

## Alzheimer's Disease

Researchers are quietly making amazing discoveries about the nature of Alzheimer's disease that may soon redefine the way we view—and treat—this dreaded condition.

Currently, conventional medicine is helpless in the face of Alzheimer's. Alzheimer's disease cannot be definitively diagnosed until after death, and there is no effective cure for the disease. People afflicted with Alzheimer's gradually lose cognitive ability as their neurons (brain cells) are attacked and destroyed. In the end stages of the disease, patients become completely disoriented and rely on caregivers for even their most basic functions.

There is a desperate need for a new approach to Alzheimer's. It is already a significant health problem and the most common cause of dementia, and will get worse as the population ages, according to experts from the National Institute of Aging. Over the past 25 years, the number of patients who have Alzheimer's disease has doubled, and the incidence is expected to increase in coming decades as the US population ages (ADEAR 2004).

Sadly, while Alzheimer's disease continues to claim more victims, evidence is building that some of the best therapies to slow its progression and lower the risk of developing the disease are being ignored.

### THE ALZHEIMER'S PUZZLE

Alzheimer's disease is characterized by two key abnormalities: amyloid plaques and neurofibrillary tangles. Amyloid plaques are clumps of a protein known as beta-amyloid. These plaques are found in the tissue between nerve cells in the brain and in degenerating pieces of neurons.

Neurofibrillary tangles, which are made of a protein called tau, are bundles of twisted filaments found within neurons. Tau is normally responsible for helping cells to function correctly; it delivers various substances throughout the cell. In people who have Alzheimer's disease, tau becomes abnormally shaped and twists into pairs of helical filaments that gather in tangles. Because of the tangles, the neurons lose their ability to function, and the neurons eventually die. No one knows why this happens but there are probably several overlapping causes of Alzheimer's disease.

Genetic factors clearly play a role. The disease runs in families, and several genes have been identified that raise the risk of Alzheimer's disease (Kasper DL et al 2004). One such abnormality affects a lipid (fat) called apolipoprotein E (apoE). There are three types of apoE. People who have one particular type of apoE (apoE4) are more likely than other people to develop Alzheimer's disease. Even this knowledge, however, is of limited use because the presence or absence of apoE in any form is not a strong enough indicator to justify using apoE4 as a widespread screening tool.

Compelling and growing evidence links inflammation and oxidative stress to Alzheimer's disease. According to the inflammation theory (discussed in dozens of recent clinical trials), inflammatory cytokines gather at the neurons of people who have Alzheimer's. These cytokines set off an inflammatory cascade. The inflammation generates high levels of free radicals that contribute directly to the formation of beta-amyloid plaques. The result is more inflammation, free radicals, and beta-amyloid plaques. Iron has also been linked to the generation of free radicals. Studies have shown that free iron accumulates on the surface of dying neurons, where it generates oxygen-derived free radicals that hasten the spread of the disease (Mandel S et al 2006).

Supporting the inflammation theory is the fact that nonsteroidal anti-inflammatory drugs (NSAIDs), taken over the long-term, actually decrease the risk of developing Alzheimer's disease and delay its onset. Of course, this presents a problem: long-term intake of NSAIDs is not a good idea. Over-the-counter NSAIDs, such as ibuprofen, are associated with gastrointestinal and kidney complications, while prescription COX-2 inhibitors have been shown to raise the risk of heart attack and stroke.

The inflammation theory of Alzheimer's disease is joined by other possible causes, including the excitotoxicity theory. In this theory, high levels of the amino acid glutamate in the brain overstimulate neurons. The overstimulated neurons release inflammatory cytokines. Glutamate excitotoxicity is mediated by N-methyl-D-aspartate (NMDA) receptors.

Other possible causes include high levels of homocysteine in the brain and specific nutrient deficiencies. Although these ideas are still developing, they have opened up exciting new targets for therapy. In clinical studies, the most cutting-edge researchers are turning to therapies such as anti-inflammatory nutrients, antioxidants that reduce oxidative stress, and metal chelating agents (such as green tea) that reduce the levels of free iron in the brain.

## DIAGNOSIS AND CONVENTIONAL TREATMENT OF ALZHEIMER'S DISEASE

The onset of Alzheimer's disease is insidious. The disease typically begins with moments of forgetfulness, or memory lapses. Over time, the memory loss becomes worse and may be diagnosed early as mild cognitive impairment, a less serious form of dementia. Slowly, however, the cognitive decline begins to interfere with daily activities, such as keeping track of information and following instructions. People who have Alzheimer's disease may become bewildered and may even be unaware of their slowly deteriorating condition.

In the next stage, language skills are affected. Words are forgotten, and the person's comprehension level is reduced. Eventually, fluency is lost. In the final stages, spatial functioning begins to deteriorate. The person may no longer be able to dress, eat, or perform simple tasks. Loss of judgment and reasoning occurs. Delusions are common. People who have advanced Alzheimer's disease are sometimes found wandering around the house at night. Up to 10 percent have delusions in which they think that their caregiver has been replaced by an imposter.

