



# LATEST RESEARCH ON ALZHEIMER'S DISEASE AND NATURAL MEDICINE

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# FROM DR. MURRAY



Dear Health Enthusiast,

In this collection of articles you will find valuable information on natural approaches to preventing and improving Alzheimer's disease including the dedicated chapter on this subject from the 3rd edition of the best-selling Encyclopedia of Natural Medicine. What the medical literature clearly demonstrates is that there is a lot that can be done with diet and supplementation to prevent and possibly reverse this dreaded disease. But, this information is only valuable if it is actually put into practice. So, please do your best and be good to your brain!!

Sincerely,

Michael T. Murray, N.D.





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# WHAT IS ALZHEIMER'S DISEASE?

Alzheimer's disease (AD) is a degenerative brain disorder that manifests as a progressive deterioration of memory and mental function—a state of mind commonly referred to as dementia. In the United States, 5 percent of the population over age 65 suffers from severe dementia, while another 10 percent suffers from mild to moderate dementia. With increasing age, there is a rise in frequency. For

example, in people over age 80, the frequency rate for dementia is more than 25 percent.

## What are the Signs and Symptoms of Alzheimer's Disease?

Progressive mental deterioration, loss of memory and cognitive functions, and inability to carry out activities of daily life are the characteristic symptoms of AD. These symptoms are related to a reduced level of acetylcholine, a key neurotransmitter in the brain that is especially important for memory.

## What Causes Alzheimer's Disease?

Alzheimer's disease is characterized by distinctive changes in the brain. The primary feature is the formation of what are referred to as neurofibrillary tangles and plaques. Simplistically speaking, these neurofibrillary tangles and plaques are "scars" composed of deposits of various proteins and cellular debris. The result is massive loss of brain cells, especially in key areas of the brain that control mental function. Genetic factors play a major role in AD. However, like most chronic degenerative diseases, environmental factors also play a significant role.

Increased oxidative damage, traumatic injury to the head, chronic exposure to aluminum and/or silicon, exposure to toxins from environmental sources, and free-radical damage have all been implicated as causes for AD. Considerable attention has been given to the aluminum concentration in the neurofibrillary tangle.

Whether this aluminum concentration develops in response to AD or whether it causes the lesions has not yet been determined, but significant evidence shows that it contributes, possibly very significantly, to the disease. It certainly seems appropriate to avoid all known sources of aluminum, including antacids and antiperspirants, pots and pans, foil used as food wrapping, and nondairy creamers.

## Which Dietary Factors are Important in Alzheimer's Disease?

In the elderly, studies have shown that mental function is directly related to nutritional status. Better nutrition equals higher mental function. Given the frequency of nutrient deficiency in the elderly population, it is likely that many cases of impaired mental function may have a nutritional cause. Also, since there is considerable evidence that oxidative damage plays a major role in the development and progression of AD, and that diets that are high in antioxidants like vitamins C and E prevent AD, it only makes sense to eat a diet rich in antioxidants, including green leafy vegetables; highly colored vegetables such as carrots, yams, and squash; and flavonoid-rich fruits like citrus, berries and cherries.

## Which Nutritional Supplements Should I Take for Alzheimer's Disease?

There are a number of products that show tremendous potential, but in general, natural products are best utilized in the early stages of any disease process. Here are my key supplement recommendations:

**Foundation Supplements.** High potency multiple vitamin and mineral formula; Vitamin D3 2,000-5,000 IU/day; Fish oil, EPA + DHA 1,000 to 3,000 mg/day.

**Phosphatidylserine** plays a major role in determining the integrity and fluidity of brain cell membranes. Normally, the brain can manufacture sufficient levels of phosphatidylserine, but if there is a deficiency of folic acid and vitamin B12, or of essential fatty acids, the brain may not be able to make sufficient phosphatidylserine. Low levels of phosphatidylserine are associated with impaired mental function and depression in the elderly. More than a dozen double-blind studies have shown phosphatidylserine improves mental function, mood and behavior in patients with AD and senility. Take 100 mg three times daily.

***L-Acetylcarnitine (LAC)*** is a vitamin-like compound that has been the subject of numerous studies on the treatment of Alzheimer's disease, senile depression and age-related memory defects. Well-controlled and extremely thorough studies show that LAC is outstanding at delaying the progression of Alzheimer's disease. Take 1,500 mg daily.

***Ginkgo biloba extract (GBE)***. Although studies involving patients with well-established Alzheimer's disease have not shown much benefit, GBE can definitely help reverse or delay mental deterioration during the early stages of AD. GBE should be taken consistently for at least 12 weeks in order to determine effectiveness. Although some people with AD report benefits within a two- to three-week period, most will need to take GBE for a longer period of time (e.g., six months) before seeing results, and will need to take GBE indefinitely to maintain the improvement. Typical dosage is 240 to 320 mg daily (can be taken all at once).

***Curcumin***, the yellow pigment of turmeric, shows promise in protecting against age-related brain damage. Researchers began exploring this effect after noting that elderly (aged 70-79) residents of rural India who eat large amounts of turmeric have been shown to have the lowest incidence of Alzheimer's disease in the world: 4.4 times lower than that of Americans. Studies with an advanced form of curcumin, Theracurmin®, show the greatest absorption of any curcumin product. Take 300 to 600 mg of Theracurmin twice daily.

***DHEA (dehydroepiandrosterone)*** is the most abundant hormone in the bloodstream and is found in extremely high concentrations in the brain. DHEA levels decline dramatically with aging, and low levels of DHEA in the blood and brain are thought to contribute to many symptoms associated with aging, including impaired mental function. Preliminary studies show DHEA is effective in enhancing memory and improving cognitive function in elderly people. The level of DHEA necessary to improve brain power in men over age 50 appears to be 25 to

50 mg per day. For women, a daily dosage of 15 to 25 mg appears to be sufficient in most cases. Taking too much DHEA can cause acne, and may increase the risk of hormone -sensitive cancers like breast and prostate cancer.

## How do I Know if the Recommendations are Working?

Improvements in mental function and memory should be apparent after two to three months on this program.

### Commentary:

In my clinical experience, I witnessed tremendous improvements in mental function and mood in patients with early stages of Alzheimer's disease who I treated with natural medicines, particularly Ginkgo biloba extract. However, I cannot say the same for patients with more advanced stages of Alzheimer's disease. The sooner treatment with natural measures can be started, the better the results. In the advanced stages of AD, these natural measures (with the possible exception of huperzine A and L-acetylcarnitine) will be unfruitful. The primary goal should be prevention by addressing suspected disease processes (e.g., aluminum and free-radical damage) and using natural measures to improve mental function in the early stages of the disease. Based upon good research, it appears that Alzheimer's disease does not have to be the price to pay for living longer—it appears it can be prevented and reversed in the early stages.





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# ALZHEIMER'S DISEASE

*Adapted From the 3rd Edition of my bestselling book: Encyclopedia of Natural Medicine*

Alzheimer's disease (AD) is a degenerative brain disorder associated with progressive dementia—a deterioration of memory and cognition. In the United States, Alzheimer's disease is now estimated to affect 1.6% of the population younger than 74, with the rate increasing to 19% in those between 75 and 84 and to 42% in those



older than 84. These numbers are striking when compared with data from the 1960s indicating an incidence of only 2% in people over the age of 85. The tremendous increase in AD in people over 85 is often referred to as the “Alzheimer’s epidemic.”

- Progressive mental deterioration, loss of memory and cognitive function, inability to carry out activities of daily life
- Characteristic symmetrical, usually diffuse brainwave pattern seen on EEG
- Diagnosis usually made by exclusion; imaging techniques can help rule out other causes of dementia
- At this time, definitive diagnosis can be made only by brain biopsy after death.

## Causes

AD is the result of damage to many aspects of brain structure and function. One characteristic feature of AD is the development of distinctive brain lesions called plaques and tangles. Plaques are hard deposits of a protein, beta-amyloid, that are found between neurons. Amyloid is a general term for protein fragments that the body produces normally, and beta-amyloid is a fragment snipped from an amyloid precursor protein (APP). In a healthy brain, these fragments are broken down and eliminated, but in Alzheimer’s disease they accumulate to form plaques. Another type of lesion, neurofibrillary tangles, occurs within brain cells. In the healthy brain cell, a protein called tau forms structures called microtubules. In Alzheimer’s disease, however, the tau protein is abnormal and the microtubules collapse into a twisted mass. It is thought that the buildup of beta-amyloid triggers the changes in the tau protein. Both types of lesions disrupt message transmittal within the brain and eventually cause cell death.

Genetic factors play a major role and are estimated to account for up to 70% of cases of AD. The key appears to be genetically linked alterations in the ability of the immune system to regulate inflammation in the brain. Although the immune cells in

the brain normally remove beta-amyloid, research is beginning to characterize a chronic and excessive inflammatory reaction to amyloid proteins in the brain that can promote AD in susceptible individuals. Therapies designed to affect these immune cells in the brain are being investigated. Chief among these strategies is to immunize AD patients with beta-amyloid peptides so they will generate antibodies that bind to beta-amyloid and enhance its clearance. Although pre-clinical studies were successful, the initial human clinical trial of an active beta-amyloid vaccine was halted owing to the development of severe inflammation in the brain in approximately 6% of the vaccinated AD patients.

Although genes have a big part in determining susceptibility to AD, lifestyle and environmental factors also play a significant role, as they do in most chronic degenerative disease. Emerging research reveals that dietary factors are especially important. Poor-quality diets with excessive amounts of saturated or trans-fatty acids may predispose neurons to environmental toxicities. Some studies suggest that abnormal sleep-wake cycles and decreased morning light exposure may play a role in the expression of AD (see the section on melatonin later in this chapter). Traumatic injury to the head; chronic exposure to aluminum, silicon (most often due to occupational exposures in the construction, sandblasting, and mining industry), or both; exposure to neurotoxins such as mercury from environmental sources; and free radical damage have all been implicated as causative factors as well. As with other chronic degenerative diseases, there is considerable evidence that increased oxidative damage plays a central role. Therapies designed to support antioxidant mechanisms (discussed later) may be quite helpful in the prevention of AD.

