuming antioxidant supplements combining C and E, but other studies found no protective effect. A protective effect for vitamin E, but not C, was found in the Baltimore Longitudinal Study of Aging when those consuming at least the RDA were compared to those consuming less. Since average intakes (167 mg/day) for vitamin C were well above suggested levels, perhaps few subjects had intakes low enough to increase risk. Most Americans consume adequate amounts of vitamin C, but many do not receive recommended levels of vitamin E from diet alone.

Vitamin E occurs in eight different forms in foods (four tocopherols and four tocotrienols). Recent research indicates that the form of vitamin E generally used in vitamin supplements (alpha tocopherol) may not be the only form that protects against AD. This may explain some of the confusion about the protective effects of vitamin E. A re-evaluation of data from the Chicago Health and Aging Project found gamma tocopherol also had a protective effect. In animal studies, gamma tocopherol was more effective than alpha tocopherol in reducing inflammation. Gamma tocopherol is high in corn and soybean oils while alpha tocopherol is high in wheat and sunflower oils.

The Nurses' Health Study gathered both diet and mental function information from about 13,000 women from 1984 to 2003. Mental scores of women who consumed more vegetables that contained high

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antioxidants (carotenes and vitamin C) declined less from 1993 to 2003 than those who ate fewer amounts of vegetables. While these results are encouraging, they can not be attributed to specific vitamins or minerals because the vegetables contain numerous compounds that may be effective. The Baltimore Study failed to find a protective effect of consuming vegetable sources of vitamin A.

B Vitamins

Deficiencies in B vitamins have been proven to cause dementia. The actions of folic acid and vitamins B₆ and B₁₂ are intertwined such that a deficiency of one affects the levels of the others. Levels of both folic acid and vitamin B₆ in diets of Americans, especially older Americans, have been reported to be low. Though vitamin B₁₂ intakes may appear to be adequate, as people age, they become less able to absorb vitamin B₁₂ from foods. Homocysteine (a protein found in the blood) builds up if people are deficient in folic acid or vitamin B₁₂ and is related to higher risk of heart disease. This compound may be toxic to brain cells. In 2000, grain foods have been fortified with folic acid. The target population was women of childbearing age and the reason for the addition of folic acid was to reduce the incidence of neural tube birth defects in their children. This fortification has had the added benefit of reducing homocysteine levels in the blood of older subjects since they consume relatively high amounts of these grain foods.

High blood homocysteine has been related to higher risk of dementia and Alzheimer's disease in case-control studies and in three large prospective studies. In an Italian study of more than 800 men and women, low blood folic acid and high homocysteine levels increased risk of developing both dementia and AD four years after initial measurements. In this study, vitamin B₁₂ did not protect against disease. The Boston-based Veterans Affairs Normative Aging

Study, which began in 1963, studies men who were originally healthy every 3-5 years. In a recent report, blood levels, food frequency intake information and mental tests of more than 300 men were collected three years apart. Both adequate diet intakes and high blood levels of vitamins B₆ and B₁₂, folic acid and low blood homocysteine reduced risk of developing AD in the three-year follow-up tests. Men with average intakes of over 523 µg folic acid and 3.1 mg vitamin B₆ a day were protected. Both of these values are above the recommended dietary allowances of 400 µg folic acid and 1.5 and 1.7 mg Vitamin B₆ for women and men, respectively. Results for vitamin B₁₂ were less clear-cut. Both the Italian and Boston studies suggest a beneficial effect of more than adequate intakes of B vitamins, but the follow-up period is not really long enough to rule out the possibility that controls may be in the early stages of the disease resulting in a false conclusion.

In the Baltimore Longitudinal Study of Aging, which began in 1958 and re-examines men and women every 2-3 years, repeated mental tests, 7-day diet records and supplement intake information were collected from 1984-1999. The follow-up period averaged 9.3 years. Mental tests initially showed no signs of mental deterioration. Both high vitamin B₆ and folic acid intakes reduced risk of developing AD in the follow-up. Vitamin B₁₂ did not protect.

These studies, though they cannot confirm a cause and effect, are very suggestive of the protective effect of both vitamin B₆ and folic acid. Results for vitamin B₁₂ are not as strong.

Minerals

Because aluminum is concentrated in the amyloid plaques found in brains of Alzheimer's patients,

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aluminum exposure was thought to be a cause in the development of the disease. Subsequent research, however, has not confirmed this hypothesis. A recent French study examined mineral content of drinking water consumed by about 7,500 older women. Aluminum was not associated with development of AD about seven years later, but low silica content was.

This study suffers from many limitations. The demented women were older, less educated and poorer at baseline. These factors may have influenced performance on the mental tests.

A certain abnormal iron compound (magnetite) also may accumulate in the brains of Alzheimer's patients. These compounds may occur because of flaws in the normal action of iron in the body and may be related to iron deficiency or imbalance of one of the many other compounds required for normal processing of iron (zinc, copper and some B vitamins).