This disease is notorious for the horrible toll it exacts on caregivers and other family members. The emotional burden can be debilitating as caregivers watch their loved one slip away. Caregivers must assume ever-increasing responsibility for the well-being of the person with Alzheimer's disease. It is essential that caregivers of people who have Alzheimer's disease take care of themselves and seek support and counseling when necessary.

The slow onset of Alzheimer's disease makes diagnosis difficult. In fact, the disease cannot be diagnosed with complete certainty until the person has died and an examination of the brain at autopsy reveals the brain plaques. In the meantime, imaging studies may be used, including computed tomography (CT) and magnetic resonance imaging (MRI), to show deterioration in the cortex of the brain. Screening tools such as the Mini-Mental State Examination are used to confirm dementia and track the progress of the disease.

At best, conventional pharmacology can reduce the symptoms of the disease, but there is no "highly effective" drug (Kasper DL et al 2004). Sadly, most people (even many physicians) remain unaware of the newest research on Alzheimer's disease, resulting in tens of thousands of people relying on medications that do not work.

Conventional medicine focuses on stimulating the neurotransmitter acetylcholine. This chemical, among other neurotransmitters, is responsible for carrying impulses along nerve fibers throughout the brain. In Alzheimer's disease, acetylcholine can no longer perform its basic function. Drugs that support acetylcholine include cholinesterase inhibitors, which prevent the breakdown of acetylcholine by inhibiting acetylcholinesterase. However, cholinesterase inhibitors (such as tacrine) are expensive, and many cause liver toxicity (Kasper DL et al 2004). Donepezil, another cholinesterase inhibitor, is the preferred treatment, but, once again, it cannot address the underlying conditions of the disease. And all cholinesterase inhibitors are ineffective in the later stages of Alzheimer's disease.

Other drugs used to treat Alzheimer's include anti-inflammatory drugs such as NSAIDs and COX-2 inhibitors. These drugs, however, have adverse effects that make them less-than-ideal candidates for long-term therapy. Also, clinical studies of these medications have been disappointing.

### NUTRITIONAL THERAPY: ANTI-INFLAMMATORY SUPPLEMENTS

The most exciting research today in Alzheimer's disease focuses on the role of inflammation and oxidative stress, as well as the role of receptors in reducing glutamate excitotoxicity. Alzheimer's disease, like so many other diseases, is being redefined as an inflammatory condition in which excess pro-inflammatory chemicals in the body cause damage to normal healthy cells. Although most doctors remain unaware of this developing hypothesis, the Life Extension Foundation has assembled the latest research to provide a comprehensive approach to preventing Alzheimer's disease.

**Curcumin.** Curcumin is showing excellent early promise as an anti-inflammatory and antioxidant compound in the treatment of Alzheimer's disease. Studies of animals have shown that curcumin directly inhibits the formation of amyloid plaques (Ringman JM et al 2005). Based on early results, curcumin has generated considerable excitement in the research community. Unlike other nutrients, or even drugs, which tend to target one aspect of Alzheimer's, curcumin has been shown to lower oxidative damage, cognitive defects, damage to neural synapses, and the deposition of amyloid plaques. In addition, it regulates the levels of cytokines in the neurons (Cole GM et al 2004). In fact, studies suggest that curcumin may be even more effective than the over-the-counter NSAIDs ibuprofen and naproxen at inhibiting the accumulation of beta-amyloid in animal models (Yang F et al 2005). As previously discussed, beta-amyloid is involved in the formation of senile neuronal plaques. One method by which curcumin reduces inflammation is reduction of nuclear factor kappa B (NF kappaB), a nuclear transcription factor that regulates the genes that control cytokine production (Aggarwal BB et al 2004).

Curcumin has also been shown to help reduce the levels of toxic metals in the neurons by chelating (binding to) them. Metals such

as iron and copper can cause amyloid aggregation by stimulating NF kappaB. Curcumin has been shown to bind to these metals, thus possibly inhibiting plaque formation (Baum L et al 2004).

**Ashwagandha.** Ashwagandha is a medicinal plant used in India to treat a wide range of age-related disorders. Its most remarkable effect may involve its ability to preserve the health of the aging brain. Research indicates that ashwagandha extract is capable of halting and even repairing damage to brain cells in an experimentally induced model of Alzheimer's disease (Kuboyama T et al 2005). Scientists in Japan induced Alzheimer's-type brain cell atrophy and loss of synaptic function in mice by exposing them to the toxic protein beta-amyloid (Kuboyama T et al 2005). In laboratory experiments in India in 2004, researchers discovered that ashwagandha root extract inhibits acetylcholinesterase in much the same way as the prescription drug donepezil, which is currently used in the treatment of Alzheimer's disease (Choudhary MI et al 2004).

### ***Breakthroughs with Omega-3 Fatty Acids and Lecithin***

Over the past 10 years, scientific studies have revealed the remarkable effects that fish consumption has on neurological function. Fish oils contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both of which are omega-3 oils. DHA is essential to brain health because it constitutes between 30 and 50 percent of the total fatty acid content of the human brain (Young G et al 2005).