The tremendous increase in AD parallels the rise in type 2 diabetes and insulin resistance, suggesting a possible connection. It is well established that type 2 diabetics have a 1.5- to 4-fold increased risk for AD as well as for non-Alzheimer's dementia caused by damage to the blood vessels of the brain. Impaired insulin signaling, insulin resistance in the brain, and a decrease in cerebral insulin receptors associated with aging may be other important factors in the development of AD.

Measures to improve blood sugar control and improve insulin sensitivity appear to be important steps in the prevention of AD.

## Diagnostic Considerations

### Comprehensive Evaluation

A comprehensive diagnostic workup is critical, as there are many conditions that can cause dementia. For example, depression is frequently seen in the elderly and can mimic dementia, and the most common reversible cause of dementia is drug toxicity. Other important causes are metabolic and nutritional disorders such as hypoglycemia, thyroid disturbances, and deficiency in vitamin B12, folate, or thiamine. A comprehensive evaluation should include the following:

- A detailed history
- Neurological and physical examination
- Psychological evaluation with particular attention to depression
- A general medical evaluation with emphasis on the detection of subtle metabolic, toxic, or cardiopulmonary disorders that can precipitate confusion, especially in the elderly
- A series of standardized neurophysiology tests such as the mini-mental state examination (MMSE) or Folstein test to document the type and severity of cognitive impairment
- Appropriate laboratory assessment (see below for recommended tests)
- An electroencephalogram (EEG)
- Imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), or others



## Fingerprint Patterns

Abnormal fingerprint patterns are associated with both AD and Down syndrome.<sup>10</sup> Compared with the normal population, Alzheimer and Down patients show an increased number of ulnar loops on the fingertips, with a decrease in whorls, radial loops, and arches. Ulnar loops (pointing toward the ulnar bone, away from the thumb) are frequently found on all 10 fingertips. Radial loops (pointing toward the thumb), when they do appear, tend to be shifted away from the index and middle fingers—where they most commonly occur—to the ring and little fingers. In patients with this fingerprint pattern, it is recommended that an aggressive, preventive approach be instituted immediately.

### RECOMMENDED LABORATORY TESTS FOR DEMENTIA

TEST	RATIONALE
CBC	Anemia, infection
Electrolytes	Metabolic dysfunction
Liver function tests	Hepatic dysfunction
BUN	Renal dysfunction
TSH, T4, T3, T3U	Thyroid dysfunction
Serum B12 and RBC folate	Deficiency
Urinalysis	Kidney/liver dysfunction
Hair mineral analysis	Heavy metal intoxication
ECG	Heart function
EEG	Focal vs. diffuse brain lesions
CT scan	Atrophy, intracranial mass

# Therapeutic Considerations

The primary areas of intervention from a natural medicine perspective are prevention (addressing suspected causative factors) and treatment with natural measures (to improve mental function in the early stages of the disease). In the advanced stages of AD, natural measures will usually provide little benefit.

## Diet

Dietary factors are clearly important in the development of AD. Food choices consistent with the standard American diet are associated with significant risk for the development of AD. A diet high in saturated fat and trans-fatty acids and low in dietary antioxidants may lead to increased serum and brain concentrations of aluminum and transition metal ions, which are implicated in oxidative stress. In addition, a poor-quality diet may cause inflammation in the brain.

Many dietary risk factors are the same for both AD and atherosclerosis. Likewise, recent studies have provided clear evidence that following a Mediterranean-type diet does not just reduce the risk of heart disease but also is definitely associated with slower cognitive decline, lower risk for both pre-dementia syndromes and AD, and decreased mortality from all causes in AD patients.

The key dietary factors that reduce AD risk are higher fish consumption (and omega-3 fatty acids), monounsaturated fatty acids (primarily from olive oil), light to moderate alcohol use (primarily red wine), and increased consumption of non-starchy vegetables and fruits. It is likely that it is the combination of all of these factors that provides the highest degree of protection, rather than any single dietary factor.

One study in particular produced some very interesting findings. Given the ability of the Mediterranean diet to reduce inflammation and improve insulin sensitivity, many

people assume that this plays a significant role in its ability to reduce AD. However, in a four-year prospective study, the lower risk of AD with the Mediterranean diet did not seem to be due to reducing atherosclerosis. It is therefore thought that other aspects of the diet or specific foods are probably responsible, possibly working directly on reducing beta-amyloid formation or deposition. For example, polyphenols found in grapes, grape seed extract, and red wine have been shown to prevent beta-amyloid formation and promote disassembly of the neurofibrillary tangles. Animal studies using grape poly-phenols marked with radioactive particles show absorption into the brain after oral administration.

Even something as simple as eating celery (*Apium graveolens*) may offer significant protection against AD. Celery and celery seed extracts contain a unique compound, 3-n-butylphthalide (3nB), that is responsible for both the characteristic odor of celery and its health benefits. In an animal model of AD, 3nB treatment significantly improved learning deficits as well as long-term spatial memory, significantly reduced total cerebral beta-amyloid plaque deposition, and lowered brain beta-amyloid levels. It was also shown that 3nB markedly directed amyloid precursor protein processing toward a pathway that precludes beta-amyloid formation. The researchers concluded that “3nB shows promising preclinical potential as a multitarget drug for the prevention and/or treatment of Alzheimer’s disease.”

The research on grape polyphenols and 3nB raises a powerful question: how many other foods contain unique compounds that address the pathophysiology of Alzheimer’s disease? From preliminary investigations it looks as if there may be a great many. Especially promising are sources of phenols, polyphenols, and flavonoids.

## Estrogen

Estrogen has been touted as offering protective and possibly therapeutic benefits in AD. However, the evidence to support the potential benefits of estrogen is contradictory. Yes, 16 population-based studies indicated that women on hormone replace-



ment therapy (HRT) had a lower rate of AD. But the problem with these studies was that women taking HRT were much healthier before taking the hormones compared with the control group, who were more likely to have hypertension, diabetes, and a history of stroke. Data from the only large randomized controlled trial published to date, the Women's Health Initiative Memory Study, did not confirm these observations and have even suggested an increase in dementia risk for women using HRT (and especially those given HRT after menopause) compared with controls. Clinical trials involving women with AD have concluded that estrogen therapy does not improve dementia symptoms in women with AD. Given the cloud of uncertainty about the benefits of HRT, at this point it seems most reasonable to consider the risks of estrogen therapy as outweighing any possible benefit in the prevention of AD.

## **Aluminum**

Considerable attention has been focused on aluminum concentrations in neurofibrillary tangles. Whether the aluminum accumulates in the tangles in response to the formation of lesions or whether it actually initiates the lesions has not yet been determined, but significant evidence shows that it contributes, possibly significantly, to the disease. There is a great deal of circumstantial evidence linking chronic aluminum exposure to AD. Increasing aluminum concentrations in the brain could explain why the frequency of AD rises with increasing age. And those with AD have significantly higher aluminum levels than both normal people and patients with other types of dementia, such as those from alcohol, atherosclerosis, and stroke. The aluminum appears to come from the water supply, food, antacids, and antiperspirants. The most significant source is probably drinking water, as the aluminum in water is in a more bioavailable and thus potentially toxic form. Researchers measuring the absorption of aluminum from tap water added a small amount of soluble aluminum in a radioactive form to the stomachs of animals. They discovered that the trace amounts of aluminum from this single exposure immediately entered the animals' brain tissue. The

frightening news is that aluminum in water not only occurs naturally but also is added (in the form of alum) to treat some water supplies.

Avoiding all known sources of aluminum—aluminum-containing antacids, aluminum-containing antiperspirants, cooking in aluminum pots and pans, wrapping food with aluminum foil, nondairy creamers containing the food additive sodium aluminosilicate, and some types of baking powder and table salt—certainly seems appropriate. In addition, citric acid and calcium citrate supplements appear to increase the efficiency of absorption of aluminum (but not lead) from water and food. Aluminum absorption can be decreased by magnesium, because magnesium competes with aluminum for absorption not only in the intestines but also at the blood-brain barrier. Focus on unprocessed foods, avoid milk and dairy products, and increase consumption of vegetables, whole grains, nuts, and seeds—all good sources of magnesium.

## Nutritional Considerations

Nutritional status is directly related to mental function in the elderly. Given the frequency of nutrient deficiency in the elderly population, it is likely that many cases of impaired mental function may have a nutritional basis.

As pointed out above, diet is critically important in the prevention and arrest of AD, with various components working together in a synergistic fashion to address many of the underlying features of AD.

### Antioxidants

As noted previously, considerable evidence indicates that oxidative damage plays a major role in the development and progression of AD. Population-based evidence suggests that antioxidant nutrients offer significant protection against AD. Prospective and clinical studies have primarily focused on vitamin C, vitamin E, and beta-

carotene, with somewhat favorable results (see the table on the next page). As with other chronic degenerative diseases, better results may be achieved with a broader range of supplemental nutrients. For example, in a French study of middle-aged adults, 13 years of daily supplementation with 120 mg vitamin C, 30 mg vitamin E, 6 mg beta-carotene, 100 mcg selenium, and 20 mg zinc compared with a placebo were significantly associated with better verbal memory, which is a cognitive domain that is particularly vulnerable to AD. These results appear to be significantly better than those achieved with vitamin C, vitamin E, and beta-carotene either alone or in combination without the minerals.