Sulfur-containing protein compounds (methionine and cysteine) are necessary for production of antioxidant compounds that remove toxic oxygen compounds from the body. Imbalance of these amino acids has been associated with the development of AD. Consumption of foods such as onions and garlic, which are high in these sulfur compounds, can help remove these toxic compounds.

Herbs

While there are a number of herbal supplements that have been touted to prevent or delay loss of mental

ability, research on them has not been well designed or controlled. Actual content of the supplements is variable and identification of the active ingredients in many has not been conclusive. Many of the purported active ingredients are antioxidant compounds. Consumption of large amounts of herbal supplements constitutes pharmacological use and can have serious consequences.



Ginkgo biloba has been studied more than most of the other supplements. Ginkgo increases blood flow to the brain, but it may also increase blood pressure. Large amounts may cause diarrhea. Concurrent consumption of other

supplements and prescribed drugs may result in excessive blood thinning. Results of well-controlled studies are inconclusive. An Austrian study of more than 500 people over 75 years old (Vienna TransDanube Aging Study) found that those consuming Ginkgo biloba for at least two years had lower levels of an amyloid blood substance (amyloid beta 42). However, while this substance is high in early stages of some AD patients, it cannot be used to diagnose the disease. Another limitation of this study is the huge number of other drugs and supplements subjects took, which may have affected blood levels of amyloid beta42.

Other herbal supplements suggested to improve memory for which there is even less solid evidence are ginseng (*Panax quinquefolius* and *Panax ginseng*), club moss (*Lycopodium*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*),

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dandelion flowers (*Taraxacum officinale*), to name just a few. Proposed causes for effects are either antioxidant properties or choline or lecithin content. Choline and lecithin increase brain levels of a substance that helps to transmit nerve impulses

(acetylcholine). Numerous studies have used choline or lecithin to improve memory in demented patients with few positive effects. Dandelion flowers, rosemary, and most nuts and legumes are high in lecithin.

A table of most of the nutrients listed in this review contains both the daily recommended dietary allowance and the upper safe limit for all sources including diet and supplements. Exceeding these limits can result in adverse consequences.

Recommended Intakes and Upper Safe Limits for Nutrients Discussed

Nutrient	Men > 50		Women > 50	
	RDA	Upper Limit	RDA	Upper Limit
Vitamin A	900 µg	3000 µg	700 µg	3000 µg
Vitamin C	75 mg	2000 mg	90 mg	2000 mg
Vitamin E	15 mg	1000 mg	15 mg	1000 mg
Folic Acid	400 µg	1000 µg	400 µg	1000 µg
Vitamin B ₆	1.7 mg	100 mg	1.5 mg	100 mg
Vitamin B ₁₂	2.4 µg	Not determined	2.4 µg	Not determined
Choline	550 mg	3500 mg	425 mg	3500 mg

Summary

Although there is not a magical food that protects against the heart-breaking decline of a loved one with AD, there are a lot of choices one can make to minimize the possibility and perhaps slow the process. These dietary suggestions are oddly similar to advice given to prevent, delay or manage type 2 diabetes, hypercholesterolemia, heart disease, hypertension, stroke, arthritis and other debilitating conditions that often accompany aging:

- ❖ Maintain a healthy weight and exercise regularly
- ❖ Drink a little, but not too much (red wine is best)
- ❖ Don't eat too much fat, especially from meat
- ❖ Eat cold water fish once a week
- ❖ Eat lots of fruits and vegetables
- ❖ Make sure you get enough vitamin E, but not too much
- ❖ Make sure you get enough folic acid, vitamins B₆ and B₁₂
- ❖ More is not always better and is sometimes dangerous

Judith Wood Hallfrisch, PhD, is a scientific advisor for the Kronos Longevity Research Institute and is an expert in the evaluation of nutritional supplements.

Who We Are!

Kronos Longevity Research Institute (KLRI) is a not-for-profit, 501(c)(3) organization that conducts state-of-the-art clinical translational research on the prevention of age-related diseases and the extension of healthier human life. KLRI tests new strategies to detect and prevent chronic diseases associated with aging and investigates the effects of innovative interventions to slow the aging process and improve health outcomes for older persons. In addition, KLRI helps the medical and lay communities understand important aging issues. KLRI research findings support a healthier quality of life and a robust lifestyle in our senior years.

Our Mission

To perform and foster clinical translational research aimed at healthier human longevity and communicate results to the professional and lay communities.

Our Governance

A distinguished board of directors, with a unique mix of scientists, longevity specialists, and community leaders governs KLRI. There is also a scientific advisory board of recognized international experts in medical and scientific fields, including nutrition, exercise, hormones, bone and joint diseases, cancer and heart disease.

What Is Translational Research?

Translational research takes promising findings from the basic research laboratory and carries them forward into the clinical arena. It is the link between basic research (experiments done with animals or cultured cells, genes, etc.) and improved clinical care. It requires controlled studies of living human subjects.