Deficiencies in DHA have been linked to cognitive decline, and human cell studies have shown that DHA reduces beta-amyloid secretion (Lukiw WJ et al 2005). DHA has been documented to increase phosphatidylserine, a naturally occurring component found in every cell membrane of the body (Akbar M et al 2005). DHA may also improve the memory of animals with Alzheimer's disease by suppressing oxidative damage in the brain (Hashimoto M et al 2005). In a 10-year study that tracked the DHA levels of 1188 elderly subjects, Alzheimer's disease was 67 percent more likely to develop in those whose DHA levels were in the lower half of the distribution (Kyle DJ et al 1999).

Scientists have recently developed a compound that takes DHA and binds it to a lecithin extract that has itself been shown to reduce the risk of cognitive dysfunction in the elderly. Laboratory studies document that this patented compound delivers higher DHA concentrations to brain cells.

At one time, soy lecithin granules were an enormously popular supplement. People would eat them straight or sprinkle them on other foods such as cereal. With the discovery of extraction methods that concentrate lecithin's active constituents, eating lecithin granules has fallen out of favor because consumers can now obtain lecithin's cognitive-enhancing benefits in a pill.

One of lecithin's most effective brain-protecting extracts is phosphatidylserine. Phosphatidylserine supports healthy levels of the neurotransmitter acetylcholine, facilitates brain cell energy metabolism, and provides structural support for brain cell membranes. Although it is available in Europe only by prescription, phosphatidylserine is sold as a nutritional supplement in the United States. Several studies confirm the benefits of phosphatidylserine as a key component in fostering healthy brain function. Additional studies suggest that phosphatidylserine is not only helpful in terms of treating cognitive decline, but also in avoiding its onset.

In one double-blind, placebo-controlled study, patients who had Alzheimer's disease who took 300 milligrams per day (mg/day) of phosphatidylserine performed significantly better on standardized memory tests at the end of the 12-week trial period than did the study participants who received placebo. It is important to note that the patients who were the least afflicted by dementia demonstrated the greatest benefit from phosphatidylserine therapy. These results support the idea that beginning supplementation very soon after symptoms of Alzheimer's disease appear, or perhaps even before the appearance of symptoms, can help prevent age-related loss of memory and other cognitive impairments (Crook T et al 1992).

Positron emission tomography (PET) imaging measures energy production across the brain. In patients who had advanced-stage Alzheimer's disease, PET scans revealed that, after taking 500 mg of phosphatidylserine every day for 3 weeks, every study participant showed significantly enhanced glucose metabolism across all brain regions, compared to baseline scans (Klinkhammer P et al 1990).

### ***Combining DHA with Phosphatidylserine***

Scientists have discovered that DHA attaches itself to phosphatidylserine molecules and acts as an important ally in the promotion of brain cell energy production. A number of brain researchers, such as Dr. Norman Salem, head of the Laboratory of Membrane Biochemistry and Biophysics at the National Institutes of Health, are convinced that phosphatidylserine with attached DHA is among the most critically important molecules for healthy brain function. Scientists believe that phosphatidylserine supplementation works optimally if DHA levels are kept commensurately high (Kidd P 2005).

In response to an increasing body of research showing the intricate relationship between DHA and phosphatidylserine, scientists have developed a phosphatidylserine-DHA (PS-DHA) compound that can be incorporated directly into the membranes of brain cells.

To evaluate the effects of PS-DHA on memory loss, a study was done on middle-aged rats that had laboratory-induced accelerated brain aging. Administering traditional sources of DHA did not have an effect on this experimental model, but the group receiving the PS-DHA compound was able to attain a great deal of protection against this neurological challenge. When the brains of these animals were analyzed, there was more DHA incorporated in the cells of the group receiving the PS-DHA than other omega-3 agents.

### ***The Value of Glycerophosphorylcholine***

Like phosphatidylserine, glycerophosphorylcholine (GPC) is a key structural component of brain cell membranes. GPC is approved as a drug in the European Union, where physicians prescribe it to their patients who have dementia and pre-dementia. In the United States, however, GPC is available as a dietary supplement. One of GPC's cognitive restoring mechanisms is its ability to maintain optimal levels of acetylcholine in the brain.

Three double-blind trials have demonstrated GPC's ability to improve mental acuity in healthy young adults. In studies with middle-aged participants, GPC supplementation led to improvements in the results of several tests of mental performance, including reaction time. Eleven trials to date have focused on the use of GPC in seniors. In studies gauging GPC's effects on a total of 1799 participants who had minor to severe cognitive deficits, GPC supplementation helped improve memory, attention, and social behavior. Many patients who received GPC developed renewed interest in relatives and friends, became more capable of caring for themselves, and showed marked improvement in degree of depression, irritability, and emotional function.

A double-blind, placebo-controlled trial was conducted at the National Institute on Aging in Mexico City. The study showed that, after 6 months of therapy, participants who took 400 mg of GPC three times a day demonstrated significant improvement on a battery of cognitive tests, including the Alzheimer's Disease Assessment Scale–Behavioral Subscale, suggesting that GPC produces marked improvements in the conditions of patients who have Alzheimer's disease (de Jesus Moreno Moreno M 2003).