It is entirely possible (and very likely) that vitamin E, vitamin C, and beta-carotene may simply be markers of increased phytochemical antioxidant intake and do not play a significant role on their own. Fruit and vegetables contain an array of antioxidant compounds beyond these three, and some of the other compounds may have considerable benefit in AD. Often researchers make the mistake of thinking that the antioxidant activity of a particular fruit or vegetable is due solely to its vitamin C, vitamin E, or beta-carotene content. However, these nutrient antioxidants often account for a very small fraction of a food's antioxidant effect—for example, only about 0.5% of the total antioxidant activity of an apple. The overwhelming antioxidant activity of fruit and vegetables comes from phytochemicals such as flavonoids, phenols, polyphenols, and other carotenoids.<sup>16</sup> In particular, as detailed above, phytochemicals are showing tremendous promise in protecting against AD beyond their antioxidant effects by interfering with beta-amyloid formation and deposition.



## PROSPECTIVE STUDIES OF ANTIOXIDANTS AND RISK OF AD

STUDY	FOLLOW-UP	FINDINGS
Rotterdam Study	6 years	Dietary vitamin E effective (more among current smokers)
Canadian Study of Health and Aging	5 years	Combination of vitamin E and vitamin C supplements and/or multivitamin consumption effective
Chicago Health Aging Study	3.9 years	Dietary vitamin E was effective only among a subset of individuals lacking a genetic risk factor (non-apoE4 carriers)
Washington Heights-Inwood Columbia Aging Project	4 years	No effect of vitamin E (diet or supplement)
Cache County Study	3 years	Vitamin E alone was not effective, but combined with Vitamin C it was effective
Honolulu-Asia Aging Study	30 years	Dietary vitamin E was not effective
Duke Established Populations for Epidemiologic Studies of the Elderly	10 years	No effect of vitamin C and/or vitamin E
Group Health Cooperative	5.5 years	No effect of supplemental vitamin E and vitamin C alone or in combination

### Thiamine (Vitamin B1)

Although severe thiamine deficiency is relatively uncommon (except in alcoholics), many Americans, and especially the elderly, do not consume even the RDI of 1.5 mg. In an attempt to gauge the prevalence of thiamine deficiency in the geriatric population, 30 people visiting a university outpatient clinic in Tampa, Florida, were tested for thiamine levels. Depending on the thiamine measurement (plasma or red blood cell thiamine), low levels were found in 57% and 33%, respectively, of the people studied.

In addition to its role as a nutrient, thiamine demonstrates some pharmacological effects on the brain. Specifically, it both potentiates and mimics acetylcholine, an important neurotransmitter involved in memory. This effect explains the positive clinical

cal results that have been noted for thiamine (3 to 8 g per day) in improving mental function in people with AD or age-related impaired mental function. High-dosage thiamine supplementation has no side effects.

These results highlight the growing body of evidence that a significant percentage of the geriatric population is deficient in one or more of the B vitamins. Given the essential role of thiamine and other B vitamins in normal human physiology, especially cardiovascular and brain function, routine B vitamin supplementation appears to be worthwhile in this age group. AD may simply be the result of chronic low intake of essential nutrients— key among which are the B vitamins.

## **Vitamin B12**

Another B vitamin linked to AD is vitamin B12. Vitamin B12 deficiency results in impaired nerve function, which can cause numbness, tingling sensations, or a burning feeling in the feet, as well as impaired mental function, which in the elderly can mimic AD.<sup>47,48</sup> Vitamin B12 deficiency also is a major cause of depression in this age group.

Several investigators have found that the level of vitamin B12 declines with age (probably due to gastric atrophy) and that vitamin B12 deficiency is found in 3% to 42% of people 65 and older. One way to determine whether there is a deficiency is by measuring the level of cobalamin in the blood. In one study of 100 geriatric outpatients who were seen in office-based settings for various acute and chronic medical illnesses, 11 had serum cobalamin levels of 148 pmol/l or below, 30 had levels between 148 and 295 pmol/l, and 59 patients had levels above 296 pmol/l. After the initial cobalamin determination, the subjects were followed for up to three years. The patients with cobalamin levels below 148 pmol/l were treated and not included in the analysis of declining cobalamin levels. The average annual decline in serum cobalamin level was 18 pmol/l for patients who had higher initial serum cobalamin lev-

els (224 to 292 pmol/l). For patients with lower initial cobalamin levels, the average annual decline was much higher, 28 pmol/l. These results indicate that screening for vitamin B12 deficiency appears to be indicated in the elderly given the positive cost-benefit ratio. Other ways of screening for B12 deficiency involve measuring the level of methylmalonic acid in the urine or measuring the level of plasma homocysteine (which also serves to determine the status of folate). Having a high homocysteine level ( $>14$  mmol/l) nearly doubles the risk of AD.

The importance of detailed examination in elderly patients with mental symptoms is highlighted by results from a study that analyzed the plasma homocysteine, serum cobalamin, and blood folate in 296 patients referred to a geriatric psychiatric ward in Sweden for diagnosis of mental disease.<sup>54</sup> Patients who were deficient in vitamin B12 or folic acid or who had elevated levels of homocysteine were given vitamin B12 (dosage not specified), folic acid (10 mg per day), or both. When individuals with low cobalamin levels were supplemented with vitamin B12, significant clinical improvements were noted.

In other studies, supplementation has shown tremendous benefit in reversing impaired mental function when there are low levels of vitamin B12.<sup>47</sup> In one large study, a complete recovery was observed in 61% of cases of mental impairment due to low levels of vitamin B12.<sup>55</sup> The fact that 39% did not respond is probably a result of long-term low levels of vitamin B12 causing irreversible damage. Several studies have shown that the best clinical responders are those who have been showing signs of impaired mental function for less than six months.<sup>16</sup> In one study, 18 subjects with low serum cobalamin levels and evidence of mental impairment were given vitamin B12. Only those patients who had had symptoms for less than one year showed improvement.<sup>56</sup> The importance of diagnosing and correcting low vitamin B12 levels in the elderly cannot be overstated.

Serum vitamin B12 levels are significantly low in AD patients. It has recently been demonstrated that an oral dose as low as 50 mcg per day can significantly increase serum vitamin B12 levels in vitamin B12– deficient elderly people. Supplementation of B12, folic acid, or both may result in complete reversal in some patients, but generally there is little improvement in mental function in patients who have had Alzheimer's symptoms for more than six months.

Vitamin B12 is available in several forms. The most common form is cyanocobalamin; however, vitamin B12 is active in the human body in only two forms, methylcobalamin and adenosylcobalamin. Although methylcobalamin and adenosylcobalamin are active immediately upon absorption, cyanocobalamin must be converted to either methylcobalamin or adenosylcobalamin. The body's ability to make this conversion may decline with aging and may be another factor responsible for the vitamin B12 disturbances noted in the elderly population.

Finally, the damaging effects of low vitamin B12 levels are aggravated by high levels of folic acid that mask a vitamin B12 deficiency. While the addition of folic acid to the food supply in 1998 helped decrease neural tube defects in infants, it may also have worsened the problems caused by low vitamin B12.

## **Zinc**

Zinc deficiency is one of the most common nutrient deficiencies in the elderly and has been suggested as a major factor in the development of AD, as most enzymes involved in DNA replication, repair, and transcription contain zinc. It has been suggested that dementia may represent the long-term cascading effects of error-prone or ineffective DNA-handling enzymes in nerve cells, possibly because of a long-term zinc deficiency. In addition, zinc is required by many antioxidant enzymes, including superoxide dismutase. With insufficient zinc, the end result could be the destruction of nerve cells and the formation of neurofibrillary tangles and plaques. Levels of zinc



in the brain and cerebrospinal fluid in patients with AD are markedly decreased, and there is a strong inverse correlation between serum zinc levels and plaque count. Zinc supplementation has demonstrated good benefits in AD. In one study, 10 patients with AD were given 27 mg per day of zinc (as zinc aspartate). Only two patients failed to show improvement in memory, understanding, communication, and social contact. In one 79-year-old patient, the response was labeled “unbelievable” by both the medical staff and the family.<sup>64</sup> Unfortunately, there does not seem to be much interest in the scientific community in following up these impressive results with zinc therapy.

There is ambivalence in recent medical literature about zinc because in vitro, zinc accelerates the formation of insoluble beta-amyloid peptide. Although zinc is neurotoxic at high concentrations and accumulates at sites of degeneration, total tissue zinc is markedly reduced in the brains of Alzheimer patients. Other research has shown a much higher concentration of copper-zinc superoxide dismutase in and around the damaged brain tissue of AD patients. This suggests that the increased concentration of zinc in the damaged areas is due to the body’s efforts to neutralize free radicals through the increased local production of dismutases. A possible explanation is that the higher localized levels of zinc result in increased amyloid formation when the free-radical-scavenging mechanisms have been inadequate.

## **Phosphatidylcholine and Other Sources of Choline**

Because dietary phosphatidylcholine can increase acetylcholine levels in the brain in normal patients and AD is characterized by a decrease in acetylcholine function, it seems reasonable to assume that phosphatidylcholine supplementation would benefit Alzheimer’s patients by providing more choline. However, the basic defect in many patients with AD relates to impaired activity of the enzyme acetylcholine transferase. This enzyme combines choline (as provided by phosphatidylcholine) with an acetyl molecule to form acetylcholine, the neurotransmitter. Providing more choline

does not necessarily increase the activity of this key enzyme, so phosphatidylcholine supplementation is not beneficial in the majority of patients with AD. In addition, choline levels are elevated in the cerebrospinal fluid in AD. When researchers measured the levels of the water-soluble metabolites of phosphatidylcholine (glycerophosphocholine [GPC], phosphocholine, and choline) in normal patients and age-matched AD patients, they found increased levels in the AD patients. GPC was increased by 76%, phosphocholine by 52%, and free choline by 39%. What these data demonstrate is that AD is associated not only with reduced acetylcholine manufacture but also with increased breakdown of phosphatidylcholine, which is a component of brain cell membranes.<sup>68</sup>

Not surprisingly, clinical trials using phosphatidylcholine have largely been disappointing. Studies have shown inconsistent improvements in memory from choline supplementation in both normal and Alzheimer patients. The studies have been criticized for small sample size, low dosage of phosphatidylcholine, poor design, and poor choice of choline form. Clinical studies with glycerophosphocholine (GPC) and citicoline (also known as cytidine diphosphate-choline or CDP-choline) have shown benefit in improving age-related memory decline; however, studies investigating the use of these agents in AD have usually shown only very slight benefits. In one double-blind study patients affected by mild to moderate AD were treated with GPC or a placebo for 180 days. Scores on standard assessments (e.g., the Alzheimer's Disease Assessment Scale and the Global Improvement Scale) after 90 and 180 days showed improvement in the GPC group, whereas in the placebo group they remained unchanged or worsened. Study results with citicoline in AD have been inconsistent.