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Board Member Profile

Damin J. Lopez, Hispanic Marketing Consultant

Damin Lopez is a Hispanic Marketing Consultant for several companies in the metropolitan Phoenix area. With more than a decade of experience in the industry, Mr. Lopez focuses on strategic planning, media analysis and placement, public relations, creative production, event marketing and promotions.

Prior to his consulting position, Mr. Lopez served as Director of Account Planning for the Martz Agency where he handled several real estate clients including Villago Master-Planned Community, Optima, Estrella and retail clients including Mach 1 Air Services, Cypress Homecare Solutions and all new business development at Martz.

Before Martz, he was the President/Managing Partner of Grupo Ñ Advertising, a full-service advertising firm that specializes in reaching out to the Hispanic community. His client list included: Coca-Cola North America, The Arizona Lottery, Anti-Smoking Campaign, Maricopa Community Colleges, Bank of America, City of Tempe, Red Devil Family

Restaurants, Macayo's Restaurants, United Phoenix Fire Fighters and Arizona Parent's Commission Against Drugs.

In addition to his corporate clients, Mr. Lopez has led several advertising and public relations campaigns for statewide initiatives and national candidates. Locally, his involvement includes the City of Phoenix Transit Campaign in 2000, the City of Phoenix Bond Election 2001, and several ballot proposition initiatives. Nationally, he served as a strategist for reaching the Arizona Hispanic community for Al Gore for President in 2000.

A second generation Hispanic American, Mr. Lopez is very active in the Hispanic and Greater Phoenix communities. He volunteers with the Phoenix Suns Charities and graduated with Valley Leadership's Class XXII. He recently completed his term as Chair-Elect for the American Lung Association of Arizona/New Mexico.

A native of the Valley, Mr. Lopez attended Pepperdine University where he received his Bachelor of Science degree in Business Administration.

DIRECTOR'S FORUM

You are cordially invited to join us for the

Director's Forum & Reception • 5:30 p.m., April 6, 2006

Topic: Nearly 7 million people in the U.S. are unaware that they have diabetes! Are you one of them?

Speaker: Robert G. Nelson, MD, PhD, *Staff Clinician*
Diabetes Epidemiology and Clinical Research Section
Phoenix Epidemiology and Clinical Research Branch
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health

Location: Embassy Suites at the Biltmore, 2630 E. Camelback Road, Phoenix

Please RSVP by calling (602) 778-7492 or email diana.vuong@kronosinstitute.org

Research Snapshots

Current Research Projects

Testosterone's Effects on the Progression of Atherosclerosis in Aging Men (TEAAM): KLRI is collaborating with the University of California at Los Angeles, Drew University School of Medicine and Boston Medicine Center, Boston University School of Medicine on a study designed to determine the effects of testosterone replacement in older men on cardiovascular disease risk. Loss of testosterone with age may lead to decreases in bone and muscle strength and contribute to frailty and poor quality of life.

Kronos Early Estrogen Prevention Study (KEEPS): KEEPS is designed to provide prospective data on the risks and benefits of early menopausal hormone therapy, particularly as it relates to the progression of atherosclerosis (heart disease). KLRI will oversee KEEPS research and eight study centers are involved in recruitment.

Kronos Statin Pilot Study: Statins are cholesterol lowering drugs that decrease the risk for cardiovascular disease. However, statins lower coenzyme Q10, a vitamin that is important for aerobic energy production. Energy is critical for normal muscle function. Many patients who take statins complain of muscle aches, cramps, and weakness. KLRI is performing a pilot study on the effects of statins on exercise capacity and skeletal muscle function during mild and moderate exercise.

Diabetes and Oxidative Stress: KLRI supports and helps with a Veteran's Administration study which measures the effects of better glucose control on oxidative stress-related risk factors for heart disease in adult-type diabetics. This study investigates how changes in these risk factors relate to the progression of coronary heart disease.

Completed Research Projects

Cancer Detection with the AMAS Test: Malignin is a protein found on the outer surface of many kinds of cancer cells. Therefore, measuring levels of anti-malignin antibody in serum (AMAS) could help diagnose cancer. KLRI completed a study in women having biopsies for breast cancer. A manuscript reporting the findings has been submitted for publication.

Validation of Oxidative Stress Assessments: Oxidative stress is the ongoing damage to an organism due to oxidation (the reaction of cell components with oxygen). This resembles the rusting of metal components in a car, and leads to loss of function. Oxidative stress is considered an important factor in the aging process. KLRI completed a study to characterize and validate laboratory methods needed to measure the effects of therapies designed to slow or reduce oxidative stress.

Omega-3 Fatty Acids and Endocrine/Immune Dysfunction in Humans: Omega-3 fatty acids are polyunsaturated fatty acids found in certain natural foods, especially fish, like salmon and tuna. They are known to help protect against heart disease. Omega-3 fatty acids may help hormone signals get into cells whose outer layer (cell membrane) has been stiffened by age. KLRI examined whether a diet high in omega-3 fatty acids may help restore normal hormone balance.



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