## **ANTIOXIDANT NUTRIENTS**

Oxidative stress is a very important factor in the development of Alzheimer's disease. Antioxidant supplements help block the oxidative process. According to one researcher: "Beta-amyloid is aggregated and produces more free radicals in the presence of free radicals; beta-amyloid toxicity is eliminated by free radical scavengers" (Grundman M 2000).

**Blueberry Extract.** When researchers analyzed fruits and vegetables for their antioxidant capability, blueberries came out on top, rating highest in their capacity to destroy free radicals (Wu X et al 2004). In 2005, scientists discovered mechanisms to explain how blueberries can improve memory and restore healthy neuronal function to aged brains. The astounding conclusion of researchers was that the favorable effects of blueberries on brain function are analogous to those seen with long-term calorie restriction (Joseph JA et al 1999; Lau FC et al 2005).

**Grape Seed Extract.** Grape seed extract has demonstrated remarkable success in blocking the formation of senile plaques. One of the most potent antioxidants available, grape seed extract possesses 20 times more free radical-fighting power than vitamin E and 50 times more than vitamin C (Shi J et al 2003). This remarkable antioxidant activity suggests that grape seed extract should become a part of any regimen to optimize brain health.

In laboratory experiments, brain cells of rats were treated with grape seed extract before exposing them to beta-amyloid. Although untreated rat-brain neurons readily accumulated free radicals and subsequently died, the cells treated with grape seed extract were significantly protected (Li MH et al 2004).

**Vitamin E.** Vitamin E is a powerful antioxidant. Deficiencies of vitamin E in patients who have Alzheimer's disease are associated with increased lipid peroxidation, which appears to cause increased platelet aggregation, a hallmark of Alzheimer's (Ciabattini G et al 2006). Community studies have shown that high doses of vitamin E, along with vitamin C, may help prevent Alzheimer's disease in the healthy elderly (Landmark K 2006). Combination therapy with vitamins C and E has been shown to reduce lipid peroxidation in people who have mild to moderate Alzheimer's disease (Galbusera C et al 2004). High doses of vitamin E alone, up to 2000 International Units (IU) daily, slow the mental deterioration of patients who have Alzheimer's disease (Grundman M 2000).

One method by which vitamin E might protect people has to do with its relation to apoE4, which is associated with an increased risk of developing Alzheimer's disease. In people with the apoE4 phenotype, researchers suspect that an impairment in the antioxidant delivery system to neuronal cells may be related to increased oxidative damage (Mas E et al 2006). Another theory suggests that vitamin E might be able to reduce the oxidative damage caused by large amounts of inducible nitric oxide synthase, a pro-oxidant that has been linked to progression of Alzheimer's disease (McCann SM et al 2005).

**Vitamin C.** Vitamin C is well-known for its antioxidant properties. Although it has not been as widely studied as vitamin E, several studies have examined their combined potential. One observational study showed that supplementation with 400 IU/day of vitamin E

and 500 mg/day of vitamin C reduced the prevalence of Alzheimer's disease (Boothby LA et al 2005). The study discouraged routine use of vitamin C until more studies could be performed, although the study noted that vitamin C is generally safe. The synergistic effect of vitamin C and vitamin E was examined by another team of researchers who found that using vitamins E and C in combination was associated with a reduced risk of Alzheimer's disease, but neither supplement used alone had any protective effect (Zandi PP et al 2004).

**Ginkgo biloba.** Ginkgo biloba is a powerful antioxidant that also functions as a mild vasodilator (it improves circulation), anti-inflammatory (via antioxidant effects), membrane protector, antiplatelet agent, and neurotransmitter modulator (Diamond BJ et al 2000; Perry EK et al 1999). Ginkgo biloba has generated considerable excitement because of promising results in clinical trials.

A randomized, double-blind, placebo-controlled study was conducted at the University of Southern California in Los Angeles. The study examined the effect of using Ginkgo biloba in cases of mild to moderate dementia of the Alzheimer's type. Although the study results were somewhat conflicting, a subgroup of patients with neuropsychiatric symptoms who took Ginkgo biloba showed significantly better cognitive performance than patients who took placebo (Schneider LS et al 2005).

In Germany, Ginkgo biloba extract was studied in the treatment of patients who had dementia. The research found that patients who took Ginkgo biloba experienced a significant improvement in their quality of life. Their caregivers also noted the improvement (Heinen-Kammerer T et al 2005). This same extract was shown to inhibit beta-amyloid production by lowering free cholesterol levels in the brain (Yao ZX et al 2004).

Additional studies have shown that Ginkgo biloba is well tolerated and may slightly benefit patients who have dementia, as evidenced by results of the Mini-Mental State Examination (Bidzan L et al 2005).