Despite the questionable benefit specifically related to AD, in cases of mild to moderate dementia we recommend a 90-day trial of either GPC or CDP at dosages of 1,200 mg and 1,000 mg per day, respectively. Given the difficulty with diagnosing AD, it is possible that many cases of dementia are related to other factors that may respond to

choline supplementation. If there is no noticeable improvement within the 90-day time frame, supplementation should be discontinued.

## **Phosphatidylserine**

Phosphatidylserine (PS) is the major phospholipid in the brain, where it plays a significant role in determining the integrity and fluidity of cell membranes. Normally the brain can manufacture sufficient levels of phosphatidylserine, but a deficiency of methyl donors (such as S-adenosyl-methionine [SAM-e], folic acid, and vitamin B12) or essential fatty acids may inhibit production of sufficient PS. Low levels of phosphatidylserine in the brain are associated with impaired mental function and depression in the elderly. To date, 11 published double-blind studies have all reported the successful use of PS in the treatment of age-related cognitive decline, AD, or depression. In the largest study a total of 494 patients between 65 and 93 years old with moderate to severe dementia were given either phosphatidylserine (100 mg three times per day) or a placebo for six months. The patients were assessed for mental performance, behavior, and mood at the beginning and end of the study. Statistically significant improvements were noted in mental function, mood, and behavior for the phosphatidylserine group.

## **L-Acetylcarnitine**

A great deal of research has been conducted with L-acetylcarnitine (LAC; also called acetyl-L-carnitine) in the treatment of AD, senile depression, and age-related memory defects. LAC is composed of acetic acid and L-carnitine bound together. This reaction occurs naturally in the human brain. Therefore it is not exactly known how much greater an effect is achieved with LAC vs. L-carnitine. However, LAC is thought to be substantially more active than other forms of carnitine in conditions involving the brain.

The close structural similarity between LAC and acetylcholine led to an interest in using LAC in AD. Research has shown that LAC both enhances and mimics acetylcholine and is of benefit not only in patients with early-stage AD but also in elderly patients who are depressed or who have impaired memory. It has been shown to act as a powerful antioxidant within the brain cell, stabilize cell membranes, and improve energy production within the brain cell as well.

In an analysis of studies of LAC in mild cognitive impairment and mild (early) AD, patients taking doses ranging from 1.5 to 3g a day were assessed at 3,6,9,and12 months. This analysis showed a significant advantage for LAC compared with a placebo. The advantage for LAC was seen by the time of the first assessment at three months and increased over time. Additionally, LAC was well tolerated in all studies.

Further studies also show its efficacy in situations where AD patients were unresponsive to standard drug therapy (acetylcholin- esterase inhibitors). One study showed LAC at 2 g per day increased the effectiveness of drugs such as donepezil and rivastigmine.

Memory impairment need not be as severe as it usually is in AD in order for LAC to demonstrate a benefit. In one double-blind study of 236 elderly subjects with mild mental deterioration, as evidenced by detailed clinical assessment, the group receiving 1,500 mg per day of LAC demonstrated significant improvement in mental function, particularly in memory and constructional thinking.

## **Dehydroepiandrosterone (DHEA)**

DHEA is the most abundant hormone in the bloodstream and is found in extremely high concentrations in the brain. Because DHEA levels decline dramatically with ag-

ing, low levels of DHEA in the blood and brain are thought to contribute to many symptoms associated with aging, including impaired mental function. In some studies DHEA supplementation has shown promise in enhancing memory and improving cognitive function. However, no effect was noted in the largest study as well as others. The only double-blind study in actual AD was a small pilot study (58 subjects) in which 50 mg DHEA was given twice a day. Although some benefit was reported at three months, DHEA did not significantly improve cognitive performance or overall change in severity.

We feel that the failure of DHEA to provide benefits may have been due to not properly qualifying the patients. Measuring DHEA levels in the blood or saliva can help determine if DHEA may be of benefit. It is not likely to be of benefit in those with satisfactory levels for their age and sex. The dose of DHEA necessary to improve brainpower in men older than 50 appears to be 25 to 50 mg per day. For women, a dosage of 15 to 25 mg appears to be sufficient in most cases. As men and women reach their 70s, they may require higher levels (e.g., 50 to 100 mg). Excessive dosages of DHEA can cause acne and, in younger women, menstrual irregularities.

## **Melatonin and Bright Light Therapy**

Test tube studies have shown that melatonin protects brain cells from heavy metal damage. For example, melatonin treatment prevented oxidative damage and beta-amyloid release caused by cobalt. Since cobalt is another toxic metal found in high levels in AD patients, melatonin may prove an important preventive treatment in AD.

One double-blind study of AD patients involved subjects who got 3 mg melatonin or a placebo at 8:30 p.m. every day for a month. Based on standard dementia and AD assessment scales, the melatonin group had significantly increased sleeping time and decreased nighttime activity, with improved levels of mental function.



Melatonin may also be helping by improving the disturbance in circadian (daily) rhythm common in AD. Circadian rhythm affects body functions such as sleep cycles, temperature, alertness, and hormone production. Impaired sleep and nocturnal restlessness place great burdens on both those who suffer from AD and their caregivers. Clinical research has shown that exposure to full-spectrum light throughout the day and darkness at night can help improve some aspects of AD, reducing agitation, increasing sleep efficiency (percentage of time in bed spent asleep), decreasing nighttime wakefulness, and decreasing nighttime activity. If natural sunlight exposure is not possible for at least an hour in the morning, light boxes are available that can simulate sunlight. Full-spectrum lightbulbs are available that can replace conventional bulbs as well.

Although bright light therapy during the day is often effective on its own, combining it with melatonin produces the best results.

## Botanical Medicines

### Ginkgo Biloba Extract

Ginkgo biloba extract (GBE) has been extensively investigated in cases of dementia, including Alzheimer's disease. In addition to GBE's ability to increase functional brain capacity, it has been shown to normalize acetylcholine receptors in the brains of aged animals, increase cholinergic transmission, inhibit beta-amyloid deposition, and address many of the other major elements of AD. However, while preliminary studies with established AD patients were quite promising, it now appears that at best GBE can help to reverse or delay mental deterioration only in the early stages of AD. Even this may be in doubt, as in several double-blind studies no benefit over a placebo was observed in halting cognitive decline. In other double-blind studies, though, the benefits of GBE in early-stage AD were quite evident, as they were in a meta-analysis

of studies of more than six months' duration. In one study, 216 patients with AD or multi-infarct dementia were given either 240 mg per day of GBE or a placebo for 24 weeks. Improvements were noted in several clinical areas, including the Clinical Global Impressions scale (described below). Similar results were seen in another double-blind study where the 240 mg dose was administered once per day.

One study worth special mention was the first U.S. clinical study on GBE published in the Journal of the American Medical Association. The study was conducted at six research centers. Harvard Medical School and the New York Institute for Medical Research approved the design of the study, in which 202 patients with AD were given either a modest dose of GBE (120 mg per day) or a placebo for one year. GBE not only stabilized AD but also led to significant improvements in mental function in 64% of the patients. There were no side effects with GBE.

Ginkgo has been used extensively as a medicinal agent worldwide for centuries. It is the most frequently prescribed medicinal herb in Europe, with hundreds of studies reporting positive effects from taking ginkgo for both prevention and treatment of various health complaints. The most dramatic benefits are reported in improving circulation in the elderly. This can enhance memory, possibly delaying the onset of Alzheimer's disease, reducing other forms of dementia, and improving tinnitus and vertigo. Ginkgo's memory-enhancing effects are reported in younger populations as well.

In the most recent study, 410 patients with mild to moderate dementia were randomly assigned to receive either 240 mg GBE or a placebo per day for 24 weeks. The results revealed that treatment with the ginkgo biloba extract led to significant improvements in the symptoms of apathy/indifference, sleep/night-time behavior, irritability/lability, depression/dysphoria, and aberrant motor behavior. These results indicate that even if GBE does not improve cognitive function, it may produce significant improvements in mood and behavior. This would at the very least help enable patients to maintain a normal life and avoid being institutionalized.

It is important to point out that studies directly comparing ginkgo with standard drug regimens indicate that they offer similar efficacy in AD, but ginkgo has fewer side effects. A comparative analysis of studies of at least six months' duration demonstrated that GBE and second-generation cholinesterase inhibitors (tacrine, donepezil, rivastigmine, metrifonate) were equally effective in treating mild to moderate AD. In a meta-analysis of 50 studies that examined the effect of ginkgo on objective measures of cognitive function in patients with AD using standardized measures of cognition, it was concluded that GBE produced benefits comparable to those of standard drug therapy.

In addition to possibly being beneficial in early-stage AD, if the mental deficit is due to vascular insufficiency or depression and not AD, GBE is usually effective in reversing the deficit. GBE should be taken consistently for at least 12 weeks in order to determine its effectiveness. Although in some people with AD benefits are reported within two or three weeks, most will need to take GBE for a longer period.