**Acetyl-L-Carnitine Arginate.** Acetyl-L-carnitine (ALC) is an antioxidant that has been shown to correct acetylcholine deficits in animals and protect neurons from beta-amyloid by supporting healthy mitochondria (Butterworth RF 2000; Dhitavat S et al 2005; Virmani MA et al 2001). In one study, researchers combined ALC with lipoic acid and found they could restore mitochondrial function in aged animals. The same research group conducted a meta-analysis of 21 double-blind clinical trials of ALC in cases of mild cognitive impairment and mild Alzheimer's disease and found significant benefit versus placebo (Ames BN et al 2004).

ALC arginate is a patented form of carnitine that encourages the growth of neurons in the brain. Studies show that ALC arginate stimulates the growth of new neurites by 19.5 percent, as much as nerve growth factor itself.

**Coenzyme Q10.** Coenzyme Q10 (CoQ10) is attracting significant attention in the treatment of a variety of diseases, including neurodegenerative diseases such as Alzheimer's. Studies have shown that levels of CoQ10 are altered in Alzheimer's disease (Dhanasekaran M et al 2005), and that brain energy levels are dramatically reduced in dementia-related diseases. CoQ10 has been suggested as part of a comprehensive, integrative approach (along with vitamins B, E, and K, and lipoic acid) to improve mitochondrial function in Alzheimer's disease (Kidd PM 2005). In one animal study, CoQ10 counteracted mitochondrial deficiencies in rats that had been treated with beta-amyloid (Moreira PI et al 2005). It has also been shown to destabilize amyloid plaques in laboratory studies (Ono K et al 2005).

**N-Acetylcysteine.** N-acetylcysteine (NAC) is a precursor of glutathione, a powerful scavenger of free radicals. Glutathione deficiency has been associated with a number of neurodegenerative diseases, including amyotrophic lateral sclerosis (Lou Gehrig's disease) and Parkinson's disease. One study showed that NAC significantly increased the glutathione levels and reduced oxidative stress in rodents treated with a known free-radical producer (Pocernich CB et al 2000). Another study of glutathione-deficient mice showed that the mice were more vulnerable to neuronal damage from beta-amyloid (Crack PJ et al 2005). A study of mice deficient in apoE found that NAC alleviated oxidative damage and cognitive decline (Tchantchou F et al 2005).

**Aged Garlic.** Aged garlic, or kyolic garlic, is rich in antioxidants, and has been shown to increase the levels of internal antioxidants, inhibit lipid peroxidation, and reduce inflammation. Studies have found that aged garlic can protect neurons against beta-amyloid toxicity and cell death (Borek C 2006).

**Vinpocetine.** Vinpocetine is known to protect cells from reactive oxygen species and other free radicals, as well as increase blood circulation and brain metabolism. Its protective effect has been demonstrated in laboratory studies in which cells were exposed to beta-amyloid protein (Pereira C et al 2003).

### ***Green Tea: Reducing Dangerous Metals in the Brain***

Excess levels of iron have been implicated in Alzheimer's disease, leading some researchers to wonder if chelating (or binding) free iron levels in the brain might benefit patients. Iron enhances and promotes the generation of free radicals, which are known to cause damage in Alzheimer's disease.

One potential chelating agent is green tea catechins. These powerful flavonoids have been shown to possess potent chelating properties, as well as antioxidant and anti-inflammatory powers (Mandel S et al 2006). Animal studies have demonstrated that the main flavonoid in green tea, epigallocatechin gallate (EGCG), can decrease levels of beta-amyloid in the brain, offering hope that green tea can help reduce the risk of developing Alzheimer's disease (Rezai-Zadeh K et al 2005).

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### THE B VITAMINS: REDUCING HOMOCYSTEINE

Elevated homocysteine levels (along with reduced levels of B vitamins such as folate, vitamin B12, and vitamin B6) are persistently associated with Alzheimer's disease and mild cognitive impairment (Quadri P et al 2005; Ravaglia G et al 2005; Tucker KL et al 2005). Based on the association between elevated homocysteine and Alzheimer's disease, strategies that lower homocysteine levels to safe ranges, including supplementation with B vitamins, are recommended.

**Vitamin B12.** Research has suggested that low cobalamin (vitamin B12) levels are related to dementias in general. In a study evaluating levels of vitamin B12 in patients who had Alzheimer's disease or frontotemporal dementia, researchers found a significant negative correlation (the lower the level of vitamin B12, the more the deterioration) between vitamin B12 and degree of cognitive deterioration (Engelborghs S et al 2004). A population-based longitudinal study in Sweden of 370 people aged 75 years or older who did not have dementia found that subjects who had low levels of vitamin B12 or folate had twice the risk of developing Alzheimer's disease over the 3-year period of the study (Wang HX et al 2001).

**Vitamin B6.** A study found significantly lower consumption of vitamin B6 after age 60 years in patients with Alzheimer's disease compared to control subjects (Mizrahi EH et al 2003). Low vitamin B6 levels are also associated with elevated numbers of lesions on the brains of patients with Alzheimer's disease (Mulder C et al 2005).

**Folate.** Folic acid is needed for DNA synthesis and to make S-adenosylmethionine (SAME). A study of 126 patients, including 30 who had Alzheimer's disease, found that the levels of folate in cerebrospinal fluid were significantly lower in patients with late-onset Alzheimer's disease (Serot JM et al 2001). Another longitudinal analysis of people between the ages of 70 and 79 years found that people who had high levels of homocysteine or low levels of folate had impaired cognitive function. The strongest association between abnormal levels and dementia was found in people who had low folate levels, leading researchers to suggest that folate might reduce the risk of cognitive decline (Kado DM et al 2005).

**Niacin.** A 2004 study (of more than 6000 people) conducted between 1993 and 2002 found that high levels of dietary niacin protect against Alzheimer's disease (Morris MC et al 2004). The authors researched the dietary habits of initially healthy people aged 65 years or older. As the study progressed, some study participants developed Alzheimer's disease and some remained healthy. Subjects who had the highest intake of niacin had a 70 percent reduction in risk of cognitive decline. Intake of dietary niacin was inversely related to the incidence of Alzheimer's disease and age-related cognitive decline (Morris MC et al 2004).

### NATURAL HORMONE REPLACEMENT

Estrogen replacement therapy (ERT) has been studied in relation to Alzheimer's disease with mixed results. Initial studies suggested that ERT protected women against developing Alzheimer's disease. Later studies from the Women's Health Initiative, however, suggested that combination ERT and synthetic progestin therapy increased the risk of dementia (Kasper DL et al 2004; Webber KM et al 2005). Hoping to reconcile these results, one research team suggested that estrogen has a healthy cell bias, meaning that estrogen therapy is beneficial when the cells are still healthy but can exacerbate Alzheimer's disease once neurological health begins to degenerate (Brinton RD 2005).

When interpreting these results, however, you must consider the complex interactions among all the hormones. Newer research has examined the role of several of the hormones that act on the hypothalamic-pituitary-gonadal axis, including luteinizing hormone and follicle-stimulating hormone. Levels of these gonadotropic hormones are altered in Alzheimer's disease. One theory suggests that increases in these hormones, rather than a decline in estrogen, may be a causative factor in Alzheimer's disease (Webber KM et al 2005). Studies have also implicated declining levels of progesterone (Singh M 2005). In normal aging, levels of luteinizing hormone and follicle-stimulating hormone are often elevated, whereas progesterone levels decline.

**Pregnenolone.** Pregnenolone is a hormone that is synthesized directly from cholesterol in the cell mitochondria. The body converts pregnenolone into other important hormones, including dehydroepiandrosterone (DHEA), various estrogens, progesterone, and testosterone (Szilagyi G et al 2005). Aging causes a steep decline in the production of pregnenolone, as well as in the hormones for which it is a precursor.

Progesterone is synthesized in the brain, spinal cord, and peripheral nerves from pregnenolone. Research strongly suggests that progesterone promotes the formation of myelin sheaths, the fatty layers of insulation that allow electrochemical signals to move efficiently from one neuron to another (Schumacher M et al 2004). Scientists believe that progesterone offers exciting treatment alternatives for the prevention of many degenerative brain conditions, as well as cognitive impairment during aging (Schumacher M et al 2004).

French researchers have shown that pregnenolone directly influences acetylcholine release in several key brain regions. They also demonstrated pregnenolone's ability to promote new nerve growth. According to the study authors: "Our data demonstrate that [pregnenolone sulfate infusions] dramatically increase neurogenesis" (Mayo W et al 2003, 2005).

**Testosterone.** Results of studies of the association between testosterone and Alzheimer's disease are conflicting. Some have found higher or comparable levels of testosterone in patients who have Alzheimer's disease compared to age-matched control subjects (Almeida OP et al 2003; Pennanen C et al 2004). Others have found that patients with Alzheimer's disease have lower levels of testosterone compared to control subjects (Hogervorst E et al 2003). However, studies have shown improved cognition in older adults who received testosterone supplementation (Cherrier MM et al 2005). Few studies have been conducted on testosterone replacement therapy in men with Alzheimer's. One such study, however, found that testosterone therapy did not improve cognitive scores, but did result in higher quality-of-life scores for patients with Alzheimer's disease, as rated by their caregivers (Lu PH et al 2006).

**Melatonin.** Known as the sleep hormone, melatonin helps establish healthy sleep patterns. However, it is also an antioxidant that has been shown to be highly effective in reducing oxidative damage to the central nervous system. Melatonin stimulates several antioxidant enzymes, including glutathione peroxidase and glutathione reductase (Reiter RJ et al 1999). In animal studies, melatonin improved cognitive function and reduced oxidative injury and deposition of beta-amyloid (Cheng Y et al 2006). Additional studies have confirmed that melatonin protects brain cells from beta-amyloid toxicity by impairing beta-amyloid generation and slowing the formation of plaque deposits (Wang JZ et al 2006).

**DHEA.** Various studies have indicated that patients with Alzheimer's disease have decreased levels of DHEA and that DHEA has neuroprotective effects (Hillen T et al 2000; Polleri A et al 2002; Weill-Engerer S et al 2002). DHEA is a neuroprotective steroid and a precursor of other sex hormones, including testosterone and estrogen. In animal studies, DHEA was shown to improve memory in rats that overexpressed beta-amyloid (Farr SA et al 2004).