## **Huperzine A**

Huperzine A, an alkaloid isolated from the moss *Huperzia serrata*, has been shown to potentiate the effects of acetylcholine in the brain by inhibiting the enzyme acetylcholinesterase, which breaks down acetylcholine. It is significantly more selective and substantially less toxic than the acetylcholine esterase inhibitors currently used in conventional medicine (physostigmine, tacrine, and donepezil). In contrast, huperzine A has been used as a prescription drug in China since the early 1990s and has reportedly been used by more than 100,000 people with no serious adverse effects.

In one of the first double-blind clinical studies, huperzine A at a dose of 200 mcg twice per day produced measurable improvements in memory, cognitive function,

and behavioral factors in 58% of AD patients. In contrast, in the placebo group only 36% showed improvement.

In a more recent double-blind study, 210 individuals with AD were randomly assigned to receive a placebo or huperzine A (200 mcg or 400 mcg twice per day) for at least 16 weeks. The 200-mcg dose did not produce any change in cognitive assessment score, but patients taking the 400-mcg dose showed a 2.27-point improvement in this score after 11 weeks compared with a 0.29-point decline in the placebo group, and a 1.92-point improvement after 16 weeks compared with a 0.34-point improvement in the placebo group.

Adverse reactions have been noted with huperzine A, including hyperactivity, nasal obstruction, nausea, vomiting, diarrhea, insomnia, anxiety, dizziness, thirst, and constipation. One trial reported abnormalities in electrocardiogram patterns (cardiac ischemia and arrhythmia).

## **Curcumin**

There is considerable experimental evidence that curcumin protects against age-related brain damage and in particular Alzheimer's disease. Researchers began exploring this effect after noting that elderly residents of rural India who eat large amounts of turmeric have been shown to have the lowest incidence of Alzheimer's disease in the world: 4.4 times lower than that of Americans. In test tube and animal studies curcumin has been shown to inhibit beta-amyloid and have other effects beneficial in AD. Unfortunately, the two clinical trials conducted to date failed to show any benefit. However, the failure to produce positive results may have been due to the poor absorption profile of the curcumin used in the trials. There now exist a number of methods and products that enhance the absorption of curcumin. In one product, Meriva, the curcumin is complexed with soy phospholipids. Absorption studies in animals indicate that peak plasma levels of curcumin after administration of Meriva were five

times higher than those after administration of regular curcumin.<sup>119</sup> Studies with another advanced form of curcumin, Theracurmin, show even greater absorption (27 times greater than regular curcumin).

## Quick Review

- AD is the result of damage to the brain that affects the activity of the neurotransmitter acetylcholine.
- Research is beginning to identify a chronic and excessive inflammatory reaction to amyloid proteins in the brain in individuals susceptible to AD.
- Although genes play a big part in determining susceptibility to AD, lifestyle and environmental factors also have a significant role.
- Traumatic injury to the head; chronic exposure to aluminum, silicon, or both; exposure to neurotoxins from environmental sources; and free radical damage have all been implicated as causative factors.
- Measures to improve blood sugar control and improve insulin sensitivity appear to be important steps in the prevention of AD. Abnormal fingerprint patterns are associated with both Alzheimer's disease and Down syndrome.
- From the perspective of natural medicine, the primary goals of intervention are prevention and using natural measures to improve mental function in the early stages of the disease.
- In the advanced stages of AD, natural measures will usually provide little benefit. There is evidence to suggest that antioxidants offer significant protection against Alzheimer's disease as well as therapeutic benefits.
- Aluminum absorption can be decreased by magnesium, as magnesium competes with aluminum for absorption pathways.



- Polyphenols found in grapes, grape seed extract, and red wine have been shown to prevent beta-amyloid formation and promote disassembly of neurofibrillary tangles.
- A significant percentage of the geriatric population is affected by B vitamin deficiencies linked to Alzheimer's disease.
- Zinc supplementation is demonstrating good results in the treatment of Alzheimer's disease.
- The results of using L-acetylcarnitine to delay the progression of Alzheimer's disease have been outstanding.
- DHEA shows promise in enhancing memory and improving mental function in the elderly.
- It appears that ginkgo biloba helps reverse or delay mental deterioration only during the early stages of Alzheimer's disease.
- Huperzine A is more selective and substantially less toxic than the acetylcholine esterase inhibitors currently used in conventional medicine.
- There is considerable experimental evidence that curcumin protects against age-related brain damage and, in particular, Alzheimer's disease.

## Treatment Summary

The primary therapeutic goal is prevention; follow the recommendations below under "Lifestyle," "Diet," and "Nutritional Supplements." When symptoms begin to appear, it is important to increase nutritional support, as described under "Therapeutic Supplements"; we also offer suggestions under "Botanical Medicines." Keep in mind that in advanced AD, treatment is less likely to be of benefit. In general, we recommend a trial for a minimum of 90 days in attempting to improve AD with natural measures. If no benefit is seen during this time, further therapy is unlikely to provide benefit.

## **Lifestyle**

- Follow the recommendations given in the chapter “A Health-Promoting Life- style.”
- Avoid aluminum (often found in anti- perspirants, antacids, and cookware).

## **Diet**

Follow the recommendations given in the chapter “A Health-Promoting Diet.” In particular, apply the principles of the Mediterranean diet; increase whole food products, including fish, cereals, vegetables, and monounsaturated fats; avoid high-glycemic foods and unhealthy fats; achieve ideal body weight; and take measures to improve insulin sensitivity.

## **Nutritional Supplements**

- A high-potency multiple vitamin and mineral formula as described in the chapter “Supplementary Measures”
- Vitamin C: 500 to 1,000 mg per day
- Vitamin E: 100 to 200 IU per day
- Fish oils: 1,000 mg EPA + DHA per day
- Grape seed or pine bark extract (>95% procyanidolic content): 150 to 300 mg per day
- In high-risk individuals, choose one of the following forms of bioavailable curcumin:
  - Meriva: 1,000–1,200 mg per day
  - Theracurmin: 300 mg per day

## **Therapeutic Supplements**

The following are in addition to all of the supplements listed under “Nutritional Supplements” above:

- Thiamine: 3 to 8 g per day One of the following:
  - Glycerophosphocholine: 1,200 mg per day
  - Citicoline: 1,000 mg per day
- Phosphatidylserine: 100 mg three times per day
- L-acetylcarnitine: 1,500 mg per day
- Methylcobalamin: 1,000 mcg upon arising each day
- Melatonin: 3 mg in the evening at least a half hour before bedtime

## **Botanical Medicines**

- Ginkgo biloba (24% ginkgo flavonglycosides): 240 to 320 mg per day
- Huperzine A: 200 to 400 mcg per day
- Curcumin, one of the following:
  - Meriva: 1,000–1,200 mg per day
  - Theracurmin: 300 mg per day



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### 3

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## NEW RESEARCH SHOWS SYNERGY WITH OMEGA 3 FATTY ACIDS AND B VITAMINS IN PREVENTING ALZHEIMER'S DISEASE

The human brain is a marvelously complex system that requires a wide range of nutrients to function properly. Intelligence, memory, behavior and concentration are all influenced by proper brain nutrition. Young or old, our nutritional status plays a vital role in determining how well our brain functions.

One of the problems with medical research is the obsession with identifying the impact of single factors and their impact on human health. When it comes to nutrition and the brain, this sort of line of research is a silly approach. A new study out of Oxford University highlights just how important it is to look and the interplay between just two key brain nutrients – omega-3 fatty acids and B vitamins – and their ability to prevent age-related mental decline.

## Background Data:

A very large body of scientific evidence has shown that intelligence, memory, behavior and concentration are all influenced by proper brain nutrition. But, for the most part, this research has looked at individual factors and not their interactions. For example, a 2014 study conducted at Oxford's Department of Clinical Neurosciences involved with 156 elderly patients who had mild cognitive impairment and a high risk of dementia and Alzheimer's disease. The patients were divided into two groups: one group took a daily supplement with 800 micrograms of folic acid, 20 milligrams of vitamin B6, and 500 micrograms of vitamin B12; the other group took a placebo supplement.

Before the trial and during the testing period, the researchers utilized magnetic resonance imaging (MRI) to measure the patients' atrophy levels of grey matter in their brains. Atrophying (shrinking) grey matter is a sign of the progression of Alzheimer's disease and other forms of dementia.

Upon completion of the two-year study, researchers found that those given the B vitamin supplement had about seven times less grey matter shrinkage than did the placebo group. The researchers also found that those whose grey matter shrunk fastest had higher levels of homocysteine, and those with higher homocysteine levels initially received the greatest benefit from the B vitamin supplements.



In their conclusion the researchers stated: “Our results show that B-vitamin supplementation can slow the atrophy of specific brain regions that are a key component of the Alzheimer disease process and that are associated with cognitive decline.”

Another key nutritional factor for proper brain function are the long chain omega-3 fatty acids EPA and DHA found in fish and fish oil supplements. The importance of omega-3 fatty acids to brain function relates to their role in the phospholipid composition of nerve cell membranes. Studies have shown that EPA and DHA influence:

- The fluidity of brain cell membranes.
- Neurotransmitter synthesis.
- Neurotransmitter binding.
- Signal transmission.
- The activity of key enzymes that break down neurotransmitters like serotonin, epinephrine, dopamine, and norepinephrine.

Clinical studies with supplemental EPA+DHA from fish oils in patients with a variety of psychological conditions including attention deficit disorder (ADD) and depression validate the importance of supplementation to boost EPA+DHA levels. Fish oils also appear to be important in protecting against age-related mental decline and Alzheimer’s disease.

## New Data:

While research has already established that B vitamin supplements and omega-3 fatty acids can help slow mental decline in older people with memory problems, the interaction between these two nutritional approaches has never really been examined until now. An international team led by Oxford University and United

Arab Emirates University has now found that having higher levels of omega-3 fatty acids in the brain boost the benefits of B vitamins in mild cognitive function.