### ***Huperzine to Support Acetylcholine***

Huperzine A, derived from a Chinese club moss, is an NMDA-receptor blocker that can help prevent or reduce the glutamate-mediated excitotoxicity that produces beta-amyloid. It also helps block the enzyme that destroys acetylcholine, much like conventional pharmaceuticals such as acetylcholinesterase inhibitors. In animals, huperzine A improved the decrease in acetylcholine activity in the cortex and hippocampus (Bai DL et al 2000; Cheng DH et al 1996; Tang XC 1996; Wang LM et al 2000). Huperzine A was also shown to be as effective, and sometimes even more effective, than traditional acetylcholinesterase inhibitors (such as donepezil and galantamine) in porcine intrinsic cardiac neurons (Darvesh S et al 2004). These results were confirmed in a follow-up human study that found huperzine has better penetration through the blood-brain barrier, higher bioavailability, and longer duration of action than the expensive pharmaceuticals (Wang R et al 2006).

Huperzine has been extensively studied in China. One Chinese study found that 58 percent of patients with Alzheimer's disease who were treated with huperzine showed improvement in memory and in cognitive and behavioral functions, compared with 36 percent who received placebo (Xu SS et al 1995). Chinese researchers also found that patients with Alzheimer's disease who were treated with huperzine A performed remarkably better on the Alzheimer's Disease Assessment Scale–Cognitive Subscale, Mini-Mental State Examination, Activities of Daily Living Scale, Clinical Global Impression Scale, and Alzheimer's Disease Assessment Scale–Non-Cognitive Subscale than those on placebo (Zhang Z et al 2002). Huperzine is currently in phase 2 trials in the United States.

## **LIFE EXTENSION FOUNDATION RECOMMENDATIONS**

There are many choices of both drugs and nutritional supplements available for patients with Alzheimer's disease. In light of new evidence that oxidative stress and inflammation are central to Alzheimer's disease, people at risk of Alzheimer's (or those who have early dementia) are advised to take supplements that reduce inflammation and oxidative damage. These include:

- **Curcumin**—900 to 1800 milligrams (mg) daily
- **EPA/DHA**—1400 mg daily of EPA and 1000 mg daily of DHA
- **Vitamin E**—400 international units (IU) daily (with 200 mg of gamma-tocopherol)
- **Vitamin C**—1 to 3 grams daily
- **Ginkgo biloba**—120 mg daily
- **Acetyl-L-carnitine arginate**—750 to 2000 mg daily
- **CoQ10**—100 to 600 mg daily
- **N-acetylcysteine**—600 mg daily
- **Aged garlic**—1200 mg daily
- **Vinpocetine**—15 to 20 mg daily
- **Green tea extract** (93 percent polyphenols)—725 mg daily

- **B vitamins**—A full complement of B vitamins (including folate, vitamin B6, and vitamin B12) to lower homocysteine. Specific suggested doses include 1000 micrograms (mcg) of vitamin B12, 250 mg of vitamin B6, and 800 mcg of folic acid.
- **Niacin**—Up to 800 mg daily. Start slowly and take with food to avoid flushing.
- **Melatonin**—1 to 3 mg each night
- **DHEA**—15 to 75 mg daily. Have blood tested in 3 to 6 weeks to determine optimal dose.
- **Huperzine**—50 mcg up to four times per week
- **Blueberry extract**—500 to 2000 mg daily. If you eat blueberries, you don't need to take this much blueberry extract.
- **Grape seed extract**—100 mg daily

Nutrients such as phosphatidylserine-DHA (PS-DHA), glycerophosphorylcholine (GPC), phosphatidylserine, vinpocetine, and ashwagandha, are available in multi-nutrient mixes. For more information call 1-800-544-4440.

The role of hormone replacement therapy has attracted considerable attention in the treatment of people with Alzheimer's disease, with somewhat conflicting results. Although testosterone and progesterone replacement therapy has shown some benefits, estrogen therapy has been more complicated. For information on blood testing to determine proper hormone levels, call 1-800-544-4440, or log on at [www.lef.org](http://www.lef.org).

## **ALZHEIMER'S DISEASE SAFETY CAVEATS**

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### **Acetyl-L-Carnitine**

- Acetyl-L-carnitine can cause gastrointestinal symptoms such as nausea and diarrhea.

### **Choline**

- Do not take choline if you have primary genetic trimethylaminuria.
- Choline can cause fishy body odor, excessive perspiration, hypotension (low blood pressure), depression, and gastrointestinal symptoms such as nausea and diarrhea.

### **Coenzyme Q10**

- See your doctor and monitor your blood glucose level frequently if you take CoQ10 and have diabetes. Several clinical reports suggest that taking CoQ10 may improve glycemic control and the function of beta cells in people who have type 2 diabetes.
- Statin drugs (such as lovastatin, simvastatin, and pravastatin) are known to decrease CoQ10 levels.