The team studied more than 250 people with mild cognitive impairment (MCI) in Oxford. MCI reflects an intermediate stage between the expected cognitive decline of normal aging and the more serious decline of dementia. People with mild cognitive impairment can have problems with memory, language, thinking and judgment, but generally not to a degree to cause significant problems in their day-to-day life and usual activities.

Mild cognitive impairment may increase the risk of later progressing to Alzheimer's disease or other dementia, but not everyone with MCI progresses to dementia.

At the start of the study, each person was given a set of tests to measure their cognition, and had a blood test to determine the levels of the omega-3 fatty acids EPA and DHA in their blood. The participants were split into two randomly selected groups, who received either a B-vitamin supplement or a placebo pill over two years. Their cognitive performance was also measured and the results compared with the baseline results from the start of the study.

What the researchers found was that for people with low levels of EPA + DHA, the B vitamin supplement had little to no effect. But for those with high baseline EPA + DHA levels, the B vitamins were very effective in preventing cognitive decline compared to the placebo. These results are game changing because they show a clear interaction and that B vitamins only slow the rate of brain atrophy in MCI in those with a good level of EPA + DHA.

The team of researchers are now designing a study to actually test the combination of B vitamins and EPA + DHA in slowing the conversion from MCI to Alzheimer's disease.

## Commentary:

Here is something that is very important to for people to know. Drugs do not work to improve MCI. In a systemic review funded by the Drug Efficacy and Safety Network of the Canadian Institute of Health Research, eight randomized clinical trials and 3 companion reports were used to evaluate the safety and efficacy of various drugs referred to as “cognitive enhancers” (donepezil [Aricept], rivastigmine [Exelon], galantamine [Razadyne], or memantine [Nemenda]) on mild cognitive impairment.

Results showed these drugs did NOT improve cognition or function among patients with MCI and were associated with a greater risk of side effects especially nausea, diarrhea and vomiting than placebo. Researchers concluded “Our findings do not support the use of cognitive enhancers for mild cognitive impairment.”

The bottom line is that the key goal to boosting brain function is to bath the brain in “super nutrition,” as numerous studies have shown that brain function is directly related to nutritional status. High nutritional status equals higher mental function.

The key dietary factors that reduce the risk of dementia and Alzheimer’s disease from population-base studies are higher fish consumption (and omega-3 fatty acids), monounsaturated fatty acids (primarily from olive oil), light to moderate alcohol use (primarily red wine), and increased non-starchy vegetable and fruit consumption. It is likely that it is the combination of all of these factors that provide the highest degree of protection versus any single dietary factor.

One food that is particularly helpful are blueberries or blueberry extracts. In animal studies researchers have found that blueberries help protect the brain from oxidative stress and memory loss.

In addition to diet, it makes sense to take a high potency multiple vitamin and mineral formula to supply the brain with super nutrition it makes sense to also take 1,000 to 3,000 mg of EPA and DHA (combined) from a quality fish oil. Higher intakes of these omega-3 fatty acids are associated with higher mood and mental function scores.

If symptoms of mental deterioration are definitely present in a person 50 years and older I would recommend taking phosphatidylserine. Phosphatidylserine (PS) is a critical nutrient for anyone with impaired mental function. PS plays a major role in determining the integrity and fluidity of brain cell membranes. Over a dozen double-blind studies have shown phosphatidylserine to improve in mental function, mood, and behavior in patients with degenerative brain disorders. The recommended dosage is 100 mg three times daily.

## Reference:

Oulhaj A, Jerneén F, Refsum H, Smith AD, de Jager CA. Omega-3 Fatty Acid Status Enhances the Prevention of Cognitive Decline by B Vitamins in Mild Cognitive Impairment. *J Alzheimers Dis.* 2016 Jan 6;50(2):547-57.



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## 4

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### DOUBLE-BLIND STUDY SHOWS RESVERATROL MAY HELP PREVENT ALZHEIMER'S DISEASE

Resveratrol is a plant compound similar to flavonoids. It is found in low levels in the skin of red grapes, red wine, cocoa powder, baking chocolate, dark chocolate, peanuts, and mulberry. Red wine is perhaps the most recognized source of resveratrol, however, red wine contains at the very most only one milligram per glass. Most resveratrol supplements use Japanese knotweed (*Polygonum cuspidatum*) as the source with dosage recommendations often 500 mg of resveratrol

up to four times daily. So it would take several thousands glasses of wine to provide the level of resveratrol that is provided through supplementation.

There has been a great deal of hype regarding resveratrol supplements, but there have also been some positive clinical studies showing positive results in improving memory and brain function in elderly subjects. A new study from Georgetown University's Department of Neurology and researchers from 21 medical centers across the United States shows that resveratrol supplements may offer significant protection against Alzheimer's disease.

## Background Data:

Resveratrol has received a lot of attention as a longevity aid, but its scientific basis relies primarily on test tube and animal studies. There is only a handful of published human studies at this time, but the results are very encouraging.

Resveratrol activates an enzyme known as sirtuin 1 which plays an important role in the regulation of cellular life spans; it also promotes improved insulin sensitivity. Either of these two effects might explain its ability to extend lifespan.

In terms of brain health, a 2010 clinical study in humans showed that resveratrol supplementation at a single dosage of 250 or 500 mg could improve blood flow to the brain, but it had no effect on mental function in this study. In a 2014 study conducted in Germany, the use of a resveratrol supplement resulted in a significant impact on the ability to remember words compared with placebo. Resveratrol users also showed a significant increase in functional connectivity of the hippocampus – the area of the brain involved with the formation, organization, and storage of memory.



## New Data:

A randomized, placebo-controlled, double-blind, multicenter study was conducted to examine the safety and effectiveness of resveratrol in 119 individuals with mild to moderate Alzheimer disease (AD).

The patients were randomized to receive either a placebo or resveratrol capsules. The initial dosage was 500 mg orally once daily, with dose escalation by 500-mg increments every 13 weeks until the final dosage of 1,000 mg twice daily was achieved. Brain MRI and cerebrospinal fluid (CSF) collection were performed at baseline and after 52 weeks of treatment.

Resveratrol and its major metabolites were measurable in the blood (plasma) and CSF in the subjects in the resveratrol treated group. The researchers looked at several biomarkers of Alzheimer's including the level of beta-amyloid in the CSF. When beta-amyloid accumulates, it leads to significant damage to brain cells and the characteristic lesions of AD. Interestingly, although accumulation of amyloid-beta in the brain is a hallmark of AD, these patients actually have lower levels of this protein in the CSF. When the researchers look at the level of beta-amyloid in the CSF in the patients in the study, they found that subjects in the resveratrol group had higher levels of beta-amyloid proteins in their spinal fluid than those in the placebo group. The results suggest that resveratrol apparently helps prevent beta-amyloid accumulating in the brain and promotes its transport out of the brain so that it can be effectively broken down.

Resveratrol and its major metabolites clearly penetrated the blood-brain barrier as they were found in the CSF. An additional finding of interest was that the patients taking resveratrol lost about two pounds during the one-year study, while the placebo group gained about 1 pound. The brain MRI results showed that the resveratrol group had a smaller brain volume than the placebo group. The explanation being that the inflammation within the brain linked to AD can cause swell-

ling and a larger brain volume. So, a smaller brain volume in this case (AD) is a positive sign.

These results clearly indicate a potential role of resveratrol supplementation in preventing AD.

## Commentary:

Over the past few months and years I have featured several newsletters highlighting studies that reflect nutritional approaches for improving brain health, memory, and/or the prevention of age-related mental decline or AD. There are a lot of natural products to choose from, but the basic underlying goals and effects are quite similar. You have to reduce inflammation, control blood sugar levels, provide necessary building blocks with super nutrition, and protect the brain from damage by consuming antioxidants from the diet and through supplementation.

While resveratrol shows some compelling data as detailed above, my feeling is that it can't do the job well enough by acting alone. It needs to be part of bigger approach that focuses on diet, lifestyle, and proper supplementation. In regards to diet, the Mediterranean or New Nordic Diet look very helpful. In regards to supplementation, there are four primary recommendations I make to people to help them design a foundation nutritional supplement program that also, not surprisingly are very important in preventing AD:

#1. Take a high quality multiple vitamin and mineral supplement providing at least the recommended dietary intake for all vitamins and minerals.

#2. Take enough vitamin D3 (typically 2,000-4,000 IU daily) to elevate your blood levels to the optimal range (50-80 ng/ml).

#3. Take extra plant-based antioxidants like flavonoid-rich extracts like grape-seed or pine bark extract; curcumin (Theracurmin); a “greens drink” product; resveratrol; or some other broad-spectrum antioxidant.

#4. Take a high quality fish oil product to provide 1,000 mg EPA + DHA daily for general health or up to 3,000 mg EPA + DHA if you have an inflammatory condition, cardiovascular disease, depression, ADHD, multiple sclerosis, or any other brain or nerve disorder; or any of the 60+ health conditions shown to respond or be prevented by fish oils.

Also, realize that in the study described above, benefits to the brain in these patients may have been secondary to improvements in blood sugar control as resveratrol has also been shown to improve insulin action. This potential link highlights the importance of using PGX, which I think is the most important supplement in North America today given its effects in supporting proper blood sugar control and weight loss. Some researchers have referred to AD as “diabetes of the brain.”

## Reference:

Turner RS, Thomas RG, Craft S, et al. A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. *Neurology*. 2015 Sep 11. [Epub ahead of print]



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## 5

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### NEW STUDY ADDS EVIDENCE THAT ALZHEIMER'S DISEASE IS "DIABETES OF THE BRAIN"

The parallel epidemics of Alzheimer's disease and type 2 diabetes share many common features. Chief among them are insulin resistance and chronic inflammation. In fact, some researchers have referred to Alzheimer's disease as diabetes of the brain and even "type 3 diabetes." A new study from researchers affiliated with Harvard and Beth Israel Deaconess Medical Center in Boston provides

additional evidence on the link between blood sugar control, inflammation, and Alzheimer's disease.