### **Curcumin**

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

### **DHEA**

- Do not take DHEA if you could be pregnant, are breastfeeding, or could have prostate, breast, uterine, or ovarian cancer.
- DHEA can cause androgenic effects in woman such as acne, deepening of the voice, facial hair growth and hair loss.

### **EPA/DHA**

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase

the risk of bleeding.

- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

### **Folic acid**

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

### **Garlic**

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

### **Ginkgo biloba**

- Do not take ginkgo biloba if you have a known risk factor for intracranial hemorrhage such as systematic arterial hypertension, diabetes, or amyloid senile plaque.
- Ginkgo biloba can cause allergic skin reactions, elevated blood pressure, and gastrointestinal symptoms such as nausea and diarrhea.

### **Green Tea**

- Consult your doctor before taking green tea extract if you take aspirin or warfarin (Coumadin). Taking green tea extract and aspirin or warfarin can increase the risk of bleeding.
- Discontinue using green tea extract 2 weeks before any surgical procedure. Green tea extract may decrease platelet aggregation.
- Green tea extract contains caffeine, which may produce a variety of symptoms including restlessness, nausea, headache, muscle tension, sleep disturbances, and rapid heartbeat.

### **Huperzine A**

- Do not take huperzine A if you have a seizure disorder, cardiac arrhythmias, asthma, irritable bowel syndrome, inflammatory bowel disease, or malabsorption syndrome.
- Huperzine A can cause excessive perspiration, blurred vision, fasciculations (involuntary muscle twitching), dizziness, bronchospasm, bradycardia, arrhythmias, seizures, urinary incontinence, increased urination, excessive salivation, and gastrointestinal symptoms such as nausea, abdominal cramps, diarrhea, and vomiting.

### **NAC**

- NAC clearance is reduced in people who have chronic liver disease.
- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

### **Niacin (nicotinic acid)**

- Do not take high doses of nicotinic acid (1.5 to 5 grams daily or more) if you have liver dysfunction, an unexplained elevation in your serum aminotransferase (transaminase) level, active peptic ulcer disease, arterial bleeding, or if you consume large amounts of alcohol.
- Consult your doctor before taking high doses of nicotinic acid if you have a history of jaundice, peptic ulcer disease, gastritis, disease of the liver or bile ducts, gout, kidney dysfunction, or cardiovascular disease (especially acute myocardial infarction or unstable angina).

- Consult your doctor before taking high doses of nicotinic acid if you have diabetes. High doses of nicotinic acid can negatively affect glucose tolerance. Monitor your serum glucose level frequently if you take nicotinic acid and have diabetes.
- Have your doctor monitor your serum aminotransferase level if you take high-doses of nicotinic acid.
- Nicotinic acid may cause flushing, principally of the face, neck, and chest. This flushing is thought to be prostaglandin-prostacyclin mediated. Histamine may also play a role in the flushing.
- Nicotinic acid can cause dizziness, palpitations, rapid heartbeat, shortness of breath, sweating, chills, insomnia, nausea, vomiting, abdominal pain, and muscle pain.
- High doses of nicotinic acid can cause blurred vision, macular edema, toxic amblyopia, and cystic maculopathy.

### **PABA (Para-aminobenzoic Acid)**

- Do not take PABA if you are taking sulfonamides or have a kidney disease.
- PABA can cause anorexia, nausea, vomiting, fever, and rash.

### **Vitamin B1 (Thiamin)**

- Consult your doctor before taking vitamin B1 for a thiamin deficiency, lactic acidosis secondary to thiamin deficiency, Wernicke-Korsakoff syndrome, Wernicke's encephalopathy, or Korsakoff's psychosis.

### **Vitamin B2 (riboflavin)**

- High doses of vitamin B2 (riboflavin) may interfere with the Abbott TDx drugs-of-abuse assay.
- Riboflavin absorption is increased in hypothyroidism and decreased in hyperthyroidism.
- If you are taking nucleoside reverse-transcriptase inhibitors, even a mild riboflavin deficiency can increase your risk of lactic acidosis.

### **Vitamin B6**

- Do not take vitamin B6 if you are being treated with levodopa, unless you are taking carbidopa at the same time.

### **Vitamin B12 (cyanocobalamin)**

- Do not take cyanocobalamin if you have Leber's optic atrophy.

### **Vitamin C**

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

### **Vitamin E**

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

### **Vinpocetine**

- Do not take vinpocetine if you have a history of allergic or hypersensitivity reactions to any vinca alkaloids.
- Consult your doctor before taking vinpocetine if you take warfarin (Coumadin). Have your international normalized ratio monitored frequently by your doctor if you take vinpocetine and warfarin.
- Consult your doctor before taking vinpocetine if you have low blood pressure (including transient low blood pressure or orthostatic hypotension). Prolonged use of vinpocetine may lead to slight reductions in systolic and diastolic blood pressures.

- Vinpocetine can cause temporary rapid heartbeat, pressure headache, facial flushing, dizziness, insomnia, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.

For more information see the Safety Appendix

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