## Background Data:

Alzheimer's disease (AD) is a degenerative brain disorder associated with progressive deterioration of memory and cognition. In the United States, Alzheimer prevalence is now estimated to affect about 20% of individuals in the 75–84 years group and 42% people older than 84 years old. These numbers are striking when compared to data from the 1960s indicating an incidence of only 2% in people over the age of 85 years. The tremendous increase in AD in people over 85 years of age is often referred to as the “Alzheimer's epidemic.”

The primary brain lesions of AD are the result of deposits of a substance known as beta-amyloid. Although the immune cells in the brain normally remove beta-amyloid and plaque, research is beginning to characterize a chronic and excessive inflammatory reaction to amyloid proteins in the brain in susceptible individuals that can promote AD.

The tremendous increase in AD parallels the rise in type 2 diabetes and insulin resistance suggesting a possible connection. It is well established that type 2 diabetics have a 1.5 to 4-fold risk for AD, as well as dementia caused by damage to the blood vessels of the brain. Insulin resistance in the brain is associated with poor uptake of glucose by brain cells and localized inflammation that leads to beta-amyloid formation. Hence measures to improve blood sugar control and improve insulin sensitivity appear to be important steps in the prevention of AD.

## New Data:

The study subjects were 65 people with an average of 66 years. Of these subjects, 35 had type 2 diabetes (T2D). All subjects were tested at the start of the study and then two years later with a MRI scan to measure blood flow, various

blood tests including C-reactive protein (a marker for inflammation) and several tests of cognitive ability.

At the end of two years, people with diabetes had greater declines in gray matter volume, composite scores on mental tests, and in rates of blood flow to the brain than those in the control group. They also had greater increases in blood measures of inflammation. Among the group with diabetes, those with more severe declines in brain blood flow had correspondingly greater declines on tests of mental skills.

These results indicate that inflammation due to insulin resistance leads to changes in blood flow and blood vessel flexibility that consequently accelerates the decline in mental function and daily activities performance in older people with T2D.

## Commentary

The take away message of this article once again highlights the importance of eating to control blood sugar levels. Preventing insulin resistance is clearly a primary goal for a longer and healthier life. In addition, dietary strategies to further reduce chronic inflammation and the formation of beta-amyloid are also critical. Key dietary practices are to focus on vegetables, fish, and mono-unsaturated fats (nuts, seeds, olive oil, etc.); liberal use of spices and herbs; avoid high glycemic load foods and unhealthy fats; and achieve ideal body weight.

As far as dietary supplements, in addition to taking a high potency multiple, sufficient vitamin D3, and 1,000 mg of EPA+DHA each day, I would recommend taking a special form of curcumin (the yellow pigment of turmeric). There is considerable experimental evidence that curcumin protects against age-related brain damage and in particular, AD. Researchers began exploring this effect after noting that elderly (aged 70-79) residents of rural India who eat large amounts of turmeric have been shown to have the lowest incidence of AD in the world: 4.4



times lower than that of Americans. In test tube and animal studies curcumin has been shown to inhibit beta-amyloid as well as other effects beneficial in AD. Unfortunately, the two clinical trials conducted to date failed to show any benefit. However, the failure to produce positive results may have been due to the poor absorption profile of the curcumin used in the trials. There now exist several products on the marketplace that enhance the absorption of curcumin. Of these, Theracurmin shows the greatest absorption. Currently there is a double-blind, placebo-controlled study underway with Theracurmin in AD being conducted at UCLA.

## Reference:

Chung CC, Pimentel D, Jor'dan AJ, et al. Inflammation-associated declines in cerebral vasoreactivity and cognition in type 2 diabetes. *Neurology*. 2015 Jul 8. [Epub ahead of print]



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## 6

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### FOR IMPAIRED MEMORY AND MENTAL FUNCTION, DON'T FOLLOW THE DRUG APPROACH

Is memory loss and decreased brain power inevitable as we age? Many people in their 40s, 50s and beyond are told that it is and there is nothing that can be done about it. Is that true? Of course not! Steps can be taken to not only stop memory loss and mental decline, but also reverse it. Unfortunately, people (and doctors) trying to accomplish these goals with drugs are going down the wrong path.

Brain cells are the most complex, long living and nutritionally demanding cells in the body. Scientific studies have shown that intelligence, memory, behavior and concentration are all influenced by proper brain nutrition. Young or old, our nutritional status plays a vital role in determining how well our brain functions. Trying to sidestep this fundamental fact by trying to address brain health solely through pharmacological aids is foolish, yet it is the dominant model in conventional medicine whether a person is showing memory loss, depression, ADHD, or other brain issue.

## Background Data:

Mild cognitive impairment (MCI) is a recently recognized distinct medical condition that reflects an intermediate stage between the expected cognitive decline of normal aging and the more serious decline of dementia. People with mild cognitive impairment can have problems with memory, language, thinking and judgment, but generally not to a degree to cause significant problems in their day-to-day life and usual activities.

Mild cognitive impairment may increase the risk of later progressing to Alzheimer's disease or other dementia, but not everyone with MCI progresses to dementia.

Because MCI is a newly recognized and affects up to 42% of seniors, the drug companies have been very busy trying to seize market share. Drugs known as cognitive enhancers used to treat Alzheimer's disease are becoming popular prescriptions for MCI, but the research does NOT show these drugs to provide any benefit despite their popularity and have the potential to cause significant side effects. One drug, tacrine (Cognex) has already been removed from the market.

## New Data:

In a systemic review funded by the Drug Efficacy and Safety Network of the Canadian Institute of Health Research, eight randomized clinical trials and 3 companion reports were used to evaluate the safety and efficacy of various drugs referred to as “cognitive enhancers” (donepezil [Aricept], rivastigmine [Exelon], galantamine [Razadyne], or memantine [Nemenda]) on mild cognitive impairment.

Results showed these drugs did NOT improve cognition or function among patients with mild cognitive impairment and were associated with a greater risk of side effects especially nausea, diarrhea and vomiting than placebo.

Researchers concluded “Our findings do not support the use of cognitive enhancers for mild cognitive impairment.”

## Commentary:

A key goal to boosting brain function is to bath the brain in “super nutrition,” as numerous studies have shown that brain function is directly related to nutritional status. High nutritional status equals higher mental function. Given the frequency of nutrient deficiency in the elderly population, it is likely that many cases of impaired mental function may have a nutritional cause.

One food that is particularly helpful are blueberries or blueberry extracts. In animal studies researchers have found that blueberries help protect the brain from oxidative stress and memory loss. When older rats were given the human equivalent of 1 cup of blueberries a day they demonstrated significant improvements in both learning capacity and motor skills, making them mentally equivalent to much younger rats. When the rats’ brains were examined, the brain cells of the rats given blueberries were found to communicate more effectively than those of the other older rats that were not given blueberries.

In addition to diet and the foundation supplements of a high potency multiple vitamin and mineral formula, a flavonoid-rich extract like blueberry or grape seed extract, and 1,000 mg of EPA and DHA (combined) from a quality fish oil, if some symptoms of mental deterioration are definitely present in a person 50 years and older I would recommend taking phosphatidylserine.

Phosphatidylserine (PS) is a critical nutrient for anyone with impaired mental function. PS plays a major role in determining the integrity and fluidity of brain cell membranes. Over a dozen double-blind studies have shown phosphatidylserine to improve in mental function, mood, and behavior in patients with degenerative brain disorders. The recommended dosage is 100 mg three times daily.

## Reference:

Tricco AC, Soobiah C, Berliner S, et al. Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. *CMAJ*. 2013 Sep 16. doi: 10.1503/cmaj.130451





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### FOR IMPAIRED MEMORY AND BRAIN FUNCTION, NUTRITION IS THE KEY

Are memory loss and decreased brain power inevitable as we age? Many people in their 40s, 50s, and beyond are told that they are, and that there's nothing that can be done about it. Is that true? Of course not!

Brain cells are the most complex, long living, and nutritionally demanding cells in the body. Studies have shown that intelligence, memory, behavior, and concen-

tration are all influenced by nutrition. Young or old, our nutritional status plays a vital role in determining how well our brain functions.

## Super Nutrition

A key goal for brain health is to bathe the brain in “super nutrition.” Simply put, high nutritional status equals higher mental function. Given the frequency of nutrient deficiency in the elderly population, it is likely that many cases of impaired mental function may have a nutritional cause.

A new study conducted at Oxford’s Department of Clinical Neurosciences involved 156 elderly patients who had mild cognitive impairment and a high risk of dementia and Alzheimer’s disease. The patients were divided into two groups: one group took a daily supplement containing 800 mcg of folic acid, 20 mg of vitamin B6, and 500 mcg of vitamin B12; the other group took a placebo.

Before and during the testing period, researchers used magnetic resonance imaging (MRI) to measure the atrophy levels of grey matter in the patients’ brains. Atrophying (shrinking) grey matter is a sign of the progression of Alzheimer’s and other forms of dementia. Upon completion of the two-year study, researchers found that those given the supplement had about seven times less atrophy than the placebo group.

The study also found that those whose grey matter shrunk fastest had higher levels of homocysteine, and those with higher homocysteine levels initially received the greatest benefit from supplementation. In their conclusion, the researchers stated: “Our results show that B-vitamin supplementation can slow the atrophy of specific brain regions that are a key component of the Alzheimer’s disease process and that are associated with cognitive decline.”

In addition to taking a high potency multiple vitamin and mineral formula to supply the brain with super nutrition, it makes sense to add 1,000–3,000 mg of



EPA and DHA (combined) from a quality fish oil. Higher intakes of these omega-3 fatty acids are associated with higher mood and mental function scores.

If symptoms of mental deterioration are definitely present in a person 50 years of age or older, consider phosphatidylserine (PS), which plays a major role in determining the integrity and fluidity of brain cell membranes. Over a dozen double-blind studies have shown that PS can help improve mental function, mood, and behavior in patients with degenerative brain disorders. Try 100 mg three times daily.

## The Best Brain Foods

The key dietary factors that reduce the risk of dementia and Alzheimer's disease from population-based studies are higher fish consumption (and omega-3 fatty acids), monounsaturated fatty acids (primarily from olive oil), light to moderate alcohol use (primarily red wine), and increased non-starchy vegetable and fruit consumption. It is likely that a combination of all of these factors will provide the highest degree of protection.

Blueberries or blueberry extracts are particularly helpful. When older rats were given the human equivalent of 1 cup of blueberries per day, they demonstrated significant improvements in learning and motor skills, making them mentally equivalent to younger rats. When the rats' brains were examined, the brain cells of those given blueberries were found to communicate more effectively than those of rats not given blueberries. An alternative to eating more blueberries is taking a flavonoid-rich extract such as grape seed or pine bark extract (100–300 mg daily).

Celery and celery seed extracts contain a compound, 3-n-butylphthalide (3nB), that has brain-health benefits. In human and animal studies, 3nB significantly improved learning deficits, as well as long-term spatial memory. Researchers

have concluded that, “3nB shows promising preclinical potential as a multi-target drug for the prevention and/or treatment of Alzheimer’s disease.”

## Herbal Approaches

Ginkgo biloba extract is a popular herbal approach to boosting brain power. Use 60–120 mg of standardized extract (i.e., 24-percent ginkgoflavonglycoside extract), one to two times daily. Do not take ginkgo with blood-thinning drugs.

Traditionally used to enhance memory, learning, and concentration in Ayurvedic medicine, bacopa is another popular herbal brain booster. Emerging clinical evidence is validating its benefits. In one study, 46 healthy volunteers (ages 18–60) were divided into treatment and placebo groups. Participants were given 300 mg daily of a bacopa extract. At the end of the 12-week study, there was a significant improvement in verbal learning, memory, and information processing in the bacopa group compared to placebo.

## What Is MCI?

Mild cognitive impairment (MCI) is a newly recognized medical condition that involves the stage between normal, age-related cognitive decline and more serious decline associated with dementia. People with MCI can have problems with memory, language, thinking, and judgment that generally aren’t severe enough to cause significant problems in their day-to-day lives and usual activities.

MCI may increase the risk of developing Alzheimer’s disease or some form of dementia, but not everyone with MCI gets dementia. Because MCI is a new diagnosis and affects up to 42 percent of seniors, pharmaceutical companies have been busy formulating drugs to seize market share. Alzheimer’s medications known as “cognitive enhancers” are becoming popular for treating MCI; however, despite their popularity, the drugs have not been shown to provide any benefit.

Worse, these drugs have the potential to cause significant side effects. One such drug, tacrine (Cognex), has already been removed from the market



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# IS PQQ THE NEXT NUTRIENT SUPERSTAR?

Pyrroloquinoline quinone (PQQ) is a novel vitamin-like compound found in plant foods that is showing a wide range of benefits to brain and body function based upon preclinical studies and initial clinical evaluation.<sup>1</sup> Although PQQ is not currently viewed as a vitamin, it is likely to be considered an essential nutrient in the future.



## What exactly does PQQ do?

PQQ stimulates growth and serves as a cofactor for a special class of enzymes involved in cellular function including cellular growth, development, differentiation, and survival.<sup>1</sup>

PQQ is also as an extremely powerful antioxidant capable of catalyzing continuous cycling (the ability to perform repeated oxidation and reduction reactions) to a much greater degree compared to other antioxidants. For example, PQQ is able to carry out 20,000 catalytic conversions compared to only 4 for vitamin C.<sup>1,2</sup>

## Are there any food sources of PQQ?

PQQ has been found in all plant foods analyzed to date.<sup>1</sup> PQQ-rich foods include parsley, green peppers, kiwi fruit, papaya and tofu.<sup>3</sup> These foods contain about 2-3 mcg per 100 grams. Green tea provides about the same amount per 4 oz serving.

## Is PQQ an essential nutrient?

Based upon the current research there is no question that it plays a critical role in human nutrition.<sup>1,4</sup> When PQQ is omitted from chemically defined diets in mammals it leads to growth impairment, compromised immune status, and abnormal reproductive function.<sup>5</sup> The nutritional requirements of PQQ are probably in line with folic acid and biotin in terms of micrograms per day versus milligrams per day. Like essential nutrients, the immune system seems particularly sensitive to low levels of PQQ. With PQQ deprivation there are multiple defects in immune function and loss of white blood cells to respond properly.<sup>1</sup>

## What is the most important function of PQQ?

One key action of PQQ involves a direct action on key enzymes involved in the energy producing compartments in our cells – the mitochondria. As a result PQQ improves energy production.<sup>1,6</sup> In addition to PQQ's powerful antioxidant effect protects against mitochondrial damage. But, PQQ not only protects mitochondria from oxidative stress—it also promotes the spontaneous generation of new mitochondria within aging cells, a process known as mitochondrial biogenesis or mitochondriogenesis.<sup>1,7,8</sup> This effect is a “fountain of youth” for mitochondrial function.

## What are the clinical uses of PQQ?

Given the nutritional importance and tremendous span of physiological effects of PQQ, there are considerable benefits in conditions that revolve around low mitochondrial function including in aging, many brain and neurological disease (e.g., Alzheimer's and Parkinson's disease), and many other chronic degenerative disease. Current research has primarily focused on its ability to protect memory and cognition in both aging animals and humans. Here are some of the effects noted in the animal studies:

- PQQ reverses cognitive impairment caused by chronic oxidative stress and improve performance on memory tests in animal models.<sup>1,9</sup>
- PQQ supplementation stimulates the production and release of nerve growth factor.<sup>1,1</sup>
- PQQ protects against the self-oxidation of the DJ-1 gene, an early step in the onset of Parkinson's disease.<sup>1,11</sup>
- PQQ protects brain cells against oxidative damage in models of strokes.<sup>1,12</sup>
- PQQ blocks the formation of inducible nitric oxide synthase (iNOS), a major source of reactive nitrogen species (RNS) that are so damaging to brain cells.<sup>1,13</sup>

- PQQ protects against the likelihood of severe stroke in an experimental animal model for stroke.<sup>1,14</sup>
- PQQ protects the brain against neurotoxicity induced by other powerful toxins, including mercury, glutamate, and oxidopamine (a potent neurotoxin used by scientists to induce Parkinsonism in laboratory animals).<sup>1,15,16</sup>
- PQQ prevents development of alpha-synuclein, a protein associated with Parkinson's disease.<sup>1,17</sup>
- PQQ also protects nerve cells from the damaging effects of the beta-amyloid-protein linked with Alzheimer's disease.<sup>1,18</sup>

## Has PQQ been studied in human clinical trials?

Yes, preliminary clinical studies are extremely encouraging and several larger clinical trials are currently either completed waiting publication or are in process.

In regards to improving brain function, while PQQ is somewhat effective on its own, when it is combined with a related compound well-known to all – coenzyme Q10 – even better results have been shown. This synergistic effect was first seen in animal studies and further demonstrated in a human double-blind, placebo-controlled clinical trial conducted in Japan in 2007.<sup>19</sup> In this study of 71 middle-aged and elderly people aged between 40-70, supplementation with 20 mg per day of PQQ resulted in improvements on tests of higher cognitive function compared to the placebo group, but in the group receiving 20 mg of PQQ along with 300 mg of CoQ10 the results were even more dramatic. PQQ and CoQ10 are both involved in mitochondrial energy production, so these results are not that surprising.

## Does PQQ have to be used with CoQ10 to see results?

No, it is active on its own. In fact, in most people under 50 there may not be a need for simultaneous use of PQQ and CoQ10 unless the person is taking a drug like cholesterol-lowering statins that interfere with CoQ10 manufacture.

One human study used PQQ in 10 subjects (5 females, 5 males) the ages of 21–34 years. The subjects were given PQQ in a single dose (0.2 mg PQQ/kg) after which multiple measurements of plasma and urine PQQ levels and changes in antioxidant potential over a 48-hour period.<sup>20</sup> Results indicated a significant increase in antioxidant potential even after this only one dosage. The same subjects were also given a daily dose of 0.3 mg PQQ/kg and had their blood measured for markers of inflammation (plasma C-reactive protein and interleukin (IL)-6 levels) and urinary metabolites related to energy metabolism before PQQ administration and 72 hours later.

PQQ supplementation resulted in significant decreases in the levels of the inflammatory markers of plasma C-reactive protein and IL-6. Furthermore, the changes in urinary metabolites consistent with enhanced mitochondria-related functions. The data are among the first to link systemic effects of PQQ in animals to corresponding effects in humans.

## What is the proper dosage?

One question regarding PQQ is what is an effective dosage? Specifically, if the nutritional requirement of PQQ is likely less than 500 mcg daily why is the recommended dosage 10 to 20 mg? In order to get a measured response in mitochondrial function in adult animals there is the need to feed higher amounts of PQQ much like why only 8 to 15 mg of vitamin C might protect against the overt signs of scurvy, the recommended dietary allowance currently stands at 75



to 90 milligram per day (for adults, excluding pregnant and lactating women) for optimal function, and even higher amounts are required for clinical applications.

The current recommendation of 10 to 20 mg of PQQ daily is based upon the equivalent dose in animals has consistently improved various mitochondrial functions. There are also some clinical and observational studies that justify the dosage, especially the 20 mg dosage for enhancing memory.<sup>21</sup>

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